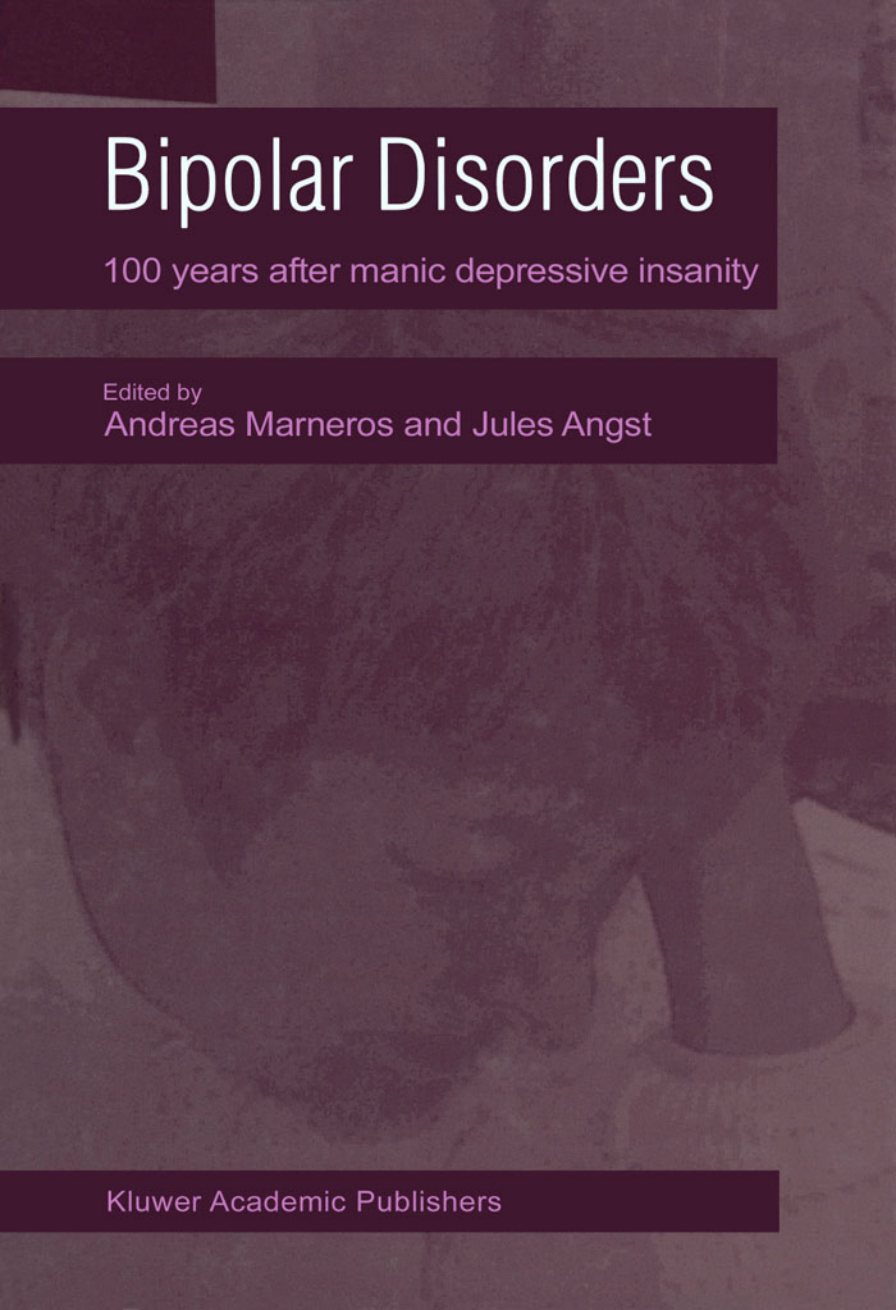
Bipolar Disorders

100 years after manic depressive insanity

Edited by
Andreas Marneros and Jules Angst



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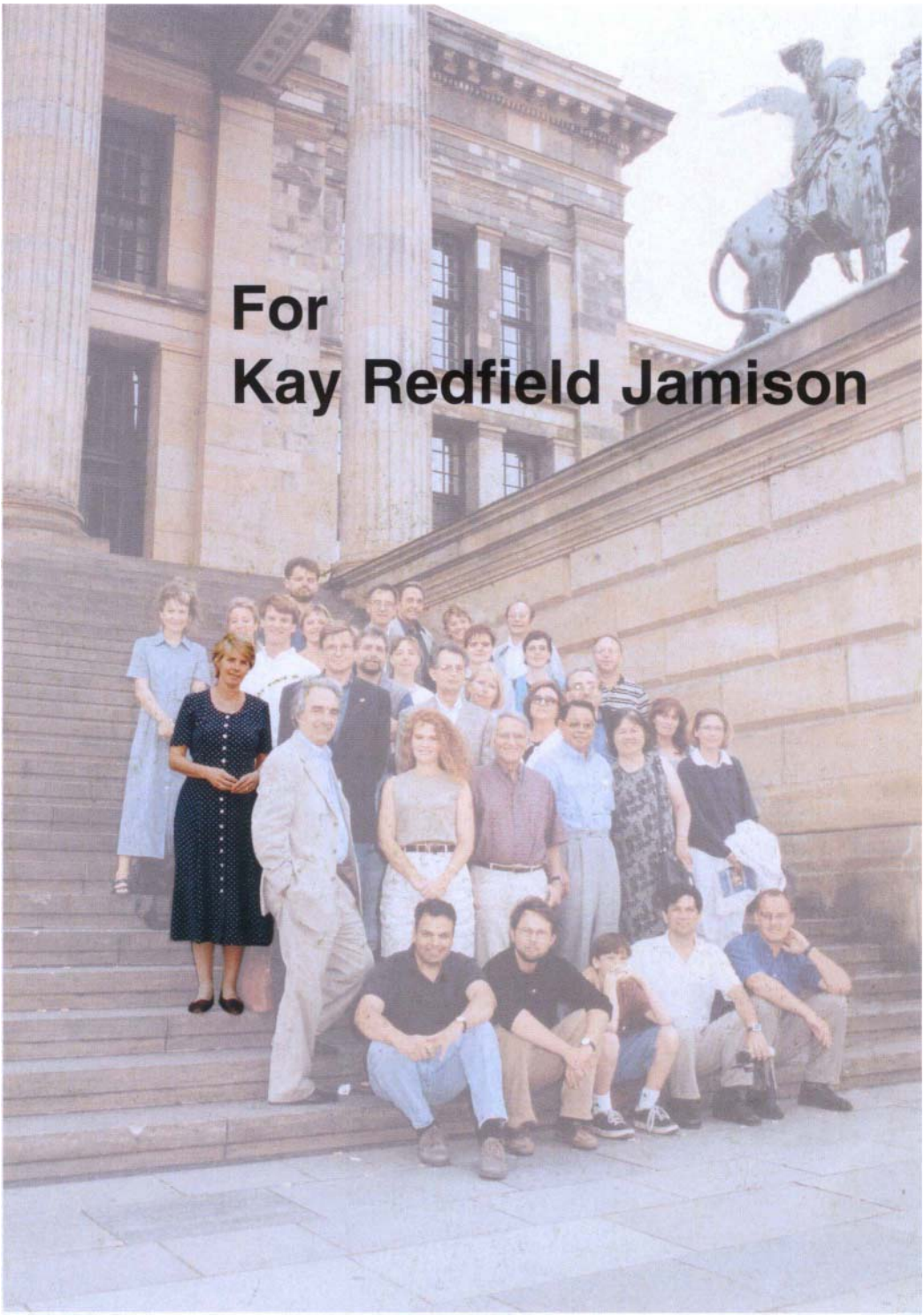
For
Kay Redfield Jamison


from the authors

Bipolar Disorders

100 years after manic-depressive insanity

Edited by

Andreas Marneros
Martin-Luther-University Halle-Wittenberg, Halle, Germany
and
Jules Angst
University Zürich, Zürich, Switzerland

KLUWER ACADEMIC PUBLISHERS
NEW YORK, BOSTON, DORDRECHT, LONDON, MOSCOW

eBook ISBN: 0-306-47521-9
Print ISBN: 0-7923-6588-7

Created in the United States of America

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Contributors

Hagop S. Akiskal
University of California at San Diego, 3350 La Jolla Village, San Diego, CA 92161, USA

Jules Angst
Psychiatrische Universitätsklinik, Lenggstraße 31, Postfach 68, 8209 Zürich, Switzerland

Lesley M. Arnold
Department of Psychiatry, University of Cincinnati College of Medicine, Ohio 45267-0559, USA

Matthias Backenstraß
Psychiatrische Klinik der Ruprecht-Karls-Universität Heidelberg, Voßstraße 4, 69115 Heidelberg, Germany

Luca Bartoli
Clinica Psichiatrica, Primo Policlinico Universitario, Largo Madonna delle Grazie, I-80138 Napoli, Italy

Jerry A. Bennett
Department of Psychiatry, University of Cincinnati College of Medicine, Ohio 45267-0559, USA

Marc L. Bourgeois
Professeur Université Bordeaux II, Hôpital Charles Perrens, 121, rue de la Béchade, 33076 Bordeaux, France

Peter Brieger
Klinik und Poliklinik für Psychiatrie und Psychotherapie der Martin-Luther-Universität Halle-Wittenberg, 06097 Halle, Germany

Joseph R. Calabrese
Professor of Psychiatry, Department of Psychiatry, Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Ohio, USA

Tim J. Crow
University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK

Arno Deister
Krankenhaus Itzehoe, Abteilung für Psychiatrie und Psychotherapie, Robert-Koch-Straße 2, 25524 Itzehoe, Germany

Lynn E. DeLisi
Professor of Psychiatry, SUNY, Stony Brook HSC, T-10 Stony Brook, New York 11794, USA

Naakesh A. Dewan
Department of Psychiatry, University of Cincinnati College of Medicine, Ohio 45267-0559, USA

Henrik Ewald
Århus Universitetshospital, Psykiatrisk Hospital, Institute for Basic Psychiatric Research, Skovagervej 2, 8240 Risskov, Denmark

Stephen V. Faraone
Pediatric Psychopharmacology Unit, Psychiatry Service, Massachusetts General Hospital, Boston, MA 02114, USA

Robert L. Findling
Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Ohio, USA

Marlene P. Freeman
University of Cincinnati Medical Center, 231 Bethesda Avenue, Cincinnati, Ohio 45267-0559, USA

Paolo Girardi
Centro Lucio Bini, Via Crescenzio 42, 00193 Roma, Italy

Heinz Grunze
Psychiatrische Universitätsklinik der Universität München, Nußbaumstraße 7, 80336 München, Germany

Nathan Herrmann
Head, Department of Psychiatry, Sunnybrook of Toronto, 2075 Bayview Avenue, North York, Ontario, M4N 3M5, Canada

Paul E. Keck Jr.
Department of Psychiatry, University of Cincinnati College of Medicine, Ohio 45267-0559, USA

Susan E. Kimmel
Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Ohio, USA

Alexia E. Koukopoulos
Università degli Studî di Roma, "La Sapienza" – 5, Piazzale Aldo Moro, 00185 Roma, Italy

Athanasios Koukopoulos
Centro Lucio Bini, Via Crescenzio 42, 00193 Roma, Italy

Klaus T. Kronmüller
Psychiatrische Klinik der Ruprecht-Karls-Universität Heidelberg, Voßstraße 4, 69115 Heidelberg, Germany

Mary J. Kujawa
Medical Director, Neurosciences Medical Development, Bristol-Myers Squibb Company, Princeton, New Jersey 08543-4500, USA

Stanley P. Kutcher
Department of Psychiatry, Dalhousie University, Queen Elizabeth II Health Sciences Center, 5909 Veterans' Memorial Lane, Halifax, Nova Scotia B3H 3E2, Canada

Mario Maj
Clinica Psichiatrica, Primo Policlinico, Universitario, Largo Madonna delle Grazie, I-80138 Napoli, Italy

Andreas Marneros
Klinik und Poliklinik für Psychiatrie und Psychotherapie der Martin-Luther-Universität Halle-Wittenberg, 06097 Halle, Germany

Susan L. McElroy
Department of Psychiatry, University of Cincinnati College, of Medicine, Ohio 45267–0559, USA

Hans-Jürgen Möller
Psychiatrische Universitätsklinik der Universität München, Nußbaumstraße 7, 80336 München, Germany

Christoph Mundt
Geschäftsführender Direktor, Psychiatrische Klinik, R.-Karl-Universität Heidelberg, Voßstraße 4, 69115 Heidelberg, Germany

Charles B. Nemeroff
Department of Psychiatry and Behavioral Sciences, Emory School of Medicine, Atlanta, Georgia, USA

Olavo Pinto
Department of Psychiatry, University of California at San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0603, USA

Daniel J. Rapport
Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Ohio, USA

Anke Rohde
Gynäkologische Psychosomatik Universitätsklinik, Sigmund-Freud-Straße 25, 53100 Bonn, Germany

Gabriele Sani
Università degli Studî di Roma, "La Sapienza" – 5, Piazzale Aldo Moro, 00185 Roma, Italy

Melvin D. Shelton
Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Ohio, USA

Kenneth I. Shulman
Head, Department of Psychiatry, Sunnybrook & Women's, 2075 Bayview Avenue, North York, Ontario, M4N 3M5, Canada

Mauricio Tohen
Zyprexa Global Physician, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, USA

Alfonso Tortorella
Clinica Psichiatrica, Primo Policlinico, Universitario, Largo Madonna delle Grazie, I-80138 Napoli, Italy

Ming T. Tsuang
Harvard Medical School, Massachusetts Mental Health Center, 74 Fenwood Road, Boston, MA 02115, USA

Preface

One hundred years ago – in 1899 – Emil Kraepelin, Professor of Psychiatry in Heidelberg and later in Munich – created, in two very important pieces of work, the concept of "manisch-depressives Irresein" ("manic-depressive insanity"). The first was entitled *Die klinische Stellung der Melancholie* (*The Clinical Position of Melancholia*), and the second publication was the sixth edition of his textbook. In the same year Kraepelin's pupil and colleague, Wilhelm Weygandt, published his book *Über die Mischzustände des Manisch-Depressiven Irreseins* (*On the Mixed States of Manic-Depressive Insanity*).

A century after Kraepelin's creation of "manic-depressive insanity", we celebrate. Is this really appropriate? We believe it is firmly established that the "folie circulaire" of Jean-Pierre Falret or the "folie à double forme" of Jules Baillarger differs from recurrent depression, which is also different from Kraepelin's "manic-depressive insanity". Yet the answer to the question of

Emil Kraepelin

Jean-Pierre Falret

whether it is appropriate to celebrate is clear: Yes. This not only because the work of Emil Kraepelin is fundamental in the true sense of the word. There can be no doubt that Emil Kraepelin is the most important founder of modern psychiatry. Just one of the many reasons for this opinion is his enormous contribution to the definition, description and diagnosis of affective disorders.

Emil Kraepelin is one of the most interesting personalities of international science. Not only because of his knowledge, and not only because of his very broad range of interests; not only because his knowledge was always based on data, on observations and clinical experience; and not only because he thought conceptually; but also because he had a marvellous character trait: namely the ability to correct himself. He was always able to change his opinion, always able to revise his theories if data-oriented research no longer supported his assumptions. He followed the principle: "Science does not follow books, but books science". An example: the change in his views regarding "Involutionsmelancholie" (melancholia in the elderly) after the findings of his pupil and colleague Dreyfus did not confirm the independence of this melancholia from the other types of "manic-depressive insanity". Another example: when another of his former pupils, Zendig, examined patients diagnosed by Kraepelin himself as having schizophrenia (dementia praecox), and found that 20% of them did not fulfil the essential longitudinal Kraepelinian criterion of deterioration, Kraepelin accepted it. In his 1920 publication "Die

Erscheinungsformen des Irreseins" ("The Phenomenological Types of Insanity") he documented his doubts with regard to the validity of a sharp dichotomy between schizophrenia and the affective disorders, leaving room for cases-in-between, the disorders later named schizoaffective. Unfortunately Emil Kraepelin's ability to correct himself was not always a trait shared by his epigones, who were in the main more dogmatic than Kraepelin himself. The consequence was that, in spite of the significant opposition to the unitary concept of Kraepelin by psychiatrists such as Carl Wernicke, Karl Kleist and Karl Leonhard, almost seven decades passed before the rebirth of the "folie circulaire".

In 1999 we celebrated not only 100 years of Kraepelin's concept of the manic-depressive insanity, but also the 33rd anniversary – 33 years being one of the definitions of a "generation" – of the rebirth of the bipolar disorders. The year of their rebirth was 1966, the date of two fundamental publications: the monograph *Zur Ätiologie und Nosologie endogener depressiver Psychosen* (*On the Aetiology and Nosology of Endogenous Depressive Psychoses*) by Jules Angst, and some months later Carlo Perris' publication "A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses".

During the past 33 years the concept of the bipolar disorders has been firmly established; the views of Falret, Wernicke, Kleist, Leonhard, Angst and Perris have become important component parts of the psychiatric knowledge and have been developed further.

One hundred years of exciting evolution!

Andreas Marneros
Halle (Saale)

Jules Angst
Zurich

Autumn 1999

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Chapter one

*Bipolar disorders: roots and evolution**

Andreas Marneros and Jules Angst

THE CLASSICAL PERIOD

''Εἰδέναι δέ χρή τούζ ἀνθρώπουζ ὅτι ἐξ οὐδενόζ ἡμῖν αἱ ἡδοναί γίνονται καί εὐφροσύναι καί γέλωτεζ καί παιδιαί ἡ ἐντεῦθεν, καί λῦπαι καί ἀνίαι καί δυσφροσύναι καί κλαυθμοί. καί τούτῳ φρονέομεν μάλιστα καί βλέπομεν καί ἀκούομεν καί διαγιγνώσκομεν τά τε αἰσχρά καί καλά καί κακά καί ἀγαθά καί ἡδέα καί ἀηδέα, τά μέν νόμῳ διακρίνοντεζ, τά δέ τῷ συμφέροντι αἰσθανόμενοι, τῷ δέ καί τάζ ἡδονάζ καί τάζ ἀηδίαζ τοῖσι καιροῖσι διαγιγνώσκοντεζ οὐ ταῦτα ἀρέσκει ἡμῖν. τῷ δέ αὐτῷ τούτῳ καί μαινόμεθα καί παραφρονέομεν, καί δείματα καί φόβοι παρίστανται ἡμῖν, τά μέν νύκτωρ, τά δέ καί μεθ' ἡμέρην, καί ἀγρυπνίαι καί πλάνοι ἄκαιροι, καί φροντίδες οὐχ ἱκνεύμεναι, καί ἀγνωσίαι τῶν καθεστώτων καί ἀηθίαι. καί ταῦτα πάσχωμεν ἀπό τοῦ ἐγκεφάλου πάντα, ὅταν ὅὐτοζ μή ὑγιαίνη ... ''

Hippocrates, ″On the Sacred Disease″

″The people ought to know that the brain is the sole origin of pleasures and joys, laughter and jests, sadness and worry as well as dysphoria and crying. Through the brain we can think, see, hear and differentiate between feeling ashamed, good, bad, happy. ... Through the brain we become insane, enraged, we develop anxiety and fears, which can come in the night or during the day, we suffer from sleeplessness, we make mistakes and have unfounded worries, we lose the ability to recognize reality, we become apathetic and we cannot participate in social life. ... We suffer all those mentioned above through the brain when it is ill... .″[1]

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*Parts of this paper have been already published in a modified form in the *Journal of Affective Disorders* (J. Angst/A. Marneros 2000, and A. Marneros 2000b).

[1] Translation of original Greek and German quotations by Andreas Marneros.

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 1–36.

What we today call depression, mania, schizophrenia, schizoaffective disorder, organic psychoses, anxiety disorder, hysteria, hypochondria, substance abuse, mental disorder and many others have been described already in the classical Greek period. But many of them were known to the Greeks of the pre-classical period as well as to other people long before the classical period (see Alexander and Selesnick 1966, Leibbrand and Wettley 1961, Howells 1975, Kudlien 1967, Berrios 1996).

The first description of a physician diagnosing a mental disorder – a physician but not a priest or magician(!) – concerns one of the two famous physicians of Homer's Ilias: namely Podaleirios. Podaleirios – diagnosed the mental insanity of Ajax by examining his "lightning eyes" (see also Kudlien 1967).

The origin of bipolar disorders has its roots in the work and views of the Greek physicians of the classical period. Mania and melancholia are two of the earliest described human diseases, although in a different or broader way than in the modern definitions (Marneros 1999, Angst and Marneros 2000). Heroes in the poems of Homer were used by ancient Greek physicians and philosophers – for instance Aristotle and Aretaeus of Cappadocia – as examples for mania or melancholia. Hippocrates (460–337 BC), however, was the first to systematically describe melancholia and mania, as well as other mental disorders, in a scientific way. We think that his work *On Sacred Disease,* that is epilepsy, could be assumed as the beginning of scientific medicine, including psychiatry: disease will be disconnected from god and punishment and will be connected with physiological processes and environment. Emotions, thinking perceptions, volition and behaviour are connected with the brain. Disturbances in them are caused by diseases of the brain. That was the logical consequence after the "revolution of thought", which began with the birth of philosophy with its rational approach to understanding nature. Already the Roman author Celsus (25 BC–AD 50) wrote in his "Proemium" to "De Medica" that one of Hippocrates' most important conributions to medicine was "separare ab studio sapientiae", the "separation of medicine from philosophy" (Celsus meant the ancient cosmological and religious view but not anthropological philosophy; see also Kudlien 1967).

Hippocrates based his work on the materialistic views of Pythagoras and his scholars Alcmaeon and partially Empedocles. The views of Alcmaeon of Crotona obviously had an especially great influence on him. Alcmaeon may have been the first Greek philosopher and scientist who experimented with brains of animals (Anaxagoras may have done so around the same time, 500–400 BC). Alcmaeon tried to find auditory and visual channels to the brain. He thought that the origin of diseases was the disturbed interaction of body fluids with the brain. Alcmaeon's work *On Nature* was probably the most fundamental text used by pre-Hippocratic writers, as Alexander and Selesnick (1966) pointed out.

Hippocrates supplemented such theories with excellent bedside observations as well as longitudinal follow-up experiences. Psychiatry was one of Hippocrates' interests and he formulated the first classification of mental disorders, namely into melancholia, mania and paranoia. Together with the so-called Hippocratic physicians he also described organic and toxic deliria, postpartum psychoses and phobias and coined the term "hysteria". Hippocrates and his colleagues made the first attempts to describe personality in terms of their humoral theories dividing the different types of personality into choleric, phlegmatic, sanguine and melancholic (Alexander and Selesnick 1966). He also described hypomanic personalities or hyperthymic temperaments. Erich Mendel reactivated Hippocrates' term "hypomania" in 1881. Hippocrates and his school, although strictly biologists, pointed out the relevance for disease (including mental disease) of biography and of the social and topographical environment, as well as the significance of a strong relationship between physician and patient (Marneros 1999).

Hippocrates assumed as a basic characteristic of melancholia the long-lasting anxiety for fear (phobos) and moodiness (dysthymia). He wrote "Ἢν φόβος καί δυσθυμίη πολύν χρόνον διατελέει, μελαγχολικόν τό τοιοῦτον"; "If anxiety (phobos) and moodiness (dysthymia) are present longer, that is melancholia".

Aretaeus of Cappadocia described the symptoms of melancholia as following:

"Τεκμήρια μέν οὖν οὐκ ἄσημα· ἢ γάρ ἥσυχοι, ἢ στυγνοί, κατηφέες, νωθροί ἔασι· ἔτι δέ καί ὀργηλοί προσγίγνονται ἀλόγως, οὐ τινί ἐπ' αἴτιη δύσθυμοι, ἄγρυπνοι, ἐκ τῶν ὕπνων ἐκθορυβούμενοι."

"The symptoms (of melancholia) are not unclear: (the melancholics) either are quiet or dysphoric, sad or apathetic; additionally they could be angry without reason and suddenly wakening with panic."

Aretaeus of Cappadocia described the symptoms of mania in chapter VI of his first book *On the Causes and Symptoms of Chronic Diseases* as follows:

Καί οἶσι μέν ἡδονή ἠ μανίη, γελῶσι, παίζουσι, ὀρχεύονται νυκτός καί ἡμέρης, καί ἐς ἀγορήν ἀμφαδόν καί ἐστεμμένοι κοτέ, ὅκως ἐξ ἀγωνίης νικηφόροι, ἐξίασι. ἄλυπος τοῖσι πέλας ἠίδέη. Μετεξέτεροι δέ ὑπό ὀργῆς ἐκμαίνονται ... ἰδέαι δέ μύριαι. Τοῖσι μέν γε εὐφύεσι τε καί εὐμαθέσι ἀστρονομίη ἀδίδακτος, φιλοσοφίη αὐτομάτη, ποίησις δῆθεν ἀπό μουσέων ... ."

"Some patients with mania are cheerful, they laugh, play, dance day and night, they stroll in the market, sometimes with a garland on the head, as if they had been winner in a game: these patients do not bring worries to their relatives. But others fly into a rage. ... The manifestations of mania are countless. Some manics, who are intelligent and well educated, are dealing with astronomy, although they never studied it, with philosophy, but autodidactically, they consider poetry as a gift of muses."

The similarity of the modern criteria is evident. Nevertheless mania is a very wide and voluminous term describing morbid and not morbid or even "divine" states, while melancholia describes morbid states or personality traits.

Although the etymology of the term "melancholia" is clear, the origin of "mania" is unclear, because of its roots in the mythological area. "Melancholia" ("melas" = black, and "cholé" = bile) was based on the humoral theories of Alcmaeon of Crotona and the pre-Hippocratic Greek physicians, who explained psychopathological states of severe sadness and other mental disorders with an interaction of body liquids, especially bile, and the brain. Later Hippocrates, as well as Aristotle, distinguished between the disease "melancholia" (nosos melancholiké) and the corresponding personality type (typos melancholicós). The etymology of "mania" is difficult in that the word has many meanings. It was used in mythology and poems (e.g. those of Homer) to describe different states. The Roman physician Caelius Aurelianus, a member of the Methodist School and student of Soranus of Ephesus, gave in his book *On Acute Diseases* (Chap. V) at least seven possible etymologies. He wrote:

"The school of Empedocles holds that one form of madness consists in a purification of the soul, and the other in an impairment of the reason resulting from a bodily disease or indisposition. It is this latter form that we shall now consider. The Greeks call it *mania* because it produces great mental anguish (Greek *ania*); or else because there is excessive relaxing of the soul or mind, the Greek word for 'relaxed' or 'loose' being *manos;* or because the disease defiles the patient, the Greek word 'to defile' being *lymaenein;* or because it makes the patient desirous of being alone and in solitude, the Greek word 'to be bereft' and 'to seek solitude' being *monusthae;* or because the disease holds the body tenaciously and is not easily shaken off, the Greek word for 'persistence' being *monia;* or because it makes the patient hard and enduring (Greek *hypomeneticos*)." (Caelius Aurelianus, translated by Drabkin 1950).

In the classical area four meanings of "mania" were described:

1. A reaction to an event in the meaning of rage or anger or excitation (like Homer in his Ilias who described "Aias maenomenos", this means "Ajax in rage").
2. A biologically defined disease (Hippocrates, Aretaeus of Cappadocia and others).
3. A divine state (Socrates, Plato).
4. A kind of temperament, especially in its mild form (Hippocrates).

Caelius Aurelianus wrote in his book on chronic diseases: "In the Phaedrus Plato declares that there are two kinds of mania, one involving a mental strain that arises from a bodily cause of origin, the other divine or inspired, with Apollo as the source of the inspiration. This latter kind, he says, is now called 'divination', but in early times was called 'madness'; that is, the Greeks now call it 'prophetic inspiration' (*mantice*), though in remote antiq-

uity it was called 'mania'. Plato goes on to say that another kind of divine mania is sent by Father Bacchus, that still another, called 'erotic inspiration', is sent by the god of love and that a fourth kind comes frome the Muses and is called 'protreptic inspiration' because it seems to inspire men to song. The Stoics also say that madness is of two kinds, but they hold that one kind consists in lack of wisdom, so that they consider every imprudent person mad; the other kind, they say, involves a loss of reason and a concomitant bodily affection." (Caelius Aurelianus, translated by Drabkin 1950). Another possible etymology of the word mania is a relation to the Indoeuropean "MAN" – meaning "think" (suggestion from Athanasios Koukopoulos).

The views of Empedocles regarding the meanings of the term "mania" have been cited above. But when Socrates, in Plato's Phaidros (Phaedrus) said: "The highest of all good things are given to us by the mania", he certainly meant the "divine mania", and also creativity in some states which today will be called "hypomania" or "hyperthymia" or "hyperthymic temperament" (as Jamison shows in her book *Touched with Fire,* 1994). But the Greeks also associated melancholia, especially melancholic personality, with genius and creativity. Aristotle asked in his book *Problemata physica:* "Why are extraordinary men in philosophy, politics or the arts melancholics?" Hippocrates himself discussed, after examining the famous "atomical" philosopher Democritus and after exciting discussions with him, the connection between melancholia and genius. He addressed to the citizens of Abdira the happy message that their fellow citizen Democritus suffered not from melancholia but he was simply a genius (see Temkin 1985).

Some authors have claimed that the concept of mania and melancholia as described by Hippocrates, Aretaeus and other ancient Greek physicians is different from the modern concepts (Ackerknecht 1959) but this is not correct. Rather, the classical concepts of melancholia and mania were broader than modern concepts [they included melancholia or mania, mixed states, schizoaffective disorders, some types of schizophrenia and some types of acute organic psychoses and "atypical" psychoses (Marneros 1999)].

Many classical Greek and Roman physicians, such as Asclepiades (who established Greek medicine in Rome), Aurelius Cornelius Celsus (who translated the most important Greek medical authors in Latin), Soranus of Ephesus and his scholar Caelius Aurelianus (who wrote down the views of his teacher, extensively on phrenitis, mania and melancholia), and later Galenus of Pergamos focussed their interest on mental disorders – especially melancholia and mania (Fischer-Homberger 1968, Alexander and Selesnick 1966). However, principally Aretaeus of Cappadocia described the connections between them.

ARETAEUS OF CAPPADOCIA: THE FIRST DESCRIBER OF BIPOLAR DISORDERS

Aretaeus of Cappadocia lived in Alexandria in the 1st century AD (his dates of birth and death are not known: some authors say he lived from around AD 30 to 90, others from AD 50 to 130). Aretaeus is the most prominent representative of the "Eclectics". The Eclectics were strongly influenced by Hippocrates and they were so called because they were not bound by any systems of therapy. Eclecticism meant choosing the best from many sources, a term which is also living today, especially in psychotherapy. Aretaeus was very careful in his description of diseases and he favoured observations of details. He was free of dogma and superstition. In his books *On the Aetiology and Symptomatology of Chronic Diseases* and *The Treatment of Chronic Diseases* he described very carefully the mental disorders. Chapter V in the former book addresses melancholia; chap. VI, mania. Mental disorders are, according to Aretaeus (in agreement with Hippocrates), biological in cause, but he differentiated between a biologically caused melancholia and a psychologically caused "reactive depression". He wrote in chap. V: "It has been reported about a man who had been assumed to suffer from an incurable melancholia, and the physicians were not able to help him. But the love of a young girl was able to cure him. In my opinion he was always in love with her but because he thought that she did not have any interest in him he became dysphoric and sad, so that he suffered from melancholia. But he did not express his feelings to the girl. When he did so, and the girl responded, his sadness, dysphoria and anger disappeared and he became happy. In this sense love was the physician."

Aretaeus was obviously the initiator of the idea of bipolar disorders (Marneros 1999) although some contemporary physicians plainly had similar views (Caelius Aurelianus, for example, was against the view that mania and melancholia belong together, but cited the contrary views of Apollonius).

Aretaeus perhaps was the first who definitively described mania and melancholia as two different images of one single disease. He wrote: *On the Aetiology and Symptomatology of Chronic Diseases* (Chap. V): "... *Δοκέει τέ δέ μοι μανίης γε ἔμμεναι ἀρχή καί μέρος ἡμελαγχολίη*"; "... I think that melancholia is the beginning and a part of mania", and: "... οἱ δέ μαίνονται, αὔξη τῆς νούσου μᾶλλον, ἢ ἀλλαγῆ πάθεος." "The development of a mania is really a worsening of the disease (melancholia) rather than a change into another disease." And some sentences later: "... *Ην δε ἐξ ἀθυμίης ἄλλοτε καί ἄλλοτε διάχυσις γένηται, ἡδονή προσγίγνεται ἐπί τοῖσι πλείστοισι· οἱ δέ μαίνονται*"; "... In most of them (melancholies) the sadness became better after various lengths of time and changed into happiness; the patients then developed a mania." The position of Aretaeus, as described in his two books, can be summarized as following (Marneros 1999):

(a) Melancholia and mania have the same aetiology, namely disturbances of the function of the brain and some other organs.
(b) Mania is a worsening of melancholia.
(c) Mania is the phenomenological counterpart of melancholia
(d) His concepts of melancholia and mania were broader than the modern concepts: depression, psychotic depression, schizoaffective disorders, mixed states, schizophrenia with affective symptomatology and some organic psychoses were involved.
(e) He differentiated between melancholia, which is a biologically caused disease, and reactive depression, a psychologically caused state.

It is therefore regretable why some authors (for example Ackerknecht 1959, and his fellows such as Fischer-Homberger 1968) do not identify Aretaeus as the first descriptor of "manic-depressive" illness.

FROM ARETAEUS TO JEAN-PIERRE FALRET

The change from mania to melancholia and vice-versa was also described by later authors, after the long mediaeval night. Wilhelm Griesinger – one of the most important founders of German scientific psychiatry – also described (1845) the change from melancholia to mania, which, in his opinion, is "usual". He believed that the disease is "a circle of both types with regular changes". Griesinger also described "seasonal affective disorders": melancholia usually has its beginning in autumn and winter, mania in spring. He also described rapid cycling and mixed types of affective disorders. Karl Kahlbaum, introducing Falret's term "folie circulaire" into German-speaking psychiatry (1863), wrote that the observations and opinions of Griesinger (1845) were decisive for the development of the concept of "folie circulaire" as well as for "folie á double forme". But long before Griesinger other European psychiatrists also described states of alteration between depression and mania or a mixture of them (as can be seen in Karl Kahlbaum's work). Especially Heinroth (who was the first German psychiatrist who had a university chair for "Mental Medicine") classified in his book (1818) in a special category concurrent and sequential alterations of manic and depressive symptoms (Marneros 2000b).

Haugsten (1995) mentioned in his history of bipolar disorders that in the 17th and 18th centuries Willis (1676), Morgagni (1761) and Lorry (1765) described the recurrent longitudinal association of mania and melancholia. As Stone (1977) observes, the development of scientific inquiry in the 18th century brought significant progress in the understanding of mental disorders: in England, Richard Mead (1673–1754) suspected that mania and melancholia were different aspects of the same process (like Aretaeus of Cappadocia). Vincenzo Chiarugi (1759–1820), in Tuscany, developed a taxonomy based on melancholia, mania and amentia (imbecility) and wrote:

"Mania signifies raving madness. The maniac is like a tiger or a lion, and in this respect mania may be considered as a state opposite to true melancholia" (Aretaeus had expressed himself similarly approximately 2000 years earlier). In the 19th century French psychiatry rose to preeminence as a consequence of its careful descriptive psychopathology (Pichot 1995). Pinel (1801) and Esquirol (1838) still adhered to the traditional concept that manic and melancholic episodes were separate syndromes of mental illness.

THE "BIRTH" OF THE MODERN CONCEPT OF BIPOLAR DISORDER

Nevertheless, neither the ancient physicians nor the psychiatrists of more modern times mentioned above drew the conclusion that bipolar disease is an entity of its own. This conclusion was drawn for the first time in France in the middle of the 19th century at the hospital La Salpêtriere in Paris by a pupil of Esquirol, Jean-Pierre Falret. In 1851 Falret published a 14-sentence-long statement in the *Gazette des Hôpitaux* ("De la folie circulaire ou forme de maladie mentale caracterisée par l'alternative réguliere de la manie et de la mélancholie"). In this statement Falret described for the first time a separate entity of mental disorder which he named "folie circulaire", characterized by a continuous cycle of depression, mania and free intervals of varying length. Jean-Pierre Falret completed his concept in the following 3 years, and published it in 1854 in the "Leçons cliniques de médecine mentale faites á l'hospice de la Salpetrière". Some weeks later he presented it in the Académie de la Médecine under the title "Mémoire sur la folie circulaire, form de maladie mentale caracterisée par la reproduction successive et régulière de l'état maniaque, de l'état mélancholique, et d'un intervalle lucide plus ou moin prolongé". He defined the sequential change from mania to melancholia and vice-versa and the interval in between as an independent disease of its own, namely the "folie circulaire" (Angst 1997a, Langer 1994, Marneros 1999, Pichot 1995).

Three years after Falret's first publication Jules Baillarger presented in 1854 his concept of "folie á double forme", both in protocols of a meeting of the Académie de la Médecine and in his paper "De la folie á double forme" (arguing very aggressively against Falret).

The conclusions drawn by the two very different, hostile "fathers" of the concept of bipolar disorders vary considerably: Baillarger assumed a type of disease in which mania and melancholia change into one another but the interval is of no meaning. In contrast, Falret involved the interval between the manic and the melancholic episode in his concept; even episodes of mania and melancholia separated by a long interval belong together, forming the "folie circulaire".

The real progress from the views of Aretaeus of Cappadocia, of Richard Mead, Vincenzo Chiarugi or Esquirol was Jean-Pierre Falret's concept of

"folie circulaire"; Jules Baillarger's concept of "folie á double form" was very similar to the views of his teacher Esquirol (Angst 1997a, Pichot 1995).

THE ACCEPTANCE OF THE CONCEPT OF "FOLIE CIRCULAIRE"

The concepts of "folie circulaire" and "folie á double forme" found widespread distribution in France, and very soon also in other European nations, especially in the German-speaking countries. In 1863 Karl Kahlbaum introduced both terms into German psychiatry in his important book: *The Grouping and Classification of Mental Disorders.* Kahlbaum supported Falret and opposed Baillarger. In the same book Kahlbaum pointed out that the observations and opinions of Wilhelm Griesinger (1845), as mentioned above, were of fundamental importance for Falret's concept. With his paper "Über cyclisches Irresein" ("On the Circular Insanity") (1882) and in "Katatonia" (1874) Kahlbaum contributed to its final establishment.

The concept of "folie circulaire" found not only enthusiastic supporters, but also critical opponents such as Ludwig Meyer (1874), who labelled it "meaningless". But in 1884 Kahlbaum presumed that the concept of "circuläres Irresein" ("circular insanity") had finally found general acceptance; this acceptance was demonstrated in other countries by publications in *Brain* (Foville 1882), and in the *American Journal of Insanity* (Hurd 1884) (see Angst 1997a, Langer 1994, Marneros 1999, Pichot 1995).

EMIL KRAEPELIN: UNIFICATION AND REGRESSION

The work of Emil Kraepelin is so fundamental that to label him "father of modern psychiatry" is absolutely justified. The dichotomy of "endogenous" psychoses into "dementia praecox" and "manic-depressive insanity" (1893, 1896) was of essential importance for the development of psychiatry, in spite of some weaknesses (of which Kraepelin himself was aware). In particular his contribution to the understanding, diagnosis and prognosis of manic-depressive illness was enormous. However, the elimination of the distinction between unipolar and bipolar forms, and the inclusion of all types of affective disorders in the unitary concept of manic-depressive illness, proved later to be a step back (Angst 1997a, Marneros 1999, 2000a). Not Kraepelin himself, however, was dogmatic, but his epigones (Angst 1999). Kraepelin himself had serious doubts. He expressed his unanswered questions and he was always seeking solutions, as he demonstrated in his last important work in 1920 ("Die Erscheinungsformen des Irreseins", "The phenomenological forms of insanity"). The unification of "circuläres Irresein" ("circular insanity") with unipolar types into "manisch-depressives Irresein" (manic-depressive insanity) was carried out in two fundamental publications in 1899: the first of them was "Die klinische Stellung

der Melancholie" ("The clinical position of melancholia", 1899a), published in the *Monatsschrift für Psychiatrie und Neurologie,* and the second was the sixth edition of his textbook (1899b). This unification was a new conclusion of Kraepelin, which is contradictory to his former opinions. In earlier editions of his textbook, in 1883 and 1887, Kraepelin described Falret's concept of "folie circulaire" as "a very well established type of mental disorder". The first roots of the unification and development of the concept of "manic-depressive insanity" originated at the beginning of the 1890s. In the edition of 1893 the concept is already clear and in 1899 complete: He wrote in "The clinical position of melancholia":

"Unfortunately our textbooks do not help us at all in distinguishing between circular depression and mania in cases where the course itself is not informative. The description of melancholic states is absolutely identical with that of circular depression and we can hardly doubt that the most beautiful and exciting descriptions of melancholia are mostly derived from observations of circular cases" (1899a, p. 328).

And some pages later:

"Apart from our experience that in a whole series of manic episodes a depressive one can occur unexpectedly, and those cases are immensely rare in which apart from manic irritability not the slightest feature of depression is visible, it is absolutely impossible to distinguish these manic fits of circular insanity from periodic mania. But if periodic mania is identical with circular insanity we cannot deny the possibility that also periodic melancholia, or at least some of the cases designated so, must in fact be understood as a kind of circular insanity in which all the episodes take on a depressive hue, just as in periodic mania they all have a manic tinge" (1899a, p. 333).

Kraepelin himself was not rigid or dogmatic concerning his taxonomies or concepts. The opposite is true; he was open to persuasion by data-orientated research, even by his own fellows, and he corrected his concepts. Doubts and remaining questions regarding his taxonomies and concepts were not taboo, but were discussed in his publications, such as his last very important publication of 1920 (already cited above). His epigones, however, lacking his elasticity, ignored the important contributions of Wernicke, Kleist, Leonhard and others. The consequence was stagnation for almost 70 years with regard to new developments in the field of bipolar disorders (Angst 1999, Marneros 1999).

THE OPPOSITION TO KRAEPELIN

In opposition to Kraepelin's view in Scandinavia "depressio mentis periodica" remained a separate affective disorder in the work of Lange (1896), Christiansen (1919) and Pedersen, Poort and Schou (1948). In 1926 Benon proposed separating periodic depression from manic-depressive disorder, but this met with little approval.

Kraepelin's unification of all affective disorders within the concept of manic-depressive illness also caused strong opposition in Germany, especially under the leadership of Carl Wernicke and later also his colleague in Halle, Karl Kleist. Wernicke differentiated very subtly the different kinds of affective syndromes. For example, he distinguished five different types of melancholia: affective melancholia, depressive melancholia, melancholia agitata, melancholia attonita and melancholia hypochondriaca (Wernicke 1900, 1906). He challenged Kraepelin's opinion that melancholia is only a part of the manic-depressive illness. In Wernicke's opinion manic-depressive illness should only be understood as described by Falret (folie circulaire) or by Baillarger (folie á double forme). Single episodes of mania or melancholia including recurrent depression or recurrent mania without changing into one another are something different from manic-depressive insanity (Wernicke 1900). The opinion of Wernicke was the basis for the work of his fellows, such as Kleist, Neele and Leonhard (Angst 1997a, 1999, Marneros 1999, Pillmann *et al.* 1999).

Karl Kleist (a colleague of Wernicke in Halle and later head of the university hospitals in Rostock and Frankfurt) opposed Kraepelin's concept of manic-depressive insanity. Kleist differentiated between unipolar ("einpolig") and bipolar ("zweipolig") affective disorders (Kleist 1911, 1926, 1928, 1953). The concepts of Wernicke and Kleist were completed by Karl Leonhard (a colleague of Kleist and later head of the Charité in Berlin), who classified the "phasic psychoses" into "pure phasic psychoses" (such as "pure melancholia", "pure mania", etc.) and "polymorphous phasic disorders" ("vielgestaltige phasische Psychosen"). To the last-mentioned category belong manic-depressive illness and the cycloid psychoses (Leonhard 1957, 1995). Neither Kleist nor Leonhard considered monopolar mania to be a component of bipolar disorders in present-day terms. On the contrary, they described monopolar mania separate from manic-depressive disorders (Leonhard 1957). This does not detract from the great significance of their role in stimulating research and paving the way for further development (Angst 1997a, Marneros 1999).

The classification of Wernicke, Kleist and Leonhard was nevertheless very complicated, with its multiple subgroups and distinctions, and did not find broad acceptance. Unfortunately, one of the most important aspects of their system, namely the unipolar/bipolar distinction, remained almost unrecognized by international psychiatry.

THE "REBIRTH" OF BIPOLAR DISORDER

The rebirth of bipolar disorders occurred in 1966 with two important publications. The first was the monograph of Jules Angst in Switzerland: *Zur Ätiologie und Nosologie Endogener Depressiver Psychosen* (*On the Aetiology and*

Nosology of Endogenous Depressive Psychoses). The second was published some months later in a supplement of *Acta Psychiatrica Scandinavica* by Carlo Perris (partly in cooperation with d'Elia) with the title: "A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses". Both publications supported, independently of one another, the nosological differentiation between unipolar and bipolar disorders. Thus, 67 years after Kraepelin's creation of "manic-depressive insanity" and some 150 years after Falret's and Baillarger's statements, the concept of bipolar disorders experienced a "rebirth" (Pichot 1995). Due to the work of Angst and Perris, as well as that of George Winokur, Paula Clayton and Theodore Reich (1969), who published similar findings in a monograph 3 years later in the USA (Winokur and Clayton 1967), not only have Falret's and Baillarger's concepts been replicated, completed and developed, but also essential aspects of the work of Carl Wernicke (1900, 1906), Karl Kleist (1928), Karl Leonhard (1934, 1937, 1957), Edda Neele (1949) and others. Therefore, the year 1966 can be seen as the "year of rebirth of bipolar disorders" (Marneros, Deister and Rohde 1991, Marneros 1999, Pichot 1995).

The study of Jules Angst was based on investigations on 326 patients, treated between 1959 and 1963 at the University Hospital of Zurich (Burghölzli). The four most important conclusions of this study were:

1. Genetic and peristatic factors have a synergic impact on the aetiology of endogenous depression.
2. Gender plays an important role in the aetiology of endogenous depression. There is a relationship between female gender and endogenous depression, but bipolar disorders are equally represented in males and females.
3. Manic-depressive illness is nosologically not homogeneous. Unipolar depression differs significantly from bipolar disorders in many characteristics such as genetics, gender, course and premorbid personality.
4. Late-onset depression (Kraepelin's "Involutionsmelancholie") seems to belong to unipolar depression and has only a weak relationship to bipolar disorders.

The study of Perris was carried out between 1963 and 1966 in Sidsjon Mental Hospital, Sundsfall, Sweden on 280 patients. Perris' findings were very similar to those of Angst (Angst and Perris 1968). They showed also that "unipolar mania" is genetically very strongly related to bipolar disorders, so that clinical and genetic factors support the assumption that the distinction of the group of unipolar mania is an artefact.

CYCLOTHYMIA

Cyclothymia also belongs to the group of bipolar disorders. "Cyclothymia" is an old and controversial term (Brieger and Marneros 1997a–c, Marneros

1999), first published by Ewald Hecker (1877) but coined by his teacher and brother-in-law Kahlbaum. He described with the term ("Cyklothymie") periodic changes of depression and "exaltation". Kahlbaum grouped cyclothymia together with dysthymia and hyperthymia as "partial mental disorder" ("partielle Seelenstörungen") with "non-degenerative outcome". By "cyclothymia" Kahlbaum meant the mildest type of bipolar disorder, a definition which was accepted also by Hecker (1898) and by Kraepelin (1899b), together with other authors at the beginning of the twentieth century. Jelliffe (1911) imported the opinions of Hecker, Kahlbaum, Falret and Kraepelin to the American psychiatric literature with his work "Cyclothymia – the mild forms of manic-depressive psychoses and the manic-depressive constitution". Ernst Kretschmer and Kurt Schneider contributed to a dichotomy of the term "Cyclothymia". Kretschmer, in his fundamental work "Physique and character" *(Körperbau und Charakter)* (1921–1950), described the "cyclothymic average man" and the cycloid temperaments. Cyclothymia is, in his opinion, "a broad constitutional overterm involving health and disease in the same way". In contrast, Kurt Schneider (1950–1992) accepted this term only for diseases, and he used it synonymously with manic-depressive illness. His influence is still existant in Germany, so that two meanings of cyclothymia persist: manic-depressive illness increasingly rare and cyclothymia according to ICD-10 and DSM-IV increasingly common. The boundaries of cyclothymia as a disorder of the bipolar spectrum or as a disorder of temperament or personality are yet not clear (Akiskal 1983a, Akiskal and Akiskal 1992, Akiskal *et al.* 1985, 1995). Also not absolutely clear is the clinical utility of this term (Marneros 1999).

HYPOMANIA

Hypomania was described, conceptualized and named by Erich Mendel in 1881 in his book *Die Manie* (oriented on Hippocrates, the first to use the term "hypomaenomenoi", i.e. "hypomanics") to characterize a type of hyperthymic personality.

Mendel wrote: "I recommend (taking under consideration the word used by Hippocrates 'ὑπομαινόμενοἰ'), the types of mania, having a lower intensity of its phenomenological picture, to name them hypomania" (Mendel 1881, p. 109).

C. G. Jung, in an early publication (1903), recorded in detail a number of cases of manic mood changes (*manische Verstimmung*), patients characterized by a stable submanic complex of symptoms, which had mostly developed in youth and lasted many years without remission. Jung found that exacerbations could occur in the course of the disorder and saw the social restlessness and social problems, alcoholism, delinquency, and what he

termed "moral insanity" characterizing these patients as submanic symptoms. The symptoms described by Jung would correspond to today's hyperthymia or very mild mania. Hypomania won more relevance in recent decades due to the descriptions of bipolar-II disorders (Dunner, Fleiss and Fieve 1976), recurrent brief hypomania (Angst 1997b) and its relations to hyperthymic temperatment (Akiskal and Akiskal 1992).

EXPANDING THE GROUP OF BIPOLAR DISORDERS

After experience in pharmacotherapy and prophylaxis of unipolar and bipolar disorders intensive research on this topic began. One of the many important consequences was the "expansion" of the group of bipolar and unipolar disorders, as well as the knowledge that they are inhomogeneous (Marneros 1999). The most important expansions concern the following points:

1. The distinction of schizoaffective disorders into unipolar and bipolar as well as mixed types.
2. The renaissance of Kraepelin's mixed states.
3. The renaissance of Kahlbaum's and Hecker's concept of cyclothymia and other bipolar spectrum disorders.

Schizoaffective disorders

Karl Kahlbaum can be considered the first psychiatrist in modern times to describe schizoaffective disorders as a separate group in "vesania typica circularis" (Kahlbaum 1863), although previously states described as melancholia or mania by previous authors, for instance by Hippocrates or Areteaus, were very often schizoaffective according to modern nomenclature (Griesinger 1845, Heinroth 1818). For this definition Kahlbaum applied cross-sectional and longitudinal observation. Emil Kraepelin was also acquainted with cases between "dementia praecox" and "manic-depressive insanity" (Kraepelin 1893, 1896, 1920). These "cases-in-between" were a problem for him, a nuisance; but on the other hand an interesting conundrum to be solved. As is well known, Kraepelin dichotomized the so-called endogenous psychoses into two groups, namely "dementia praecox" (with a poor outcome) and the "manic-depressive insanity" (with a favourable outcome). But he already knew that not all cases of endogenous mental disorders can readily be classified into the two categories. Some cases of mixed states, delirious mania and other mental disorders described by Kraepelin (1893, 1920) could be allocated to either category or to neither of them. In a critical appraisal of his own taxonomy, Kraepelin wrote in his important paper of 1920 ("Die Erscheinungsformen des Irreseins") ("The phenomenological forms of insanity"), that mental disorders can have ele-

ments of both groups of mental disorders, namely "dementia praecox" and "manic-depressive insanity" and they can also have a different course and a different prognosis than "dementia praecox". He knew that the boundaries between the two groups of mental disorders are elastic and that there are bridges connecting them. His doubts became stronger in the wake of an investigation by his pupil and collegue Zendig. Zendig reported in his paper "Contributions to differential diagnosis of manic-depressive insanity and dementia praecox" (1909) that approximately 30% of Kraepen's sample diagnosed with "dementia praecox" (using Kraepelin's guidelines) had a course and outcome not corresponding to that of "dementia praecox"; Zendig attributed the good outcome to an incorrect diagnosis. Later Kraepelin saw in such cases a weakness of his dichotomy concept. He wrote: "The cases which are not classifiable (namely to manic-depressive insanity or dementia praecox) are unfortunately very frequent" (Kraepelin 1920, p. 26). Two pages later he made a decisive and for him certainly not easy statement: "We have to live with the fact that the criteria applied by us are not sufficient to differentiate reliably in all cases between schizophrenia and manic-depressive insanity. And there are also many overlaps in this area" (i.e. between schizophrenia and affective disorders) (Kraepelin 1920, p. 28).

As early as 1966, Jules Angst investigated the schizoaffective disorders (under the term "Mischpsychosen" – "mixed psychoses") as a part of the affective disorders. This was an outlier's position, not only against the "Zeitgeist", but also contrary to the opinion of his teacher Manfred Bleuler, who assumed them to be a part of schizophrenia. Later investigations by Angst and his group (1979, 1990), by Clayton, Rodin and Winokur (1968), by other members of the Winokur group (Fowler *et al.* 1972), by Cadoret *et al.* (1974) and the comparative studies of Marneros and co-workers (1986a–c, 1988a–c, 1989a,b,d–f, 1991) supported more and more the opinion that the relationship between schizoaffective and affective disorders is stronger than that between schizoaffective and schizophrenic disorders.

Studies in the last three decades (Angst 1989, Marneros 1999, Marneros *et al.* 1989a,b,d–f, 1990a–d, 1991, Marneros and Tsuang 1990) have yielded evidence that:

1. Schizoaffective disorders should be separated into unipolar and bipolar, like affective disorders.
2. Bipolar schizoaffective disorders have a stronger relationship to bipolar affective disorders than either group has to unipolar schizoaffective disorders.

Marneros and co-workers proposed that bipolar schizoaffective disorders belong together with bipolar affective disorders, and unipolar schizoaffective disorders together with unipolar affective disorders, in two voluminous groups (Marneros *et al.* 1990a–d, 1991, Marneros 1999).

MIXED STATES

In recent years there has been renewed interest in so-called mixed states or mixed bipolar disorders, especially in the USA (i.e. Akiskal 1992, 1997, 1999, McElroy *et al.* 1995), but also in Italy (e.g. the Pisa group), in Germany (Marneros und co-workers 1991, 1996a,b, 2000) and in other European countries (see also Marneros 2000b). Although the creator of the concept is doubtless Emil Kraepelin, albeit with the strong assistance of his co-worker Wilhelm Weygandt (1899) (see Marneros 1999), such disorders were observed and described much earlier. The first descriptions of mental disorders which could be characterized as "mixed states" are rooted in the work of the Greek physicians of classical times, especially Hippocrates (460–337 BC) and Aretaeus of Cappadocia (1st century AD).

The broader concepts of melancholia and mania (including what we today call "schizoaffective", some types of schizophrenic and transient psychoses or other psychotic disorders, as well as "mixed states") continued up to the end of the 19th century (Leibbrand and Wettley 1961, Fischer-Homberger 1968, Schmidt-Degenhardt 1983). Nevertheless, the clinical descriptions illustrate the broad concepts and allow us to identify "mixed states" involved in them (Marneros 2000b).

As Koukopoulos and Koukopoulos (1999) have pointed out, the nosologists of the 18th century, such as Boissier de Sauvages and William Cullen, classified among the melancholias such forms as melancholia moria, melancholia saltans, melancholia errabunda, melancholia silvestris, melancholia furens, and melancholia enthusiastica which are practically "mixed". Also Lorry (1765) described the "mania-melancholica".

Heinroth (1773–1843), the first Professor of "Mental Medicine" at a German university (Leipzig) classified mental disorders in his textbook *Disorders of Mental Life or Mental Disorders* (1818) into three voluminous categories (see Table 1). The first category comprised the "exaltations" ("hyperthymias"). The second category embraced the "depressions" ("asthenias"), and the third category the "mixed states of exaltation and weakness" ("hypo-asthenias") (Heinroth used the German word "Mischung", which can be translated as "mixture"). This last category of "mixed states" was divided into

(a) "mixed mood disorders" ("animi morbi complicati");
(b) "mixed mental disorders" ("morbi mentis mixti");
(c) "mixed volition disorders" ("morbi voluntatis mixti").

It is evident that mainly in the categories "mixed mood disorders", and "mixed volition disorders" mixed affective and schizoaffective disorders according to modern definitions are involved. In addition to the above-mentioned mixed states, Heinroth described the pure forms of exaltation ("hyperthymias") including "melancholia erotica" and "melancholia meta-

Table 1 Mixture of exaltation and depression (according to Heinroth 1818) (from Marneros 2000b)

"Mixture of exaltation and depression (weakness)" *(Hyper-Asthenias)*
First group
Mixed mood disorders
(animi morbi complicati)
1. Ecstasis melancholica
2. Melancholia moria
3. Melancholica furens
4. Melancholia mixta catholica
Second group
Mixed mental disorders
(morbi mentis mixti)
1. Paranoia anoa
2. Paranoia anomala
3. Paranoia anom. maniaca
4. Paranoia anom. catholica
Third group
Mixed volition disorders
(morbi voluntatis mixti, athymia)
1. Panphobia, melancholia hypochondriaca
2. Athymia melancholica
3. Athymia paranoica
4. Athymia melancholico – maniaca

morphosis". "Melancholia saltans", however, is defined by Heinroth as a form of mania.

The French psychiatrist Joseph Guislain described in his book *Treatise on Phrenopathias or New System of Mental Disorders* (1838) a category of mixed states named "Joints of Diseases". He allocated in this category "the grumpy depression", "the grumpy exaltation" and "the depression with exaltation and foolishness" (to the last one belongs also "depression with anxiety"). The first type especially has long episodes and unfavourable prognosis (Guislain 1838).

Wilhelm Griesinger – one of the most important founders of German scientific psychiatry – described in his book *Pathology and Treatment of Mental Illnesses* (1845, 1861) mixed states of melancholia and excitation, as well as rapid cycling forms and seasonal affective disorders. Griesinger divided mental diseases into only three voluminous categories: "mental depression states" ("psychische Depressionszustände"), "mental exaltation states" ("psychische Exaltationszustände"), and "mental weakness states" ("psychische Schwächezustände").

Melancholia belongs to the first category, mania to the second. Griesinger also described the so-called "mid-forms" ("Mittelformen") "in which a change from depression in the manic exaltation occurs" (Griesinger 1845, p. 207). He allocated "melancholia with destructive drives" and "melancholia with longlasting exaltation of volition" to the "mid-forms" (the latter type is, according to Griesinger, the most typical "mid-form"). His view that the "mid-forms" are dependent on character traits, and that in their mild form they are indistinguishable from personality deviations, is interesting (pp. 207–208). (Griesinger's view is reminiscent of that of Hagop Akiskal, developed 150 years later – see the section entitled "Renaissance", below.) Additionally, Griesinger assumed a relation between depression and mania in a way very similar to Aretaeus of Cappadocia. He also described manic states that arise from melancholic ones. During the development of melancholia into mania a conglomerate of "manic and depressive symptoms can be observed" (Griesinger 1845, pp. 212–214).

From a practical point of view it can be said that almost all pre-Kraepelian authors described mixed states, as can be seen in tables from the most prominent old diagnostic classifications (presented by Karl Kahlbaum in his book of 1863) (Marneros 2000b).

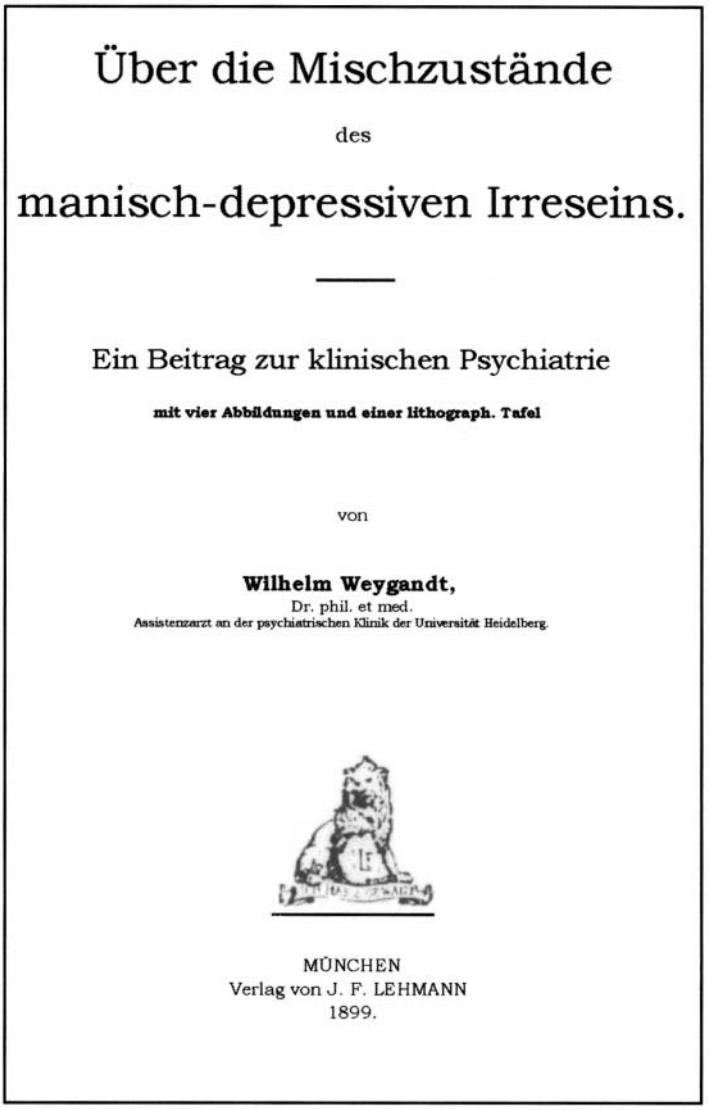
In 1852, Pohl, in Prague, in a large monograph on melancholia, described mixed states occurring during the transition from melancholia to mania (pp. 121, 127), "poriomanic" melancholia (p. 186) and marked anxiety states as transitional phenomena of depression (pp. 111–121). He also described rapid cycling between melancholia and brief mania (p. 111), later described as a more regular alternation of cyclicity by Focke (1862), as lasting 3–4 weeks by Jules Falret (1879, pp. 58, 66) or just a few (6) days by Kelp (1862).

Emil Kraepelin distilled, conceptualized and categorized previous knowledge regarding mixed states as well as other mental disorders. Kraepelin used the term "Mischzustände" ("mixed states") or "Mischformen" ("mixed forms") for the first time in the 5th edition of his textbook (1896, p. 634) although in 1893 he described the "manic stupor" (one year after Kraepelin's description of manic stupor Dehio referred to it during the 1894 meeting of "South-western German Alienists"). He practically completed their theoretical conceptualization in the 6th edition (1899, pp. 394–399), although their final categorization and nomination came with the 8th edition in 1913 (see Table 2).

Wilhelm Weygandt (pupil and colleague of Kraepelin in Heidelberg) published, in the same year as Kraepelin's 6th edition (1899), the first book in the psychiatric literature on mixed states: *Über die Mischzustände des manisch-depressiven Irreseins* (*On the Mixed States of Manic-Depressive Insanity*). However, Weygandt referred to the 6th edition of Kraepelin's textbook as a source, so it can be assumed that Kraepelin's textbook was published earlier in the year or that Weygandt knew his teacher's manuscript. In 1893 Kraepelin did not use the term "mixed states" *expressis verbis,* but the

Table 2 The development of Kraepelin's concept of "mixed states" (from Marneros 2000b)

1893	*1899*	*1904*	*1913*
1. *"Manic stupor"* ("manischer Stupor")	1. *"Manic state with inhibition"* ("manische Zustände mit Hemmung) 2. *"Depressive states with excitation"* ("depressive Zustände mit Erregung")	1. *"Furious mania"* ("zornige Manie") 2. *"Depressive excitation"* ("depressive Erregung") 3. *"Unproductive mania with thought poverty"* ("unproduktive gedankenarme Manie") 4. *"Manic stupor"* ("manischer Stupor") 5. *"Depression and flight of ideas"* ("Depression mit Ideenflucht") 6. *"Manic inhibition"* ("manische Hemmung")	1. *"Depressive or anxious mania"* ("depressive oder ängstliche Manie") 2. *"Excited depression"* ("erregte Depression") 3. *"Mania with thought poverty"* ("ideenarme Manie") 4. *"Manic stupor"* ("manischer Stupor") 5. *"Depression with flight of ideas"* ("ideenflüchtige Depression") 6. *"Inhibited mania"* ("gehemmte Manie")



Über die Mischzustände

des

manisch-depressiven Irreseins.

Ein Beitrag zur klinischen Psychiatrie

mit vier Abbildungen und einer lithograph. Tafel

von

Wilhelm Weygandt,

Dr. phil. et med.

Assistenzarzt an der psychiatrischen Klinik der Universität Heidelberg.

MÜNCHEN

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1899.

Figure 1 The first book in the psychiatric literature on mixed states (Weygandt 1899).

formulation "the cases are mixed" (pp. 366–367). But even before the first use of the term "mixed states" in 1896, Kraepelin described "manic stupor" (1893, pp. 366–367) later characterized by him as the most convincing type of mixed state (1899b, p. 396). In the final description of the mixed states

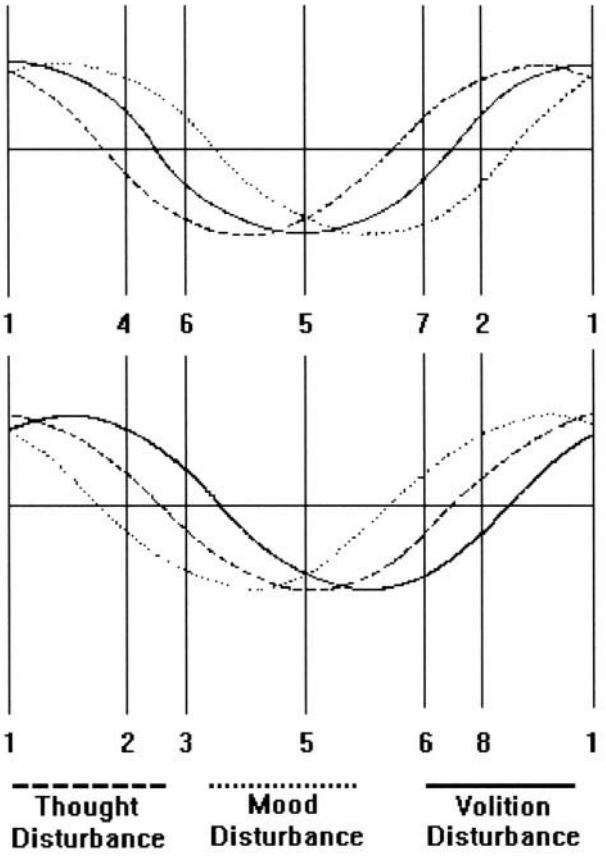

Figure 2 The development of mixed states (according to Kraepelin 1913).

(8th edition of the handbook in 1913, pp. 1284–1303) Kraepelin defined six types of mixed states.

Although Kraepelin is undoubtedly the creator of the concept in the sense of clarification of previous reviews and their systematization, the work of Wilhelm Weygandt makes it difficult to distinguish the respective roles of the two men with regard to the development of the final concept. It is, however, beyond any doubt that the clarification of former views, the systematic descriptions, and the theory are the work of Kraepelin. Mixed states belonged to the core of Kraepelin's "manic-depressive insanity" (Angst and Marneros, 2000, Koukopoulos and Koukopoulos 1999, Marneros 1999). However, it can be assumed that their final clinical description, their categorization and the systematic gathering of data on the topic is the common work of both men.

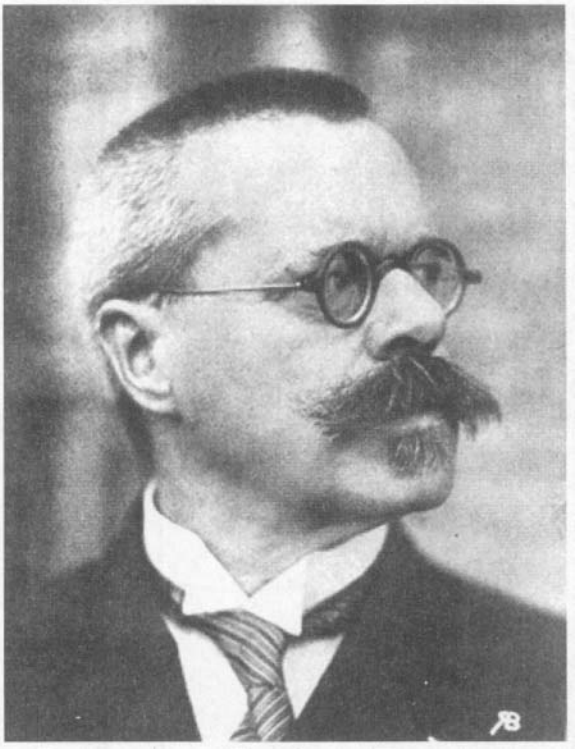

Figure 3 Wilhelm Weygandt: the author of the first monograph on mixed states (1899).

In his slim, 63-page monograph *Über die Mischzustände des manisch-depressiven Irreseins,* Weygandt (1899) gives a very plastic description of mixed states in a style very similar to that of Kraepelin. But a year before the publication of his monograph Weygandt had presented his findings during the 29th meeting of "South-western German Alienists", held in Heidelberg on 27 November 1898. (His contribution was cited pedantically, including the exact time of the session, "1.15 p.m. to 3.45 p.m.") In his presentation (published a year later, 1899) he spoke about many possible types of mixed states, of which three ("manic stupor", "agitated depression", and "unproductive mania") were in his opinion the most important (Weygandt 1899).

Weygandt wrote in his book:

"It is very common, both in the manic and in the depressive episodes of manic-depressive or circular insanity, for there to be not only periods of time which are mostly without symptoms, but also, often, hours or days when the symptoms switch to the opposite pole. So during a manic episode the *euphoria* can suddenly change into a *deeply depressive* mood, while the other symptoms of exaltation, such as hyperkinesia and hyperactivity, distractability and excitability, logorrhea, and flight

of ideas persist; or after a monthlong *depression* suddenly a smile can be observed on the face of the patient and the depressive mood can change for hours or days into a high or manic mood, but without any change in psychomotor behaviour, in the inhibition or, sometimes, in the severe stupor. Less common, but actually frequent enough if observation is careful, is a temporary change in psychomotor behaviour while the affective aspects of the psychosis continue without any change; the patients remain euphoric, but the manic *excitability* changes into a *psychomotor inhibition.* Instead of tireless hyperactivity the patients stay in bed, show slowness of movements and less or no mutism. In patients with the phenomenological picture of depression with stupor, one can sometimes observe a change to mild excitability, agitation and urge to speak lasting for hours or days, while the depressive mood continues. …

We have additionally to consider one or more opposite pairs of symptoms, because only in this way can we touch all the relevant points in their totality. Similar to the euphoric mood and the psychomotor excitability for mania are also morbid changes in the domain of thinking, the *flight of ideas.* …

In depressive episodes, instead of flight of ideas, one sees *thought inhibition.*

These states, very well known but because of their short duration usually less noted, are a mix of manic and depressive episodes of circular insanity" (Weygandt 1899, pp. 1–2).

Weygandt concluded:

"The co-existence of the main symptoms of both typical episodes of manic-depressive insanity, mostly only of short duration, is extraordinarily frequent; in some cases the mixed states can occupy the entire episode or at least the greater part of its duration; usually the later episodes have the tendency to change to long-lasting mixed states; the course is in many aspects somewhat more chronic than that of the pure manic or depressive episodes, but in other ways the prognosis regarding the recovery of the episode is exactly the same" (Weygandt 1899, p. 63).

Weygandt explained the manifestation of mixed states as follows:

"It is relevant to consider that the two symptom lines, i.e. euphoric mood, psychomotor excitability and flight of ideas on the one hand and depressive mood, psychomotor inhibition and thought inhibition on the other hand, are not stable. But the disorders are characterized by lability in the domain of mood, psychomobility and thought, and this is a characteristic of the whole circular or manic-depressive insanity" (Weygandt 1899, p. 5).

The mixture of the three opposite pairs of symptoms mentioned above could give arise to six possible types of mixed states (but occasionally, and only for a short period, perhaps more than six). "We are forced by reasons of practical psychiatry, because we are opposed to speculation, to distinguish and describe only three groups of mixed states as the most relevant; they are the most frequent and have the longest duration … *manic stupor … agitated depression …* and *unproductive mania"* (Weygandt 1899, p. 20). He used the remaining two-thirds of his book to describe only these three types of mixed states, not the other three possible types, which he mentioned but

did not name (pp. 20–36). Five years later Kraepelin gave extensive descriptions of all six types of mixed states (Table 2).

According to Koukopoulos and Koukopoulos (1999), Weygandt introduced the term "agitated depression" ("agitirte Depression") for the first time in his book, although in fact the syndrome had been described by Frank Richarz ("melancholia agitans") more than 40 years earlier (1858). Weygandt himself quoted Richarz's paper, almost 40 pages long, in his book (pp. 41, 42). [The paper of Koukopoulos and Koukopoulos contains a very interesting discussion on the origin and the allocation of agitated depression. The authors argue that agitated depression is in fact a form of a mixed state, as Kraepelin and Weygandt assumed. Perhaps the term "hyperthymic depression" introduced by Akiskal and Pinto (see Chapter 2), can be associated more strongly with mixed states as the term "agitated depression".]

According to Kraepelin, the first three types of mixed states, i.e. "depressive or anxious mania", "excited or agitated depression" and "mania with thought poverty" are based on the three fundamental symptoms of mania, namely flight of ideas, euphoria and hyperactivity (see Figure 2).

A depressive or anxious mania can arise if two of the three basic symptoms of mania, namely flight of ideas and hyperactivity, are present, but euphoria is replaced by depressive mood. If additionally the symptom "flight of ideas" changes to "inhibition of thought", only the hyperactivity remains as manic symptom and so "excited" or "agitated depression" can arise. Mania with thought poverty occurs if poverty of thought is associated with the manic symptom "euphoria" and perhaps also "hyperactivity".

The basis of the next three types of mixed states is – according to Kraepelin – the fundamental symptomatology of depression, namely "inhibition of thought", "depressive mood" and "weakness of volition": "Manic stupor" (which is for Weygandt the most important type of mixed state and for Kraepelin the most convincing) arises when depressive mood is replaced by "euphoria", but depressive thoughts and abulia persist. "Depression with flight of ideas" comes into being when the poverty of thoughts is replaced by flight of ideas, while the two other basic symptoms of depression (depressive mood and abulia) continue. If, in addition to flight of ideas, depressive mood changes to euphoria, "inhibited mania" arises. Kraepelin separated "inhibited mania" from "manic stupor" because flight of ideas is absent in manic stupor but present in "inhibited mania".

Kraepelin distinguished two groups of mixed states:

(a) "Transitional forms": a stage in between, when depression changes to mania and vice-versa.
(b) "Autonomic forms": a disorder on its own.

Between these two groups are relevant differences. The autonomic group is "the most unfavourable form of manic-depressive insanity". The course

is longer, with a tendency to chronicity, and the individual episodes are longer than in other types of manic-depressive insanity (Kraepelin 1899b, 1904, 1913, Weygandt 1899) a finding confirmed 100 years later. Also confirmed (for example by Akiskal and Puzantian 1979, Akiskal 1992, 1997b, Goodwin and Jamison 1990, McElroy *et al.* 1995, 1997, Swann *et al.* 1995, 1997, Himmelhoch 1992, Himmelhoch *et al.* 1976a,b, Marneros 1999, Marneros *et al.* 1996a,b, 1991, Winokur, Clayton and Reich 1969) are the two following findings of Kraepelin and Weygandt:

1. Females are more frequently represented in a group of mixed states.
2. Using broad definitions, more than two thirds of patients with manic-depressive illness have a mixed state (usually a "transitional form") at least once; even using narrow definitions approx. 20% of them experience mixed states (Marneros 2000b).

An interesting enrichment – really the first new conceptual aspect since 1899 – was contributed by Akiskal, based on Kraepelin's "mixed concept" (Akiskal 1981, 1992, 1997b, Akiskal and Mallya 1987, see also Marneros 2000b). Kraepelin suggested a mixing of manic or depressive symptoms with cyclothymic, hyperthymic or depressive temperament. The mixing of symptoms and temperament created, in Akiskal's opinion, three different types of mixed states:

Type I: depressive temperament + psychosis
Type II: cyclothymic temperament + depression
Type III: hyperthymic temperament + depression

In the past two decades a *"mixed type of schizoaffective disorders"* has also been described, which is a combination of mixed bipolar affective disorders and schizophrenic symptoms (Marneros *et al.* 1986a–c, 1988a,d, 1991, 1996a,b). The mixed type of schizoaffective disorder is analogous to the mixed type of affective disorders (Marneros 1999).

BIPOLAR SPECTRUM

The concept of a spectrum of manic conditions developed by Kretschmer (1921–1950) and Eugen Bleuler (1922) has undergone various modern attempts at elaboration into subtypes (Angst 1997a, Marneros 1999). Klerman (1981) distinguished six subtypes of bipolar disorders: mania, hypomania, hypomania or mania precipitated by drugs, cyclothymic personality, depression with a family history of bipolar disorder and mania without depression. Angst (1978) based his approach on a continuum distinguishing between hypomania (m), cyclothymia (md), mania (M), mania with mild depression (Md), mania and major depression (MD), and major depression and hypomania (Dm). More recently, brief hypomania, lying

under the threshold of DSM-IV hypomania, with a duration of as little as 1–3 days, has been described, and there is also some evidence for a valid subcategory of recurrent brief hypomania (Angst 1990, 1997a–c, Angst *et al.* 1990, Angst and Merikangas 1997).

Over the past 20 years Akiskal has provided evidence, based on good clinical observation and sound knowledge of the classical literature, for the desirability of enlarging the continuum to encompass several diagnostic subgroups, including what he terms the "soft" bipolar spectrum (Akiskal 1983a,b, Akiskal and Mallya 1987, Akiskal *et al.* 1977, 1979). A new concept includes bipolar III (pseudo-unipolar disorders, defined as recurrent depressions without spontaneous hypomania but often with hyperthymic temperament and/or bipolar family history) (Akiskal 1996). This bipolar III category also includes recurrent depression, switching to hypomania under antidepressant treatment. The problem with "drug-induced hypomania", however, is that hypomanic symptoms have not been the object of systematic assessment in clinical trials of antidepressants, and there is no proof emerging from placebo-controlled studies.

There is good evidence supporting Kraepelin's assumption that subjects with hyperthymic temperaments belong to the bipolar spectrum. In addition, certain subtypes of personality disorders ("histrionic-sociopathic" or "borderline-narcissistic") may belong to cyclothymic temperaments (Akiskal *et al.* 1977). The borderline concept propounded by Kernberg (1967, 1975) has given further impetus to research into bipolar disorder. A subgroup of borderline syndromes was shown to be closer to the manic-depressive than to the schizophrenic spectrum by a careful family study (Stone 1977, 1986). The affiliation to manic-depressive disorder would also explain the excellent prognosis of such special cases. But there are also difficulties in identifying this subtype of borderline personality disorders as indicated by Gunderson (1998) and Gunderson, Zanarini and Kisiel (1996). The authors pointed out that boundaries between borderline disorders and recurrent and labile mood disorders (Akiskal *et al.* 1985) needed further clarification. The modern concept of bipolar spectrum would embrace all these conditions and include the hyperthymic and cyclothymic temperaments. Marneros (1999) suggested a continuum between normal fluctuations of an "adjustable homeostasis" of affectivity to highly psychotic disorders according to the Figure in the chapter "On entities and continuities of bipolar disorders".

FUTURE WORK

Research into the subgroups of bipolar disorders is undoubtedly still in its infancy. Most studies have so far been restricted to mania and have reported, for instance, low lifetime prevalence of bipolar disorder (0.2–1.6%) (Picinelli

and Gomez Homen 1997). The inclusion of hypomania, brief hypomania and cyclothymic disorders raises the rates to 3–7% (Angst 1995a,b, 1998) and underlines the significance of the "bipolar spectrum" concept. Further studies are needed in order to distinguish clearly between hyperthymic and cyclothymic temperaments on the one hand and recurrent brief hypomania or recurrent brief cyclothymia on the other. The same is true for the subgroups M, Md, MD, DM, md, m (Angst 1978), a classification that moves beyond the dichotomy between bipolar I and bipolar II disorders. In 1976 Dunner and co-workers distinguished bipolar II from bipolar I disease. The essential feature of bipolar I disorder is a clinical course characterized by the occurrence of one or more manic episodes or mixed episodes (Dunner, Fleiss and Fieve 1976, APA 1994). The essential feature of bipolar II disorders is a clinical course characterized by the occurrence of one or more major depressive episodes, accompanied by at least one hypomanic episode. It is probable, in fact, that there is no clear delineation among all the subtypes, which may be artificially constructed on a natural continuum from transient to persistent hypomanic and manic manifestations of varied length, frequency and severity. It is this spectrum concept that currently attracts the most interest.

However, the group of schizoaffective disorders have to be investigated from the point of view of bipolarity, as well as of the sequential changes of the type of episodes. There is good evidence that, on a longitudinal axis, cases with change between schizophrenic and affective episodes also belong to the schizoaffective spectrum (Marneros *et al.* 1986a–c, 1991, Marneros 1999).

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Chapter two

The soft bipolar spectrum: footnotes to Kraepelin on the interface of hypomania, temperament and depression

Hagop S. Akiskal and Olavo Pinto

In association with states of depression … [hypo]manic symptoms can be demonstrated with extreme frequency, as temporary exalted mood, laughing, singing, dancing, feeling of happiness in the time of recovery″ (Kraepelin 1899/1921)

Impressive advances have been made in the field of unipolar and bipolar disorders (recently reviewed in Akiskal 1999b, Marneros 1999). Although the distinction between these two affective forms has made an important contribution to the methodology of clinical and biological investigations, there is still a substantial proportion of apparently ″unipolar″ patients whose depressions show bipolar affinity. We learn about these patients when we examine pedigrees of bipolar patients and discover that many first-degree relatives have suffered from recurrent depressions (Gershon *et al.* 1982, Akiskal *et al.* 1985, Tsuang *et al.* 1985). Some, though not all, of these patients have hypomanic episodes. Thus, the category of bipolar II (Dunner *et al.* 1976), which subsumes recurrent depressions with clear-cut hypomania (and now officially sanctioned in both ICD-10 [1992] and DSM-IV [1994]), does not fully cover this large territory. The first author has proposed the concept of ″soft bipolar spectrum″ (Akiskal and Mallya 1987) as a more inclusive term.

Although Kraepelin (1899) devoted several passages to protracted hypomanic episodes, as well as to short-lived elation and/or merriment during

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 37–62.

Table 1 The soft bipolar spectrum between the extremes of full-blown manic-depressive and strict unipolar disorders

Bipolar I:	Full-blown manic depressive illness (with at least one episode of mania or mixed mania)
Bipolar II:	Recurrent depression with spontaneous hypomania and/or cyclothymic temperament.
Bipolar III:	Recurrent depression without spontaneous hypomania – arising from a hyperthymic temperamental background and/or bipolar family history. Hypomania occurring solely during antidepressant or other somatic treatment should also be classified here.
Strict Unipolar Depression:	Absence of mania, hypomania, cyclothymic and hyperthymic temperaments, as well as bipolar family history.

Summary from Akiskal (1983, 1996).

recovery from depressive episodes (as described in the opening quote above), he did not see the necessity of separating depressive states with hypomania from full-blown manic-depressive illness. He suggested instead that subtle features of excitement, temperamental inclinations towards mania, follow-up course, and/or family history for manic-depression would sooner or later clarify the manic-depressive nature of recurrent depressive states. As a result, this large terrain of depressive conditions lying between the extreme poles of contemporary unipolarity and bipolarity, continues to occupy a nosologic limbo. Although bipolarity in the absence of full-blown mania is the most common expression of bipolar disorder, the scientific literature continues to emphasize full-blown bipolar disorder and, to the best of our knowledge, only one monograph entirely devoted to bipolarity other than classic mania has been published (Akiskal 1999b).

Because mixed bipolar states are covered elsewhere in this volume, in this chapter we focus largely on contemporary research efforts to chart the realm of cyclical depressive states in the absence of full-blown mania. Variously termed "pseudo-unipolar depression" (Mendels 1976), "bipolar II" (Dunner *et al.* 1976), "Dm" (Angst *et al.* 1980), and "cyclothymic depressions" (Akiskal 1994), this realm of soft bipolarity covers a broadening constellation of depressions in association with hypomania and/or labile, driven, flamboyant temperaments. Table 1 presents, in schematic form, the overlapping territories of the foregoing constructs broadly situated between mania and strict unipolarity deriving from earlier work conducted largely in the University of Tennessee Mood Clinic (Akiskal 1983, 1996, Akiskal and Akiskal 1988). In this schema, bipolar II included not only depressions in association with hypomanic episodes, but also those arising from a cyclothymic temperament. Under bipolar III we had lumped depressions without spontaneous hypomanic episodes, but deemed to belong to the soft bipolar

realm by virtue of lifelong hyperthymic traits and/or bipolar family history; hypomanic episodes documented solely during antidepressant pharmacotherapy were also categorized as bipolar III. This chapter will further expand on the concept of bipolar spectrum, to delineate clinically meaningful subtypes in the interface of full-blown bipolar (manic-depressive) and strict unipolar disorders. In doing so we will present new evidence for an expanded, revised bipolar schema (Akiskal and Pinto 1999), which goes beyond the crowded tripartite bipolar typology presented in Table 1. We use case material derived from earlier work (Akiskal and Pinto 1999) to illustrate the evolving bipolar spectrum through prototypes. As our concept of the bipolar spectrum has evolved over two decades, this chapter heavily draws on concepts and material from previous work (Akiskal *et al.* 1979, Akiskal 1983, Akiskal and Mallya 1987, Akiskal and Akiskal 1988, Akiskal 1996, Akiskal and Pinto 1999).

LITERATURE REVIEW

Kraepelin (1899) envisaged a continuum between manic and depressive states. His grand vision, developed at the turn of the nineteenth century, was based on clinical observation, longitudinal course, and family history. Many patients who began with depression ended up with mania and vice-versa; other depressives went as far as hypomania, but not beyond; there were also patients who had a cyclical course without discernible excited episodes, but who were temperamentally like manic-depressive patients. Most importantly, in a considerable number of patients, mania and depression were often intermixed in the same episode. Finally, patients with recurrent depression often came from families with manic-depressive illness and/or alcoholism. Kraepelin concluded that all of these were manifestations of a single morbid process which expressed in a variety of clinical forms, and which were linked by common temperamental and familial-genetic factors. In brief, his grand scheme included not only what today we consider bipolar I, bipolar II, and cyclothymic disorder, but also much of the large terrain of recurrent major depressions.

Kraepelin's "unitary" position dominated psychiatry until the 1960s. Since then, the bipolar-unipolar dichotomy has gradually replaced it: first in the research literature (Leonhard 1959, Angst 1966/1973, Perris 1966, Winokur *et al.* 1969), and eventually in formal classification systems such as the DSM-IV and the ICD-10. In the authors' opinion this latter classification has been largely at the expense of bipolar disorders. Today, based on influential US (Regier *et al.* 1988) and cross-national (Weissman *et al.* 1996) epidemiological studies using relatively narrow definitions of bipolarity, it is widely believed that major depression and dysthymia constitute 80%, or more, of all mood disorders. But the pendulum seems to be swinging back

to the Kraepelinian schema. Taylor and Abrams (1980) were among the first to argue for the need to return to such a schema. The concept of bipolar spectrum (Akiskal 1983), originally representing a minority position, is gaining momentum. Goodwin and Jamison (1990) have largely endorsed the spectrum schema in their modern classic monograph devoted to manic-depressive illness. Ongoing international research during the decade of the 1990s is beginning to provide robust support for broadening the boundaries of bipolar disorders. This concept would enlarge the territory of bipolar subtypes, up to 50% of all mood disorders (Akiskal and Akiskal 1988, Cassano *et al.* 1992, Manning *et al.* 1997, Benazzi 1997, Perugi *et al.* 1998, Hantouche *et al.* 1998). This enlargement is largely due to new developments in the realm of "soft bipolar disorder", which covers bipolar II and related disorders with even milder expressions of hypomania than the 4-day threshold in DSM-IV (Akiskal and Mallya 1987). Furthermore, an authority such as Jules Angst, whose 1966 monograph was decisive in favouring the bipolar-unipolar distinction, has published new epidemiological data which indicates that at least 5% of the general population has bipolar spectrum disorders (Angst 1998). He and others (Lewinsohn *et al.* 1995, Szádóczky *et al.* 1998) have thus challenged the conventional figure of 1% for bipolar rates in the general population. Earlier studies in college students (Depue *et al.* 1981, Eckblad and Chapman 1986) too, had revealed rates of 4-6% for cyclothymia and hypomania. In brief, studies both in clinical and community settings have shown the high prevalence of bipolar spectrum conditions.

One of the problems in clinically validating the concept of a broad bipolar spectrum is that less than manic affective conditions are not easy to define operationally. The original distinction between bipolar I and bipolar II, a seminal contribution by Fieve and Dunner (1975), was based on hospitalization for mania. The excited phase is so disruptive – and often psychotic – that the need for hospitalization is undeniable in bipolar I cases (before the era of managed care!). Other patients, who may need hospitalization for depression, experience brief, though sometimes extended, periods of hypomania which do not compromise their functioning, and for which they obviously would not seek psychiatric help; these patients, who are now formally categorized as bipolar II, present with clinical depression, and the documentation for hypomania is obtained primarily by history. Because bipolar II patients often pursue a variable and stormy course (Dunner *et al.* 1976, Akiskal 1981), the diagnosis of bipolar II might prove unreliable (Rice *et al.* 1986): it is left to the vagaries of the patient's history and the skill of the interviewer. Dunner and Tay (1993) have recently demonstrated that clinicians specifically trained in making the diagnosis of hypomania by history, outperform structured interviewing. Furthermore, follow-up of patients over time will provide the opportunity to validate the diagnosis of hypomania by direct observation. Observation beyond the time frame of

acute depressive episodes will also give clinicians the chance to re-interview the patient about hypomanic symptoms; it is particularly crucial to obtain collateral information from significant others as well. Hypomania can occur spontaneously or during pharmacotherapy (Akiskal *et al.* 1979, Hantouche *et al.* 1998).

The dramatic behavioural sequence of events in the switch process from depression to hypomania and vice-versa – whether spontaneously or in association with antidepressant somatotherapies – has been well documented since the classical studies by Bunney *et al.* (1972). Although observed by many other talented researchers and clinicians worldwide, hypomania associated with antidepressant use solely (and other somatic therapies) is denied official bipolar status in DSM-IV and ICD-10. This has been a tragic fault of our formal diagnostic system, because the evidence is compelling about their bipolar status (Akiskal *et al.* 1979, 1983, Strober and Carlson 1982, Wehr and Goodwin 1987, Menchon *et al.* 1993, Altshuler *et al.* 1995) within the soft spectrum, yet the failure to classify them as bipolar robs them of proper mood stabilization. As described later in this chapter, these patients should be recognized as having a less penetrant variant of bipolar II, which can be provisionally categorized under bipolar III disorder (Akiskal *et al.* 2000). The same consideration, in our view, should apply to patients who first exhibit hypomania upon abrupt discontinuation of a mood stabilizer. There also exist clinically depressed individuals who do not give history for hypomanic episodes, but are extroverted, cheerful, optimistic, confident, energetic and driven during much of their lives (trait hypomania or hyperthymic temperament); we contend that, based on family history of bipolarity (Cassano *et al.* 1992), these individuals too should be classified as part of the bipolar spectrum, perhaps as bipolar type IV. Originally (Akiskal 1983 – see Table 1), we had lumped both conditions (depressions with antidepressant-associated hypomania and those arising from a hyperthymic temperament) under bipolar III; but the differences between the two are sufficiently compelling to deserve separate coding. Our revised new schema (Akiskal and Pinto 1999) appears in Table 2.

In this chapter we go beyond the external validation of the bipolar spectrum (Akiskal 1983, 1996). To aid in clinical distinctions, in true Kraepelinian spirit, we present clinical vignettes that can serve as prototypes of bipolar spectrum disorders – with special focus on soft bipolarity. We strongly believe that proposals for classification should not come solely from nosological positions which rely primarily on operational rigor. We need to go beyond nosologic exercises of a theoretical or statistical nature, to embrace a diagnostic schema supported by clinical experience, as well as external validators. We feel that we can presently make a strong case for bipolar types I, II, III, and IV. But we remind the reader that Kraepelin, after charting 18 patterns of affective phases in his very large manic-depressive sample, found that there were so many other patterns that the task of

Table 2 The evolving spectrum of bipolar disorders

Bipolar ½:	schizobipolar disorder
Bipolar I:	manic-depressive illness
Bipolar I½:	depression with protracted hypomania
Bipolar II:	depression with spontaneous discrete hypomanic episodes
Bipolar II½:	depression superimposed on cyclothymic temperament
Bipolar III:	depression plus hypomania occurring solely in association with antidepressant or other somatic treatment
Bipolar III½:	marked mood swings in the context of substance and/or alcohol (ab)use
Bipolar IV:	depression superimposed on a hyperthymic temperament

Updated from Akiskal and Pinto (1999).

delineating specific course patterns within the manic-depressive realm could not be achieved. For this reason we have decided to provide intermediary cases that we consider ½, I½, II½, and III½. The very existence of these intermediary conditions reflects the clinical realities within the bipolar spectrum. Obviously a great deal of research needs to be done in further validating the new bipolar schema we have proposed. What distinguishes the present effort from previous proposals for multiple bipolar subtypes (Klerman 1982, Endicott 1989) is the extensive clinical and familial validation we provide for the individual subtypes within a spectrum model (Akiskal and Pinto 1999).

Nonetheless, there is the distinct possibility of genetic heterogeneity within the bipolar spectrum. One of the most provocative developments in this field is the comorbidity between soft bipolarity, atypical depressions, and anxiety disorders (Perugi *et al.* 1998, 1999). Research at Johns Hopkins has demonstrated not only that bipolar II is the most common phenotype of bipolar disorder (Simpson *et al.* 1993), but that the comorbidity between panic and bipolar II disorders increases heritability estimates (MacKinnon *et al.* 1998). This is in line with Kraepelin's vision – i.e. genetic strategies that would ultimately validate his concept of manic-depressive disease and its variants. He further hoped that temperamental dispositions, which characterized the interepisodic and premorbid phase of depressive illness, would one day be proven to be fundamental in understanding the origin of the illness. In our view the classification of mood disorders in future diagnostic systems (DSM-V and ICD-11) should return to a position closer to that of Kraepelin – i.e. course, temperament, and familiality should play a more decisive role in diagnostic subtyping of mood disorders. The schema offered below (Akiskal and Pinto 1999) is written with the aim of reclassifying a large chunk of the terrain of recurrent major depression within the bipolar realm. We offer them as footnotes to Kraepelin's grand scheme.

BIPOLAR ½: SCHIZOMANIC OR SCHIZOBIPOLAR DISORDER

Some, though not all, authorities would classify schizoaffective disorder as an extreme form of bipolar disorder (Gershon *et al.* 1982, Marneros and Tsuang 1990). In the schizobipolar variety, manic excitement occurs in association with prominent mood-incongruent features beyond what is considered "permissible" in bipolar I disorder; this diagnosis is particularly likely to be given when the occurrence of such features persists during the inter-episodic phase, when mania has abated. As this chapter is devoted to pseudo-unipolar and soft bipolar conditions, it is beyond the scope of the chapter to go into greater depth regarding this subtype. Although schizoaffective patients whose excitement does not go beyond hypomania do exist, we are not aware of any systematic studies of this phenomenon. For all these reasons we are bypassing this severe end of the bipolar spectrum in the present chapter.

BIPOLAR I: FULL-BLOWN MANIA

Manic-depressive illness often has an explosive manic onset with psychosis; that is actually what "mania" means in Greek. Other patients exhibit a mixture of depression and mania (dubbed "dysphoric mania" in the literature). Cyclical alteration of manic and depressive states – and their mixed coexistence – is one of the most distinctive clinical conditions in the entire field of medicine. This extremity of full-blown bipolar disorder will serve as the defining edge for describing the various levels of soft bipolarity in a comparative fashion.

In many bipolar patients, depressive episodes often precede any frank signs of bipolarity. Because in this chapter our emphasis is on the depressive aspects of the bipolar spectrum, the case that we provide below - with a very long latency between the first depression and the first clear-cut manic episode – illustrates the never-ending risk for bipolar conversion in recurrent depression (Akiskal *et al.* 1983).

In chronological order, the psychiatric history of this 48-year-old divorced white male started at the age of 18 with an overdose of an over-the-counter sleeping pill, 6 months into his freshman year in college. He had profound insomnia, did not enjoy life and found it without purpose, and felt he was wasting his parents' money in college. This episode subsided within a few months, and he received no treatment for it. He had several similar episodes without suicidal behaviour, and then in his junior year he again sank into a profound depression during which he nearly hung himself in the bathroom; the rope broke loose, he was "discovered", and he had to speak to a school counsellor twice; he failed to follow up with the strong recommendation to seek psychiatric help, and instead started heavy alcohol drinking "because of the insomnia". He had no difficulty obtaining a Bachelor's and eventually a Master's degree in mathematics with honours. He married subsequently, and was

divorced within 6 months due to his repeated infidelity; the "ensuing depression" was treated with full doses of doxepine and later imipramine without benefit, and eventually resolved without further treatment over a period of 1 year. He continued to drink which, again, did not seriously interfere with his career as a freelance statistical consultant for a period of 10 years. He said most of his life he had been a pessimist, like his "manic-depressive father" – an alcoholic who had committed suicide – and claimed alcohol gave him a sense of competence without which he could not function. During an insurance company checkup his liver enzymes were found elevated and he was instructed to stop drinking, with which he complied promptly; this led to a suicidal depression for which he was prescribed sertraline, up to 150 mg/day, again with no clear-cut benefits over a 4-month period, at which point he took back to the bottle. He continued to function with daily drinking over the next few years.

His first manic episode occurred at the age of 37, following a romantic disappointment that led to total insomnia, and soon transformed into rushing thoughts, non-stop activity, euphoria, and grandiosity to the point of believing that he was a "descendant of Don Juan"; for many succeeding weeks he frequented many bars, drinking and paying the bill for everyone and visiting prostitutes – until he went bankrupt. He was hospitalized "exhausted from madness" and placed on lithium; within a year he had quit alcohol because on lithium "I did not experience insomnia, nor pessimism". He had continued successful prophylaxis on this salt until he was 46. At that age, during a routine chest x-ray, a pulmonary mass was discovered which he was told could be malignant. He delayed submitting himself to definitive diagnostic tests over a period of 2 months, during which he became extremely worried and stopped the lithium: he had severe insomnia, morning accentuation of depression, crying on a daily basis with extreme mood lability (but no euphoria), and suicidal ideation associated with the conviction that he had been a "bad son – a total failure – which drove my father to despair and ultimately to his suicide". This led to his second hospitalization. He was extremely anxious, dejected and agitated, and expressed the view that people should "spit" on him for his lifetime habit of "using pornographic aids during masturbation"; he also experienced racing thoughts and told the nurses that he was "solving mathematical puzzles". He failed to respond to clonazepam, 8 mg/day, but responded to thioridazine, 150 mg/day within a week. Only then was he amenable to receive full work-up for his pulmonary mass, which turned out to be benign. Lithium was re-instituted and thioridazine gradually withdrawn over a period of 4 weeks. He continued to do well on lithium during the subsequent 18 months of follow-up.

It is noteworthy that this patient had six depressive episodes over a 19-year period before he had his first clear-cut mania. In reconstructing his psychiatric history, three factors suggested the pre-bipolar nature of these depressions (Akiskal *et al.* 1983). First, the family history for manic-depressive illness; the fact that the patient's depressions had shown no appreciable response to antidepressants and, more provocatively, history obtained from the patient about his "hypersexual nature" which persisted even *during* depressive episodes; this trait was attenuated under lithium treatment. It is also noteworthy that during his second hospitalization, for an agitated depressive episode, the patient displayed manic features, though far below the DSM-IV criteria needed to diagnose a mixed state; he obviously needed a neuroleptic rather than an antidepressant to recover from that episode! It is also remarkable

that this patient had two long periods free of major psychiatric episodes: 10 years under alcohol (with a severe protracted depressive relapse with its discontinuation), and 10 years with lithium (with a hospitalized mixed state upon its discontinuation). This patient is also testimony to the clinical observation – that some might consider heresy – that alcohol use in moderation can serve as a mood stabilizer in selected patients. Actually, recent research (Winokur *et al.* 1998) has shown that alcoholism in the setting of bipolar disorder does not represent a comorbid disorder, but more of a "complication" of bipolarity in the form of self-treatment and/or enhancement of moods. Finally, we would like to note that lithium – known to prevent suicide in mood clinics (Schou 1998) – represents the preferred prophylaxis in such cases where there is both personal and family history of suicidal behaviour.

BIPOLAR I½: DEPRESSION AND PROTRACTED HYPOMANIA

Where hypomania ends and mania begins is not clearly demarcated. Certainly, individuals with hypomania do not experience significant impairment, whereas mania is unmistakably disabling. There exist patients between these extremes, with protracted hypomanic periods, which cause trouble to the patient and significant others, without reaching the destructive potential which is almost always the case with the extreme excitement of full-blown manic psychosis. What Kraepelin (1899) said about hypomania is instructive in this regard:

"The slightest forms of manic excitement are usually called 'hypomania,' mania mitis ... 'folie raisonnante'... indeed psychic activity, attention are not infrequently even increased; the patients may appear livelier, more capable than formerly ... increased busyness is the most striking feature ... a stranger to fatigue ... [they] enter into numerous engagements ... daring undertakings ... at the same time the real capacity for work invariably suffers."

The vignette that follows illustrates why we have opted to classify some patients – who might otherwise meet the DSM-IV criteria for bipolar II – in between bipolar I and bipolar II.

This 45-year-old never-married male presented to our care because of history of "treatment-resistant depression". He stated that he had always been somewhat shy, yet had "passionate sexual desire". The mixture of these two meant that he was unable to approach the women that he coveted. Since his late teens he had been irritable – even cantankerous – and at least once had lost a high-paying job because of his "attitude" towards his boss. This led to a severe suicidal depression at the age of 38, which responded minimally to different tricyclic antidepressants. He was prescribed lithium because of a family history of frank bipolar disorder in his father who had committed suicide. He recovered from the depressive episode, but he eventually stopped the lithium due to weight gain and became his usual "miserable" self. He found a new job, where he did not have much contact with any bosses, and was able to maintain it for 5 years: "Misery and working go together", he commented. He fell in love with a co-worker, and secretly stalked her, finally having the courage to confess his love, only to be rebuffed by her. He was unable to sleep

Table 3 Signs and symptoms of a hypomanic episode*

Three or more of the following, which must represent departure from patient's habitual baseline:
Cheerfulness and jocularity
Gregariousness and people-seeking
Heightened sexual drive and behaviour
Talkativeness and eloquence
Overconfidence and overoptimism
Disinhibition and carefree attitudes
Little need for sleep
Eutonia and vitality
Overinvolvement in new projects

*Expanded from Akiskal *et al.* (1977, 1979).

that night, and by the morning he was convinced that he could have any woman he wanted; he was full of energy, would pick up one woman on the street and take her to a bar, only to approach another woman; he was viewed as "funny and the women were amused". This lasted for a period of 5 *months non-stop*. Despite spending nights at bars he was able to work, but felt extremely frustrated that he had only slept with one woman during that entire period. Subsequently he "crashed" into a depressive period which was treated with SSRI that made him "impotent"; bupropion failed to reverse his sexual dysfunction. This depression gradually improved, but was replaced with extreme social phobia of speaking to women, and had panic attacks on the streets, with extensive avoidance (but for going to work). In retrospect, he said "perhaps I was protecting myself from women who had ruined my life". We discontinued the bupropion and treated him with 1200 mg of gabapentin. The patient's GAF score of 55 changed to 75 within 4 weeks, and has been maintained at this level through 9 months of follow-up. He is gainfully employed again.

The protracted hypomanic episode is the only such period we could document in this patient. It was not associated with marked impairment at work, though the non-stop restless busyness he exhibited in bars distracted him from one woman to another, without achieving his sexual or romantic aims, leaving him extremely frustrated and unhappy in the midst of his hypomania!

BIPOLAR II: DEPRESSION WITH HYPOMANIA

These patients by definition have moderately to severely impairing major depressions, interspersed with hypomanic periods of at least 4 days duration without marked impairment (Table 3): although behaviour is coloured by the elated mood, confidence and optimism, judgement is relatively preserved compared to mania. Nonetheless, the cyclic course of the disease may involve periods of significant dysfunction, even serious suicidal attempts (Dunner *et al.* 1976, Akiskal 1981, Ayuso-Gutierrez and Ramos-

Brieva 1982, Vieta *et al.* 1997, Rihmer and Pestality 1999). By the same token the cyclic mood changes permit normal to super-normal periods of functioning (Akiskal *et al.* 1979, Jamison *et al.* 1980, Akiskal and Akiskal 1988, Goodwin and Jamison 1990). A not-inconsiderable number of these patients are able to rebound from their difficult periods, to attain new conjugal or occupational status. These individuals are often regarded as "sunny bipolar IIs" (Jonathan Himmelhoch, personal communication, 1996) – but the spectre of impulsive risk-taking in professional and personal domains is always present.

This 38-year-old woman presented with the complaint that "when it comes to marriage, I'm a failure". She presented to her first interview wearing a flamboyant red hat. She had sought help upon the insistence of a friend who gave her an internet article on bipolar II. The patient then realized "she was a textbook case". Since her mid-teens she had experienced hypersomnic-retarded depressions lasting initially for a few weeks at a time and more recently for as long as 4 months; she estimated that she had had approximately one such episode per year, though she had skipped two years in a row twice. There was no conspicuous seasonal pattern to these depressions, nor did they have a distinct relationship to her menses. She had been hospitalized on two occasions; the first time her family had been concerned about her not getting out of bed for days in a row, and the second time because of a severe postpartum episode during which she had been alternating between extreme fatigue and agitation and had verbalized thoughts of suicide. She was a successful writer, who wrote fiction, and had acquired considerable fame and wealth. Several times per year she experienced periods of decreased need for sleep, increased libido, intense joy, overconfidence, increased plans and activities both at work and in her personal life. These hypomanic periods – which could last from a few days up to a week – sometimes occurred at the tail end of a depression, but at other times happened independently, after a night of sleep loss, typically "because of intense work". She had had a "rich romantic life", leading to three marriages and two divorces. She said that men found her "too intense, too passionate", which has "wrecked my personal life". She had been faithful to her first two husbands, but the separation from her third husband was precipitated by a brief affair she had – with another woman – during a hypomanic episode. She now felt extremely guilty and confused (because this was "experimentation, an incidental, impulsive act which did not reflect my dominant heterosexual identity"). She also felt extremely heartbroken because she still loved her last husband; furthermore, in child custody she had lost her 6-year-old daughter to her husband. The patient had never been treated before. After considerable discussion she was placed on 1200 mg of lithium carbonate (blood level = 0.7 mEq/L) and individual psychotherapy; this was followed by conjugal therapy and in 6 months the family was reunited. The patient complained of "loss of intensity", and after normal thyroid testing her regimen was changed to 600 mg of lithium (blood level = 0.4 mEq/L) and 600 mg of divalproex. She has been followed on this regimen essentially euthymic with no adverse effects. However, she harbours the fear that she "may mess up things again".

This patient's history illustrates the common clinical situation whereby hypomania can be both an asset and a liability. It is not possible to draw rigid categorical

Table 4 Distinguishing mania from hypomania*

One or more of the following indicate that the threshold of mania has been crossed:
Meaningful conversation is difficult to maintain for any length of time
Euphoric or ecstatic mood which deteriorates into querulous belligerence when thwarted
Frank delusions in any of the following domains: of grandiose ability or identity, of assistance, persecution, reference, or love
Loss of insight and judgement to such a degree that frenzied expansive activity leads to serious social impairment

Based on Akiskal *et al.* (1977, 1979).

operational lines between bipolar II where hypomania is largely adaptive, and mania where it could be destructive. The separation, of course, is possible in the extreme (Table 4). In brief, even "sunny" bipolar IIs often have a "dark" side to their illness.

BIPOLAR II½: CYCLOTHYMIC DEPRESSION

According to the DSM-IV schema, bipolar II patients must have clinical depression with hypomania of 4 days duration or longer. Current research indicates that the more modal distribution for hypomania is 1–3 days (Akiskal *et al.* 1979, Wicki and Angst 1991). This means that a great many soft bipolar patients will not meet the strict DSM-IV criteria for bipolar II. This is unfortunate because patients with short hypomania often have a recurrent pattern of periods of excitement, which are followed by mini-depressions, thereby fulfilling the criteria for cyclothymic disorder. When a major depressive episode is superimposed on this baseline, the diagnosis of bipolar disorder may be entirely missed because the instability in the life of a cyclothymic may be of such a degree that these patients might meet criteria for Axis II cluster B personality disorders at the trait level. In brief, in North America they are likely to be labelled as "borderline" rather than as affectively ill (Akiskal 1981, Akiskal *et al.* 1985). This is changing though, because experienced clinicians in North America are refusing to take DSM-IV *ex-cathedra* (Levitt *et al.* 1990, Deltito *et al.* in press).

This 24-year old, unmarried female presented with history of "moodiness" since her menarche. The patient said one day she would be "high like a kite" and the next day she would stay in bed. Her moods changed every few days, sometimes daily, but she was able to finish high school and worked as a receptionist in various jobs. At age 18 she started having more protracted "depressive" episodes twice a year, in the autumn and in the spring, lasting for 3–4 weeks. Upon closer scrutiny she indicated that the one in the autumn was characterized by sleeping too much and overeating, and the one in the spring by "a peculiar mixture of physical slowing, irritability, mental restlessness and hypersexuality". She had received numerous

antidepressants for both types of "depression", to no avail. The response to these was generally disappointing, indeed she insisted that her "PMS" got worse. She was prescribed fluoxetine 20 mg/day, after 3 weeks she felt suddenly energized – her mind "running 200 miles a minute" – she could literally "climb the mountain" where she lived, was overconfident, and slept with several men daily, the entire episode lasting 2 weeks. The patient had lived in six cities in three states since she was 18; she would simply take off unsatisfied with the place or the people. Over the past year she was hospitalized once for bulimic behaviour, and another time for hurting herself with cigarette butts and hair curlers. She had tried "crystal meth" a few times, but did not like it. Family history was significant in that the mother, considered "a flamboyant bitch", had been divorced four times, and had many lovers well into her 70s; a maternal aunt, diagnosed manic-depressive, died in a mental institution. Her biological father drank alcohol excessively. Mental status examination revealed a young woman who complained that she was plump, with a distinctive flair in her attire – she actually looked like a Hollywood star. She used rich and dramatic expressions in describing her life and moods. Although her facial expression displayed bright affect, she said if lightning struck her dead, she would thank God. She spoke about her "utter failure to do anything right in life, despite being endowed with reasonably good, native intelligence". She added, "I guess, I have no idea who I am or what I shall do in life". She said her sister was like her, "only worse, because she uses all kinds of substances, especially uppers". The patient concluded the interview by saying that she was a "borderline person" because she had been "orally abused" by several of her mother's lovers post-pubertally; that she was "grateful for therapy that had helped her come to this realization", of which she had had only vague prior memory.

Some, perhaps many, would say that this patient at the trait level would meet the criteria for *"borderline* personality" – which was indeed the diagnosis in her past records – yet she suffers discrete mood episodes with a special seasonal pattern; spontaneous hypomanic episodes were of short duration, never making the DSM-IV threshold of 4 days. Although the hypomania after fluoxetine would be disqualified as hypomania in DSM-IV, phenomenonolically it has the distinct qualities of a hypomanic episode. Her spring "depressions" are better described as depressive mixed states, though again they are below the DSM-IV threshold. The family history points to a strong bipolar diathesis. Clinically, therefore, it would make a great deal of sense to consider this patient as continuously shifting between cyclothymia and major depression. This formulation has significant therapeutic advantages, because it would dictate the use of mood stabilizers almost to the exclusion of antidepressants. Failure to appreciate bipolarity had robbed her of therapeutic opportunities that would have given her a more rewarding life.

We initially treated this patient with valproate, which led to hair loss. She subsequently made a dramatic recovery on lamotrigine monotherapy (slowly increased over 2 months to a dosage of 200 mg/day). At last follow-up a year later she no longer spoke of having been abused, but said "I am so like my mother that I must have imagined that her lovers did to her what I had fantasized as unacceptable sex." This 1 year on lamotrigine monotherapy is the only period in her postpubertal life free of mood instability. She also found stable gainful employment as an actress for the first time in her life.

Table 5 Trait mood lability in self-report predictive of prospective hypomania in major depressive patients

Mood often changes, happiness to sadness, with and without my knowing why
Have frequent ups and downs in mood, with and without apparent cause
Often feel guilty without a very good reason for it
Feelings are rather easily hurt
There are times when my future looks very dark
Ideas run through my head so that I cannot sleep
I keep in fairly uniform spirits (negative predictor)
Often find it difficult to go to sleep because of thinking what happened during the day
Often feel disgruntled

*Summarized from Akiskal *et al.* (1995).

Table 6 Self-rated items loading heavily on the cyclothymic temperament in affectively ill outpatients

.601	I constantly switch between being lively and sluggish
.578	My mood often changes for no reason
.564	My ability to think varies greatly from sharp to dull for no apparent reason
.538	My mood and energy are either high or low, rarely in between
.532	The way I see things is sometimes vivid, but at other times lifeless
.514	I often feel tired for no reason
.506	I get sudden shifts in mood and energy
.504	I often start things and lose interest before finishing them
.484	I often have a strong urge to do outrageous things
.445	I feel all emotions intensely

Akiskal *et al.* (2000).

Mood lability, which is a trait characteristic in such patients, need not manifest in DSM-IV hypomanic periods. In a prospective NIMH study we have shown that mood lability (Table 5), represents the most powerful predictor of which major depressive patients would develop frank hypomania (Akiskal *et al.* 1995). It is noteworthy that, except for the first two traits, lability is in a depressive direction. This is a prevalent form of cyclothymia in both clinical and non-patient populations (Akiskal *et al.* 1977,1979, Depue *et al.* 1981). We have more recently tested self-rated traits (Table 6) defining the most discriminatory items for the cyclothymic disposition (Akiskal *et al.* 2000), which gives greater weight to cyclic hypomanic tendencies below the threshold of clinical hypomania.

BIPOLAR III: ANTIDEPRESSANT-ASSOCIATED HYPOMANIA

Many patients with spontaneous hypomanic and manic episodes also often develop these episodes during antidepressant treatment; this is often mediated by cyclothymic temperamental tendencies (Akiskal *et al.* 1979), of which hypomania is a natural expectation. This process appears quite different from clinically depressed patients who experience hypomania solely during antidepressant treatment. Our clinical observations suggest that many of the latter patients have a depressive temperament or, to use DSM-IV language, have early-onset dysthymia as the baseline disorder (Akiskal *et al.* 1980). It may appear counter-intuitive that such patients should develop hypomania, but this has also been observed by others (Klein *et al.* 1988, Rihmer 1990, Kovacs *et al.* 1994). What distinguishes these patients from the more garden-type variety of dysthymics is the fact that their family history is often bipolar (Rosenthal *et al.* 1981). These patients can be considered phenotypic variants within the bipolar spectrum, representing less penetrant forms of a putative bipolar genotype.

This 47-year-old married woman gave a history of having been gloomy for as long as she remembered. She was pessimistic and derived little pleasure from life. Her sleep was often long, yet unrefreshing. Members of her family and colleagues would exhort her "to smile at life, so that life would smile at you". She said her stereotypical response would be breaking into tears; she was simply unable to smile. Despite these temperamental traits, the patient was a successful school teacher, well liked by students and parents. The patient said she had little energy, but devoted most of it to her students and their welfare. Despite a successful career of 25 years in the teaching domain, she felt "grossly inadequate". Her sense of inadequacy was reinforced by her husband of about the same duration: He often "abused her emotionally", by which she meant he called her "stupid" and complained of her "sexless nature". When their only daughter left home at age 22, the patient made a suicide attempt with aspirin in a deepening depression with hopelessness, guilty ruminations, poor concentration, and *racing thoughts.* She was treated (initially on an inpatient psychiatric unit), with a succession of full doses of at least one antidepressant from all existing classes of antidepressants; her response was negative except for a transient 4-day sense of unusual well-being and euphoria on tranylcypramine, 40 mg/day. Despite various upward manipulations of the dosage of tranylcypramine, she relapsed back into her morose episode, for which, over a 4-year period, she received numerous antidepressants and combinations thereof as one antidepressant after another hit the US market. None worked, and our team was asked to reevaluate her at this juncture. We found that her father had been treated for full-blown psychotic, manic-depressive illness; a paternal aunt had committed suicide, and a paternal uncle was a successful politician who was known to sleep very little. On mental status examination, the patient *spoke with great rapidity* and complained of extreme irritability. She cried while reminiscing her 4-day euphoria on the MAOI; she said she was crying because of all the joy that she had missed in life, and she knew that this state of mind would not last very long. The patient was prescribed divalproex, 750 mg/day on top of her tranylcypramine. Within 2 weeks she had

completely cleared from her depressive symptoms. Over the next 6 months the dosages of the two medications were adjusted in such a way that she had drive and energy without irritability, continued interest in her work and life, occasional "tears of happiness", while maintaining some degree of reservation about how good life, marriage and men could be. The couple received marital counselling which helped to rekindle some of the lost romance in their marriage.

By DSM-IV criteria this patient would be an enigma in the sense that a dysthymic disorder evolved into a double depression, which remained refractory to all antidepressants, except for two brief MAOI-induced hypomanic switches. It is also noteworthy that, *while* depressed, she exhibited at least one hypomanic symptom - racing thoughts or rapid speech. The family history helped in reclassifying this patient in the bipolar realm, and provided the clinical rationale for the divalproex augmentation.

BIPOLAR III½: BIPOLARITY MASKED – AND UNMASKED – BY STIMULANT ABUSE

In types I and II there are discrete episodes of excitement of, respectively, manic and hypomanic intensity; in type III the occurrence of these episodes is in association with antidepressant use, as well as other somatic treatment. There are also patients whose periods of excitement are so closely linked with substance or alcohol use/abuse that it is not always easy to decide whether these periods would have occurred in the absence of such use/abuse. In these cases that we propose designation with the rubric of type III½, excitement is more discreet than discrete. The reason for creating this category is to bring the possible benefit of mood stabilization (Sonne and Brady 1999) to this group of patients who otherwise might be classified as substance-induced or substance withdrawal-induced mood disorders.

This 29-year-old journalist had long indulged in cocaine and amphetamines in an attempt to make "my strong moods last longer". She had used these drugs with such regularity that it was not possible to define her "strong moods" independently from the use of these agents. Again, what she termed "driven state" referred to how she had been for at least 10 years, roughly the duration of her stimulant abuse. She consulted us because, following self-initiated withdrawal from stimulant use, she had deteriorated. She had been treated in a drug rehabilitation programme, and had actually gotten worse; a psychiatrist who examined her obtained family history for manic-depressive illness on the father's side, and recommended that she receive more specialized treatment in a mood disorders programme.

The chronology of her drug withdrawal mood state was as follows. Gradually, over a period of several months, she evolved into a state of "unpleasant nervous slowness". She complained of severe anxiety in the mornings, panic attacks, and stated that meeting people was an "ordeal"; she felt "totally engulfed in a profound sadness" that she could not shake, unable to enjoy anything, culminating in the "unbearably painful realization" that she had failed in everything she had done in life. She consulted us because she was feeling hopeless, believing that her condition

Table 7 Attributes of the hyperthymic temperament*

Four or more of the following attributes, which are not episode-bound and constitute part of the habitual long-term functioning of the individual:
Upbeat and exuberant
Articulate and jocular
Overoptimistic and carefree
Overconfident and boastful
High energy level, full of plans and improvident activities
Versatile with broad interests
Overinvolved and meddlesome
Uninhibited and risk-taking
Habitual short sleeper (less than 6 hours/night)

*Modified from Akiskal *et al.* 1979; Akiskal 1992.

had become chronic and recalcitrant. Off stimulants she had gained 35 lb. Her turmoil was accentuated by a state of agitation at night which prevented her from finding relief in sleep; alcohol that had helped her in the past had completely lost its efficacy. Six months into this condition she had been prescribed antidepressants (from three different classes), and conventional neuroleptics: this only "deepened" her misery, accentuated her "racing thoughts", and made her "super-agitated". When divalproex was proposed, she protested, insisting that she needed an antidepressant. After much psychoeducation she consented to try this anticonvulsant, and within 3 weeks, she had relief from panic, agitation, and painful depression. Topirimate 100 mg h.s. first helped her with better sleep and, over a period of 4 months, led to a 25 lb weight loss. She is now employed, again in a "regular" job rather than being a "freelance" journalist. When last seen she stated "I have my life back – but on a smooth ride, rather than a roller coaster".

BIPOLAR IV: HYPERTHYMIC DEPRESSION

For this category we propose patients with clinical depression that occurs later in life and which is superimposed on a lifelong hyperthymic temperament (Table 7). They are typically males in their 50s whose lifelong drive, ambition, high energy, confidence, and extroverted interpersonal skills helped them to advance in life, to achieve successes in a variety of business domains and/or political life (Akiskal 1984, 1992). The major external validator for the bipolar status of depressions in association with hyperthymic temperament is familial bipolarity comparable to that of bipolar II patients (Cassano *et al.* 1992).

The patient was referred because of "being stuck in a depression for 3 years". He was a 53-year-old, extremely successful lawyer whose life now appeared ruined because of this "never-ending depressive ordeal". Much of his life had been endowed with excessive energy, high confidence, drive and ambition. Before gradua-

tion from a top law school he had been hired in a leading law firm and, within a short period, he had climbed to the top of the law firm. He had amassed great wealth, prestige, and political connections. He felt on top of the world, flying his own plane to diverse destinations in the world. He had never needed more than 4 hours of sleep, and always handled "a hundred tasks at a time". Alcohol was needed for his "galloping nerves." He had a sharp intellect and was an eloquent speaker. "Doc, I never lost a case". All of these attributes formed his habitual self throughout his life, and which "did not recognize defeat". Although he had been married only one time to his present wife, he had three other families in other countries. These women and children knew of each other, but tolerated him, because he had been generous with all of them. He loved gourmet food and in recent years had become overweight. This had led to coronary artery problems that did not require surgery, but responded to balloon arteriography. He was super-compliant to an exercise programme that he pursued vigorously, but soon he started worrying about his "terminality", and started waking up tired, losing his upbeat spirit, indeed becoming irritable, wanting to sleep up to 10 hours a day, not attending to his law firm; in brief "I was going down the drain". He was diagnosed with major depression and treated with essentially every class of antidepressant available. He was first treated by internists, he had also consulted six different psychiatrists. With each new antidepressant he would improve for a short while, and then he would get more agitated. He insisted that ritalin was the best treatment for a few hours in the morning, because it helped his inordinate fatigue; but in the afternoon he would become suicidal. This is the juncture at which he consulted one of us, "at the end of my rope". During the first interview he stated that curiously the depression which had "invaded" his body and spirit, did not prevent him from experiencing sexual passion on an intermittent basis; also he had experienced "rush of ideas", which were unpleasant because he didn't have the energy to execute any of them. All antidepressants – and the ritalin – were discontinued, bupropion 150 mg b.i.d., coupled with 750 mg of divalproex, were prescribed to him. In 3 months he was out of his depression, and there was no further need for the bupropion. Maintained on divalproex for 2 years at this writing, the. patient is in the process of expanding his law firm and its international connections.

Hyperthymics have a strong sexual appetite, which often leads to the search for new partners. Unlike the true psychopath these individuals are generous with their women, and those who work for them. Unlike the short-lived hypomanias of bipolar II and III, the hyperthymic traits of these individuals are maintained for much of their lives at a more or less stable level. Many seem protected from depression and, if they would succumb to clinical depression, this usually happens later in life. There is a variant to this pattern, however, whereby the temperamental characteristics are not as sanguine and lead to a great deal of trouble in their lives, often associated with recurrent depression.

This 50-year-old divorced man, admitted to the hospital for intense suicidal preoccupations, gave a history of three previous hospitalizations for depressive episodes with suicide attempts, including one overdose that had necessitated a stay in a critical-care unit. The first of these depressions occurred in the context of divorce

from a 7-year marriage, when he was 40 years old. She had left him because of repeated marital infidelity. His depression had not responded well to antidepressants of the SSRI type, though his second episode had melancholic features and had shown a satisfactory response to nortriptyline. Despite this, the present episode had failed to resolve on 150 mg of this secondary amine tricyclic.

Despite this convincing affective disorder history the patient had carried the primary diagnosis of polysubstance abuse with antisocial traits. Upon careful review of his history we could not document the persistent antisocial pattern that characterizes this disorder. At age 8, he had been diagnosed as "hyperactive", admitted to a psychiatric hospital and given ritalin which had questionably reduced his unruly behaviour and truancy. He was an average student and managed to graduate from high school. He said he had always been a "high-energy, high-activity and overconfident individual". He said that he liked "being in the driver's seat and never following anybody". He believed his marriage had failed, not because of his sexual indiscretions, but because his wife, from a rich family, was too spoiled and was not satisfied with a man like him – even if he worked three jobs to satisfy her. He was a good provider to his two children before and after the divorce. He liked to undertake risky occupations such as climbing on ladders to paint designs on high ceilings. This behaviour was all the more risky because he was, since his early teens, indulging in heroin, alcohol, and cocaine; he insisted that all three calmed his "nervous temperament, high moods and racing thoughts", and helped him function.

Although his current admission was for a suicidal depression, he was flirting with the nurses and making "lecherous passes". He had been drug-free and sober in the past on at least one extended period of 3 years, yet his restless disposition had remained essentially unchanged. The patient was eventually managed successfully on bupropion 150 mg b.i.d. and divalproex 750 mg/day. For the first time in his life his "drive for constant action" has been moderated. The patient also remarked that for the first time in his life he had come to appreciate what "reflection" means. His pattern of promiscuous unprotected sexual life changed in tandem with the greater control over his impulsivity.

Both patients depicted as bipolar type IV can be said to be hyperthymic. The first one is best described as a sanguine hyperthymic, with largely the positive attributes of this temperament; on Axis II these patients can be classified as having narcissistic traits. The second patient has a more restless disposition; so much so that he was considered "hyperactive" as a child; these patients encounter greater difficulties in life, which may earn them "psychopathic" labels. The differentiation of these patients from cases of real attention-deficit-hyperactivity disorder is that they have some of the positive attributes of the hyperthymic temperament such as confidence, caring for others, cheerful moods, interpersonal charm.

When hyperthymic individuals become depressed, usually the initial episode is hypersomnic-retarded. The use of antidepressants tends to destabilize, it would seem, the underlying hyperthymic temperament. Eventually, elements of this temperament appear in the depression. These typically include increased sexuality and racing thoughts. These are depressive mixed states (Akiskal and Mallya 1987) – which can be quite protracted

Table 8 Clinical picture of (bipolar) depressive mixed state*

Meets minimum criteria for major depressive disorder plus three or more of the following:
Unrelenting dysphoria, irritability, and lability
Dramatic expressions of suffering
Psychomotor agitation against a background of retardation
Intense sexual excitement
Extreme fatigue with racing thoughts
Free-floating anxiety, as well as panic attacks
Suicidal obsessions and impulses

*Modified from Akiskal and Mallya (1987).

– yet they are not part of the official nosology (Table 8). Koukopoulos and colleagues (1992) have elsewhere described these patients as "excited depressives".

CONCLUDING REMARKS

In this chapter we have placed emphasis on the depressive manifestations of a range of bipolar conditions which are best regarded as "pseudo-unipolar". We have not considered the severe psychotic end of bipolar disorder (Akiskal and Puzantian 1979), nor have we presented the emerging fascinating data about the offspring of bipolar parents (Akiskal *et al.* 1985). The main thesis of this chapter has been that many major depressions in the DSM-IV schema are in reality part of the bipolar spectrum. Sceptics must examine a classic NIMH study by Gershon and colleagues (1982) that clearly demonstrates that the majority of the first-degree relatives of manic-depressive probands pursue a predominantly depressive course. In practice this means that, when confronted with a clinically depressed patient, one must not undertake treatment before a careful family history for bipolarity. Using family history as a diagnostic probe is not discussed in the DSM-IV manual, but we submit this can be extremely useful to the practitioner (Akiskal *et al.* 1983).

We could have completed the list of bipolar prototypes through V and VI. There are "atypical" seasonal depressions without discernible hypomanic states, but activation in the spring. Related to these forms are periodic depressions with abrupt onset and offset; bipolar family history is often detected during systematic evaluation of such cases. Other patients may present with episodic obsessive–compulsive symptomatology, periodic states of irritability, and/or acute suicidal crises in the absence of a clear-cut affective symptomatology. Then there are patients with episodic neurasthenic or sleep complaints, or those with severe brief depression. We have

elected to hold back definitive judgement on whether they too belong to the bipolar spectrum. The foregoing conditions require further study before the link to bipolarity is validated. For types I through IV we feel sufficiently confident on clinical grounds, as well as from that of the supporting research literature documented in this chapter.

The main emphasis of this chapter has been on the clinical phenomenology of bipolar subtypes. But in a disorder that has remissions and exacerbations it is not possible to divorce the clinical picture from treatments received. As practising clinicians we are convinced that extending the concept of bipolar spectrum to include what others might consider unipolar territory, substance abuse, or Axis II pathology, will help in the cause of protecting these patients from possible negative effects of antidepressants unprotected by mood stabilizers. We are aware that many distinguished scientists and practitioners might disagree with the latter position. In particular, aggravation of the course of bipolar disorder by antidepressants is considered controversial in the scientific literature (see, for instance, Lewis and Winokur 1982, Angst 1985, Kupfer 1988). In our opinion this controversy is largely based on a literature which has studied patients who are not representative of the larger universe of patients seen in contemporary clinical practice. Our ongoing collaboration (Akiskal and Pinto 1999) addresses the challenge of making sense of patients who do not become research subjects.

We have presented research data, as well as illustrative clinical case material, which supports their inclusion in a broad bipolar spectrum. The emergence of "hard" data (external validators) does support Kraepelin's hypothesis that many recurrent depressions are variants of manic depression - and which we have classified as "soft" bipolar (that can be defended on clinical grounds as well). Despite the scepticism of some authorities (Kupfer *et al.* 1988), the necessity of categorizing bipolar II and related conditions as distinct from full-blown bipolar, as well as unipolar, disorders has gained momentum (Endicott *et al.* 1985, Huen and Maier 1993, Akiskal *et al.* 1995, Vieta *et al.* 1997). Ultimately, molecular genetic strategies might help in a more natural classificatory schema. As Coryell *et al.* (1984, 1989) have argued, some bipolar IIs can be related to bipolar I, most appear to be autonomous, and few could be related to the unipolar universe. In other words, bipolar II represents a heterogeneous clinical spectrum belonging predominantly to the realm of bipolar disorders. A distinct non-psychotic variety might "breed true" with overlapping phenotypes (II–IV), while others might belong to a more severe psychotic mood disorder (½–II). The subclassification we have developed is not the final word on the bipolar spectrum: we offer it as a tool to facilitate genetic, clinical, and therapeutic research.

As practising clinicians in a specialized university mood centre, we are overwhelmed with the number of patients who are destabilized by extensive

antidepressant intake. It is vital to recognize their soft bipolar tendencies prior to this complication. This decade has seen the development of many anticonvulsant mood stabilizers, which have been enormously helpful in minimizing or preventing such destabilization. Much of this use is presently based on informed clinical experience. The phenomenon of increased cycling in bipolar disorder was not as commonly observed in the 1950s, 1960s, and 1970s (Akiskal and Puzantian 1979, Angst 1985, Wolpert *et al.* 1990) when we had fewer antidepressants, and classical neuroleptics were often used as adjunctive treatments in affective disorders. Given the spectre of tardive dyskinesia, the use of classical neuroleptics in bipolar disorder has been viewed as problematic, though it is widely used in clinical practice (Sernyak *et al.* 1997). In our experience the short-term use of small doses of such agents as thioridazine (25–100 mg) is often helpful in bringing rapid control to the insomnia, excitement, impulsivity, and risk-taking behaviour often observed in the entire spectrum of bipolar disorders (Akiskal 1999a). With the advent of atypical neuroleptics – which seldom give rise to extra-pyramidal side-effects – we have been more lately using them in moderation and in low doses in those soft bipolar patients in whom rapid control of risk taking was necessary to prevent tragic consequences, or in situations where anticonvulsant mood stabilizers failed to bring appreciable clinical results. We have even observed that in selected cases an atypical neuroleptic such as olanzapine (2.5–5.0 mg/day), used as monotherapy, can bring remission to patients within the soft bipolar spectrum. Obviously, a great deal of systematic research needs to be conducted in further clarifying the role of both anticonvulsant mood stabilizers and atypical neuroleptics in the bipolar spectrum. We wished to close this chapter with a therapeutic note in order to emphasize that, beyond its use in helping classification and research, the ultimate purpose of any revision in our diagnostic system is to improve the way we clinically manage the patient. In this context it is also important to emphasize the vital role of a specialized mood or bipolar clinic in the overall management of these patients. For many of these patients their periodic visit to such a clinic and their physician or therapist, represents the only, or the main, stable human contact during extended troubled phases of their life. By the same token, such a clinic is the optimum setting in which the tempestuous spectrum of disorders described in this chapter can be properly studied.

Acknowledgements

The case histories in this chapter are reproduced from Akiskal and Olavo Pinto 1999.

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Chapter three

The mixed bipolar disorders

Susan L. McElroy, Marlene P. Freeman
and Hagop S. Akiskal

INTRODUCTION

Emil Kraepelin was among the first psychiatric nosologists to stress the clinical and theoretical importance of the co-occurrence of manic and depressive symptoms in bipolar disorder (see also Chapter 1 of this book and Marneros 2000). In his 1921 treatise *Manic-Depressive Insanity* Kraepelin stated that "very often we meet temporarily with states which do not exactly correspond either to manic excitement or to depression, but represent a *mixture* of morbid symptoms of both forms of manic-depressive insanity" (p. 99). He called such co-occurrences of manic and depressive symptoms mixed states and defined them broadly, in that a patient needed to exhibit only one of three abnormal components of mood states (manic or depressive mood, thought, and behaviour) in a polarity opposite to the other two to qualify for a mixed-state diagnosis. He thus specified six types of mixed states, based on various combinations of manic and depressive mood, thought, and behaviour. These were: (1) depressive or anxious mania, (2) excited depression, (3) mania with poverty of thought, (4) manic stupor, (5) depression with flight of ideas, and (6) inhibited mania.

Although authorities since Kraepelin have continued to stress the importance of mixed states in understanding the fundamental nature of bipolar disorder (Akiskal *et al.* 1998, Bauer *et al.* 1994, Berner *et al.* 1983, Campbell 1953, Dilsaver *et al.* 1999, Freeman and McElroy 1999, Goodwin and Jamison 1990, Himmelhoch 1979, Himmelhoch *et al.* 1976, McElroy *et al.* 1992, Swann *et al.* 1997, Marneros 2000), major psychiatric diagnostic systems have minimized the importance of such states, providing definitions of mixed states that are far narrower than those proposed by Kraepelin. For example, in the DSM-IIIR (American Psychiatric Association 1987), mixed bipolar disor-

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 63–87.

der is defined as the co-occurrence of DSM-IIIR defined mania and depression. The ICD-10 (World Health Organization 1992) stipulates that mixed bipolar disorder is to be diagnosed only if manic and depressive symptoms "are both prominent for the greater part of the current episode". In the DSM-IV a mixed episode is defined in an even narrower manner, including only those patients meeting full criteria for both a manic episode and a major depressive episode occurring concurrently for 1 week. All three systems exclude patients with a variety of subsyndromal mixed states – mania with subsyndromal depressive symptoms, major depression with hypomanic symptoms, and various combinations of hypomanic and dysthymic symptoms.

Fortunately, increased empirical attention has recently been given to mixed states, especially over the past 10 years. In this chapter, we review the literature on the phenomenology, epidemiology, course and outcome, biology, and treatment response of mixed states, with emphasis on recent studies. We conclude that recent studies, like many older ones, support Kraepelin's conceptualizations that mixed states should be broadly and dimensionally, as well as categorically, defined, that they have important features that distinguish them from pure states, and that theoretical models that explain bipolar disorder must account for them.

CLINICAL CHARACTERISTICS AND PHENOMENOLOGY OF MIXED STATES

In categorizing mixed states in Chapter 7 of *Manic-Depressive Insanity,* Kraepelin provided what is still one of the best clinical descriptions of the many ways mixed states can present. For example, he described "depressive or anxious mania" as "a morbid state … composed of flight of ideas, excitement, and anxiety … mood is anxiously despairing". He characterized "excited depression" as "extraordinary poverty of thought but, on the other hand, great restlessness … mood is anxious, despondent, lachrymose, irritable, occasionally mixed with a certain self-irony".

In his 1953 book *Manic-Depressive Disease: Clinical and Psychiatric Significance,* Campbell wrote:

"The mixed type of manic-depressive psychosis epitomizes the entire cyclothymic process, in that it contains the symptoms characteristic of the various phases. Whether it is a sustained reaction or represents a phase of metamorphosis between the major forms, the mixed type emphasizes the underlying similarities between the depressive and hypomanic, the fact that the manic and depressive reactions may be superimposed, and that the same individual possesses the potentialities for either form".

Campbell also observed:

"There is nothing static about this autonomic–emotional–psychic disturbance; it is a dynamic and ever-changing process, with innumerable degrees of depression as well as mania. It is not mania and depression, or two distinct forms, but manic-depressive, a continuous process involving essentially a dysfunction in the emotional sphere. Indeed, there are more mixed reactions of this disease than is generally realized. It could truly be stated, to some extent, all manic-depressive reactions are 'mixed' types, in that the symptomatology is anything but static".

Many modern authorities have also provided excellent descriptions of bipolar mixed states. Patients have been described as displaying varied combinations of a wide range of mood, neurovegetative, cognitive, and behavioural symptoms, particularly variability or lability in mood and psychomotor activity, and a "pleomorphic" presentation with "innumerable" combinations "of often contrasting symptoms" (McElroy *et al.* 1992). For example, in stressing the phenomenological complexity of mixed episodes, Himmelhoch (1979) remarked that they are "chameleon-like in their presentation, appearing in some patients like schizophrenia, in others like psychotic depression and in still others like labile, hysteroid states, thereby creating a set of difficult diagnostic conundrums for the clinician".

More recently, several groups have begun to systematically investigate the phenomenology of mixed states using modern empirical methodologies (Akiskal *et al.* 1998, Bauer *et al.* 1994, Cassidy *et al.* 1998a,b, Dilsaver *et al.* 1999, Perugi *et al.* 1997 and in press). These studies (which are described below) are confirming earlier reports that depressive signs and symptoms are common in mania and hypomania, that manic features occur in depression, and that mixed states should be conceptualized and defined broadly and dimensionally, as well as categorically, and not narrowly.

DEPRESSIVE SYMPTOMS IN MIXED/MANIC STATES

Virtually every depressive sign and symptom, as well as every degree of depressive syndrome – minimal, mild, moderate, and full – has been reported to occur in mania. For example, Bauer *et al.* (1994) tested five definitions of dysphoric (mixed) hypomania and mania in 37 bipolar outpatients during hypomanic or manic episodes. These definitions were (from least to most restrictive): (1) any depressive symptom endorsed on a 12-item depression scale modified from the Hamilton Depression Rating Scale (HDRS) (Hamilton 1967) to reflect purely depressive symptoms (depressed mood, guilt, suicidality, work, retardation, hypochondriasis, libido, weight loss, and two each on anxiety and somatic symptoms) (HD12); (2) depressed mood item endorsed on the HD12; (3) more than two items endorsed on the HD12; (4) more than four items endorsed on the HD12; and (5) a mixed episode that met criteria for both a DSM-IIIR major depressive episode and

(hypo)mania. The authors found that depressive symptoms were continuously rather than bimodally distributed and did not support a clear dichotomous distinction between dysphoric and non-dysphoric hypomania or mania. They concluded that dimensional as well as categorical approaches were needed to distinguish dysphoric from non-dysphoric states.

McElroy *et al.* (1995) examined the relationship between mixed and pure mania using both narrow (DSM-IIIR) and intermediate (three or more associated depressive symptoms) criteria to define mixed mania. Compared with pure manic patients, DSM-IIIR mixed patients had significantly more depressive symptoms, were more likely to be female, experienced more prior mixed episodes, had higher rates of comorbid obsessive compulsive disorder, and had longer hospitalizations. However, when mixed mania was defined more broadly, differences in sex distribution and hospitalization duration were lost. It was concluded that dimensional rather than categorical systems to describe the degree of associated depression might be a more meaningful method of classifying mania.

More recently, in a French multisite collaborative study, Akiskal *et al.* (1998) assessed 104 hospitalized patients with DSM-IV bipolar mania according to a dimensional scheme progressing from "pure mania" (absence of depressive symptoms), to "doubtful dysphoric mania" (presence of one depressive symptom), to "probable dysphoric mania" (presence of two depressive symptoms), and finally, to "definite dysphoric mania" (presence of three or more depressive symptoms). Depressive symptoms included all of the DSM-IV criteria for major depression except for insomnia and agitation. Dysphoric mania defined as two or more depressive symptoms was distinguished from pure mania on various features, including: higher HAM-D scores; female over-representation; lower frequency of typical manic symptoms such as elation, grandiosity, and excessive involvement; and higher prevalence of psychotic features, mixed first episodes, and depressive and cyclothymic temperaments. The authors concluded that the presence of two or more depressive symptoms was a clinically meaningful way to define mixed mania. They also concluded that depression associated with mania, or "mixity" of mania, ran "along a spectrum that is without firm cutoffs", that the DSM-IV and ICD-10 definitions of mixed states were "far removed from clinical reality", and that categorical and dimensional definitions of dysphoria during mania could both be useful. Moreover, they suggested that quantifying the degree of concurrent depressive symptomatology during a manic episode could be done by assessing the number of depressive symptoms as well as rating the intensity of depression using a depression rating scale such as the Hamilton Depression Rating Scale (HDRS) (Hamilton 1967) or Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery *et al.* 1979).

Cassidy *et al.* (1998a) evaluated 316 inpatients meeting DSM-IIIR criteria for bipolar disorder, manic or mixed by rating them for 20 mixed state

signs and symptoms. Dysphoric mood, mood lability, anxiety, guilt, suicidality, and irritability were the only symptoms significantly more common in the mixed group, whereas grandiosity, euphoric mood and pressured speech were significantly more common in the manic, group. However, substantial rates of dysphoria (19–29%), lability (36–65%), anxiety (17–32%), and irritability (47–73%) were seen in the pure manic patients, leading the authors to conclude that a "less restrictive definition of (DSM-IIIR) mixed states would be more appropriate". In a similar study, Cassidy *et al.* (1998b) rated 237 patients with DSM-IIIR bipolar disorder experiencing manic (n = 204) or mixed (n = 33) episodes on 15 classic features of mania and five features related to "dysphoric mood". They identified five independent factors representing psychomotor pressure, psychosis, increased hedonic function, irritable aggression, and dysphoric mood. The dysphoric mood factor included positive ratings of depressed mood, anxiety, guilt, mood lability, and suicide, and a negative rating of euphoric mood. The authors concluded that the bimodal distribution of the dysphoric mood factor was consistent with the possibility that mixed bipolar disorder was a distinct state.

Most recently, Dilsaver *et al.* (1999) conducted a factor analysis of 37 behaviour rating items from the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott *et al.* 1978) obtained from 105 inpatients hospitalized for DSM-IIIR manic episodes. The analysis revealed four factors corresponding to manic activation, depressed state, sleep disturbance, and irritability/paranoia. Cluster analysis separated the patients into two groups, which differed only with respect to depressed mood. Further analysis, however, suggested three groups of manic patients differing regarding the severity of associated depressive symptoms: mania with minimal depressive symptoms, mania with full superimposed major depression, and mania with depressive symptoms intermediate between the other two. Dilsaver *et al.* (1999) concluded that manic episodes could be naturally classified as classic (predominant euphoric), dysphoric, or depressed. Moreover, they suggested that pathological affective states should be viewed as "orthogonal combinations of elemental behavioural disturbances, each with specific biologic substrates and pharmacologic sensitivities, rather than as many fragmented syndromes", involving derangements in reward, activity, and arousal – similar to Kraepelin's proposal that mixed states were due to abnormalities in mood, activity, and thought.

In summary, numerous modern phenomenology studies, including factor-analytic studies, have confirmed the occurrence of depressive symptoms in mania, and have provided support for the hypothesis that mixed mania (mania with depressive features) may be distinct from pure or euphoric mania (mania without depressive features). Moreover, these studies suggest that systems used to define mixed states should be broad and dimensional as well as categorical, rather than overly narrow. As

Goodwin and Jamison (1990) wrote, "in general, it is best to consider the depressive spectrum and the manic spectrum as independent and capable of interacting in a variety of combinations and permutations". Patients can have various combinations of various degrees (none, mild, moderate, severe) of manic and depressive symptoms, thereby allowing more accurate diagnosis and, hence, more appropriate treatment.

MANIC SYMPTOMS IN DEPRESSED STATE

Although less well studied than depressive symptoms in mania, modern studies have reported manic symptoms in patients with major depressive syndromes. Comparing 143 mixed-state bipolar patients in whom mixed states were broadly defined as "sustained instability of affective manifestations of opposite polarity" with 188 DSM-IIIR manic patients, Perugi *et al.* (1997) identified three types of mixed states. They described one of these as agitated depression with pressure of speech and flight of ideas, and noted that it was similar to Kraepelin's excited depression and Koukopoulos *et al.*'s mixed depressive state. These observations repeatedly suggest that mixed bipolar states can present as full syndromal depression with subsyndromal mania, and that modern diagnostic systems should be modified to reflect this.

SUICIDAL SYMPTOMS

As noted, suicidality has repeatedly been observed in bipolar mixed states. Moreover, suicidal ideation (Dilsaver *et al.* 1994, Strakowski *et al.* 1996) and attempts (Perugi *et al.* 1997) have been demonstrated to occur more frequently in mixed as compared to pure manic episodes. For example, Dilsaver *et al.* (1994) found that 24 (55%) of 44 patients with mixed episodes were suicidal, compared with one (2%) of 49 patients with pure mania, when assessed with the SADS suicide subscale. Also, Strakowski *et al.* (1996) studied patients consecutively admitted with DSM-IIIR bipolar manic or mixed episodes, and found that nine (26%) of 34 patients with mixed mania had suicidal ideation as assessed by the suicidality item of the HRSD, compared with four (7%) of 57 patients with pure mania episodes.

ANXIETY SYMPTOMS

Although not as well studied as depressive symptoms, symptoms of anxiety are also common in mixed states. As noted, Kraepelin (1921) described the mood of both depressive or anxious mania and excited depression as often having an anxious component. Winokur *et al.* (1969) reported that 43% of

14 episodes of mixed mania in 10 patients were accompanied by anxiety attacks. Among 48 unmedicated patients with acute mania, Post *et al.* (1989) found that degree of anxiety correlated with degree of depression during mania ($r = 0.75$). More recently, factor-analytic studies of the signs and symptoms of mania have found that anxiety loads with depressed mood in mania (Cassidy *et al.* 1998a, Dilsaver *et al.* 1999).

PSYCHOTIC SYMPTOMS

Mixed states are often accompanied by psychotic symptoms, especially mood-incongruent delusions. Kraepelin (1921) noted "the frequent contradiction between the content of the delusions and the colouring of mood. A patient told me with laughing that his nerves were dried up and his blood circulated only as far as his neck. A depressed female spoke of the inward voice, which she heard, as of a 'grace'. … Many patients speak cheerfully of their approaching death" (p. 110). More recently, in a study of 108 female inpatients with bipolar disorder, Dell'Osso *et al.* (1991) found that the mixed state was associated with greater frequency of mood-incongruent psychotic features. Specifically, 63.2% of mixed psychotic episodes were mood-incongruent, compared with 37.5% of manic psychotic episodes, as defined by DSM-IIIR criteria. Studies are inconsistent, however, as to whether the overall incidence of psychosis differs between mixed and pure manic states. Of the 108 inpatients evaluated by Dell'Osso *et al.* (1991), mixed and manic patients displayed comparable rates of episodes with psychotic features (33% and 30%, respectively). Similarly, in the study by Cassidy *et al.* (1998a), in which 316 bipolar inpatients with DSM-IIIR manic or mixed episodes were evaluated for 20 mixed-state signs and symptoms, mixed and manic patients displayed similar rates of paranoia. By contrast, other studies have found higher rates of psychosis in mixed than in pure states. Of 39 patients consecutively admitted for the treatment of mania, all 21 mixed patients had psychotic features compared with 13 (72%) of the 18 – non-mixed patients ($p = 0.02$, Fisher's exact test) (Dilsaver *et al.* 1993). Similarly, defining dysphoric mania as the presence of two or more depressive symptoms, Akiskal *et al.* (1998) found that, in 104 hospitalized manic patients, dysphoric mania was associated with a higher rate of psychotic features than was pure mania.

Formal thought disorder is also common in mixed states. Secunda *et al.* (1985) reported that bipolar patients with mixed mania displayed greater degrees of cognitive impairment than non-mixed patients. More recently, Sax *et al.* (1995) found that patients with DSM-IIIR mixed manic episodes had significantly higher negative formal thought disorder scores (including measures of poverty of speech, poverty of speech content, and thought blocking), but lower positive formal thought disorder scores, than patients with non-mixed manic episodes.

EPIDEMIOLOGY

Authorities have disagreed as to the prevalence of mixed states, with some believing they were uncommon (Kraepelin 1921, Winokur *et al.* 1969) and others that they were more frequent than realized (Campbell 1953). Indeed, the reported prevalence rates of mixed states in patients with bipolar disorder from modern studies ranges from 5% (Bauer *et al.* 1994, Keller *et al.* 1986) to 70% (Carlson and Goodwin 1973, Evans and Nemeroff 1983), with an overall mean prevalence across 17 studies of 31% (305 of 981 patients) (McElroy *et al.* 1992). The wide variability in prevalence rates across different studies is probably due in part to the use of different criteria to define mixed states (McElroy *et al.* 1992). For example, in their study testing five definitions of dysphoric mania and hypomania in 37 outpatients, Bauer *et al.* (1994) found that 69% of episodes met the broadest definition (any of 12 depressive symptoms), 52% met the intermediate definition (more than two of 12 depressive symptoms), and only 8% met the DSM-IIIR criteria for a mixed episode. McElroy *et al.* (1995) tested two different definitions of mixed mania in a sample of 71 patients with bipolar disorder hospitalized for a manic episode. Twenty-four (34%) met criteria for the more restrictive DSM-IIIR criteria for a mixed episode, whereas 28 (40%) met the broader criteria of three or more associated depressive symptoms for mixed mania.

More recently, Akiskal *et al.* (1998) evaluated several definitions of dysphoric mania in 104 hospitalized bipolar manic patients: 47% of manic patients had at least one coexisting depressive symptom; 22% had definite dysphoric mania (defined as the presence of two or more concurrent depressive symptoms), and only 6.7% had a mixed episode as defined by DSM-IV (presence of five or more concurrent depressive symptoms). In short, rates of mixed mania increase as the degree of depression required for its definition decreases.

Certain patient populations may be at higher risk than others for experiencing mixed states. Many studies suggest mixed mania may occur more commonly in women than in men, especially when defined by higher degrees of associated depression (Akiskal *et al.* 1998, Arnold *et al.* 2000, McElroy *et al.* 1992, 1995). However, no significant differences have been found between men and women with mixed mania in suicidality, outcome, biological abnormalities, and treatment response (Arnold *et al.* 2000). Childhood and adolescent mania may also be characterized by higher rates of depressive features than is adult mania (Geller and Luby 1997, McElroy *et al.* 1997).

COURSE OF ILLNESS AND OUTCOME

The course of bipolar disorder characterized by mixed states has been studied, but results are inconsistent. Patients with mixed mania have been

reported to have a younger (Nunn 1979, Post *et al.* 1989), similar (Delucchi *et al.* 1991, Perugi *et al.* 1997), and older (Strakowski *et al.* 1992) age of onset of illness, as well as a similar (Post *et al.* 1989) and longer (Nunn 1979, Dell'Osso *et al.* 1991) overall duration of illness as compared to those with pure mania. Regarding episode duration, mixed manias have also been reported to be shorter than (Calabrese and Delucchi 1990), equal to (Winokur *et al.* 1969), and longer than (Dell'Osso *et al.* 1991, Keller *et al.* 1986, Perugi *et al.* 1997) pure manias.

Data regarding whether or not patients with mixed states experience more episodes of illness than patients without mixed states are inconsistent. From a retrospective chart review of 112 bipolar patients, Nunn reported that mixed-state patients did experience more affective episodes. However, Perugi *et al.* (1997) compared 143 bipolar patients with broadly defined mixed episodes and 118 manic patients without mixed episodes and found the opposite; that is, patients with pure manic episodes experienced more episodes than mixed-state patients.

Studies are also inconsistent as to what types of episodes patients with mixed states have had in the past. Nunn (1979) reported that patients who had experienced mixed episodes were more likely than patients without mixed episodes to experience depression early in the course of the illness. Dell'Osso *et al.* (1991) studied 108 female inpatients with bipolar disorder, and found that, in patients with mixed mania, the polarity of the first episode was mixed in 24.5%, depressive in 65.3%, and manic in 8.2%. Patients with pure mania were more likely to present initially with a manic episode (37.3%), but similarly likely to present with a depressive episode (59.3%). In another study comparing patients with DSM-IIIR bipolar disorder with mixed mania defined narrowly (by DSM-IIIR) and broadly (presence of 3 depressive symptoms) with non-mixed manic patients, mixed patients by either definition were more likely to have experienced prior mixed episodes (McElroy *et al.* 1995). More recently, in a study of 104 hospitalized acutely manic bipolar patients, Akiskal *et al.* (1998) found that patients with more broadly defined mixed mania (presence of two and presence of three or more depressive symptoms during mania) had statistically significantly higher rates of mixed first episodes (20% and 24%, respectively) than patients with pure mania (absence of depressive symptoms; 3%), but similar rates of depressive first episodes (40% and 48% vs 38%), respectively.

Regarding outcome, Kraepelin (1921) wrote that "the course of mixed states occurring as independent attacks appears in general to be lingering; they may be regarded as unfavorable forms of manic-depressive insanity". Many modern studies have supported Kraepelin's observation. Compared with patients with pure mania, patients with mixed mania have been reported to take longer to recover from an acute episode (Keller *et al.* 1986, McElroy *et al.* 1995, Perugi *et al.* 1997), to do less well on short-term (Cohen

et al. 1988) and long-term follow-up (Himmelhoch *et al.* 1976), to be more likely to relapse (Prien *et al.* 1988) or to relapse sooner (Tohen *et al.* 1990) after recovery, and to respond less well to lithium and possibly other mood stabilizers (Dilsaver *et al.* 1993; see Response to Treatment section). Other studies, however, have found that patients with mixed and manic episodes have similar short-term (Winokur *et al.* 1969) and long-term (Keck *et al.* 1998) outcomes.

ASSOCIATED CONDITIONS

Three studies systematically assessing rapid cycling among patients with mixed states have suggested that the two conditions may not be related. Himmelhoch *et al.* (1976) reported that patients with mixed and non-mixed mania showed similar rates of "mood circularity" (defined as episodes of mania and depression not separated by periods longer than 2 months). Post *et al.* (1989) reported that patients with "dysphoric mania" were significantly less likely to exhibit rapid cycling in the year before index admission than were patients with pure mania. Also, although both rapid- and non-rapid-cycling patients showed equal peak manic severity at their index episodes, rapid-cycling patients showed significantly less dysphoria, anxiety, and psychosis during mania. More recently, Perugi *et al.* (1997) found that the rates of rapid cycling were similar between 143 bipolar patients with broadly defined mixed states and 118 DSM-IIIR manic patients.

Patients with rapid cycling, however, have been reported to experience frequent mixed episodes (Bowden *et al.* 1999, Calabrese and Delucchi 1990, Himmelhoch 1979). Of 75 treatment-refractory bipolar patients receiving lamotrigine treatment, 51% of 41 rapid-cycling patients had more than 10 lifetime mixed episodes, compared with 7% of 34 non-rapid-cycling patients (Bowden *et al.* 1999). Also, mixed states and rapid cycling may share a greater prevalence among females and of thyroid abnormalities, poorer response to lithium, induction and/or exacerbation by antidepressants, and possible better response to valproate (Chang *et al.* 1998). Further, the rapid mood shifts displayed by patients with mixed mania (Himmelhoch 1979, Post *et al.* 1989) resemble the 24-hour mood alterations described by some bipolar patients with ultra-rapid cycling (Bauer *et al.* 1990).

Indeed, in patients with mixed symptoms it is often difficult to assess whether manic and depressive symptoms occur simultaneously, alternate rapidly, or both. If manic and depressive symptoms alternate rapidly, it is often difficult to determine how rapidly they do so (e.g. within minutes, hours, or days). This suggests that not only can mania be associated with varying degrees of depression along a dimension, but that the temporal relationship between manic and depressive symptoms may also vary dimensionally (McElroy *et al.* 1995). In other words, there may be indepen-

dent or related dimensions of mixity and cyclicity which, because of ultra-rapid cycling, are either pathophysiologically distinct but clinically indistinguishable or pathophysiologically similar (e.g. ultra-rapid cyclicity may progress into mixity).

The comorbidity of mixed states with other psychiatric conditions is also receiving increasing attention. Higher rates of comorbid substance abuse have been found in patients with mixed states compared to patients without mixed states in some (Himmelhoch *et al.* 1976), but not all (McElroy *et al.* 1995), studies. For example, Himmelhoch *et al.* evaluated 84 patients with bipolar disorder and found that 12 (46%) patients with mixed episodes had comorbid substance abuse as compared to 14 (20%) of 69 patients without mixed episodes. Also, higher rates of comorbid obsessive compulsive disorder have been found in patients with mixed episodes compared to patients with pure manic episodes (McElroy *et al.* 1995).

Few empirical data, however, are available regarding the relationship between mixed states and personality disorders. Mixed states have sometimes been seen as expressions of borderline personality disorder, largely because these conditions share phenomenological similarities (i.e. affective instability), a higher prevalence rate in females, and poor response to lithium (Akiskal 1987, 1996, Akiskal and Mallya 1987, Cassano *et al.* 1983). Akiskal's group, however, has argued that many individuals diagnosed with borderline psychopathology may in fact have mild forms of bipolar disorder, including cyclothymia with brief mixed states and chronic mixed hypomania. Although Akiskal's group has noted that the abrupt mood shifts in these individuals may give rise to serious characterological disturbances, they have also observed that psychotherapy is generally ineffective in the absence of adequate psychopharmacological treatment of the underlying affective instability.

Increasing studies are examining the relationship between mixed states and premorbid temperament. These studies suggest that mixed mania may be associated with a higher prevalence of depressive and possibly cyclothymic temperaments and a lower or similar prevalence of hyperthymic temperament compared with pure mania. In their cohort of 108 hospitalized women with bipolar disorder, Dell'Osso *et al.* (1991) found that patients with mixed episodes had a statistically significantly lower frequency of hyperthymic temperament and a non-significantly higher frequency of depressive temperament compared with patients with pure manic episodes. Perugi *et al.* (1997) similarly assessed the temperaments of 261 bipolar patients with more broadly defined mixed ($n = 14$) versus pure ($n = 118$) states. Mixed-state patients were statistically significantly more likely to have depressive temperament (32% vs 13%), but less likely to have hyperthymic temperament (28% vs 57%), than manic patients (3%). More recently, Akiskal *et al.* (1998) assessed 104 hospitalized acutely manic bipolar patients and found that those with mixed mania (defined dimensionally as probable

[two depressive symptoms] and definite [three or more depressive symptoms] during mania, had higher levels of depressive, but not hyperthymic, temperament. Patients with definite mixed mania also displayed significantly higher levels of cyclothymic temperament. Moreover, when all cases were segregated by polarity of temperamental traits with respect to mania (opposite versus same), two-thirds of patients with pure mania had no depressive or cyclothymic temperament, whereas two-thirds of mixed-manic patients had depressive or cyclothymic temperaments ($p = 0.02$). Akiskal *et al.* (1998) hypothesized that mixed states occur when mood episodes arise from baseline temperaments of opposite polarity (e.g. mixed mania from mania and depressive temperament; mixed depression from depression and hyperthymic temperament).

Himmelhoch and Garfinkel (1986) have suggested that, compared with pure mania, mixed mania occurs more frequently in bipolar patients whose illness had been complicated by a second neuropsychiatric condition in general. For example, they reported that 45 (71%) of 63 patients with mixed mania, compared with seven (12%) of 58 patients with pure mania ($p < 0.001$), had concomitant neuropsychiatric abnormalities. These abnormalities included paroxysmal EEG abnormalities ($n = 20$), alcohol and drug abuse ($n = 12$), developmental disorders ($n = 8$), migraine ($n = 6$), seizure disorders ($n = 5$), substantial head injuries ($n = 4$), and neurological illnesses ($n = 2$). By contrast, Strakowski *et al.* (1992) reported that eight patients with DSM-IIIR mixed bipolar disorder showed no differences from 33 patients with non-mixed bipolar disorder regarding medical and psychiatric comorbidity.

FAMILY HISTORY

Although the few studies examining the relationship between family history and mixed states have yielded inconsistent findings, taken together they suggest an increased prevalence of depressive disorders in the families of probands with mixed states. Dell'Osso *et al.* (1991) assessed family history in 108 female inpatients with bipolar I disorder, 49 with mixed episodes and 59 with pure manic episodes. They found no differences between the two groups in familial loading for mood disorders, suicide, or suicide attempts. Depressive disorders, however, were more common in the family histories of patients with mixed episodes than those with pure manic episodes. In a study which found that adolescent manics were more likely to be mixed than adult manics, adolescents displayed significantly higher rates of mood disorder in general, major depression in particular, and drug abuse or dependence (but not bipolar disorder or alcohol abuse or dependence) in their first-degree relatives (McElroy *et al.* 1997). In contrast, in a study by Perugi *et al.* (1997) of 261 patients with bipolar disorder with

mixed ($n = 143$) or pure manic states ($n = 118$), no differences in family history between the two groups were found regarding any major psychiatric disorder. However, in a subsequent paper, Perugi *et al.* (in press) reported that when a mixed state is dominated by depressive symptoms, the family history for depression is denser.

NEUROBIOLOGICAL MEASURES

Studies of the neurobiology of mixed states have primarily examined the hypothalarnic–pituitary–adrenal (HPA) axis function, plasma or cerebrospinal fluid (CSF) concentrations of neurotransmitters or their metabolites, and, more recently, thyroid function. Regarding cortisol function reports in mania are inconsistent, with some studies finding normal cortisol suppression on the dexamethasone suppression test (DST) (Carroll 1979, Evans and Nemeroff 1983, Schlesser *et al.* 1980), and others finding rates of non-suppression similar to those found in depression (Godwin *et al.* 1984, Graham *et al.* 1982, Stokes *et al.* 1984). However, several studies have suggested that patients with mixed mania may be more likely than those with pure mania to exhibit DST non-suppression. For example, Evans and Nemeroff (1983) studied 10 bipolar patients with acute mania and found that the mixed-episode patients ($n = 7$) exhibited cortisol non-suppression, while pure episode patients ($n = 3$) exhibited normal cortisol suppression. Krishnan *et al.* (1983) evaluated 10 consecutive bipolar patients with simultaneous manic and depressive symptoms with the DST, and all 10 displayed abnormal cortisol suppression. Swann *et al.* (1992) studied eight patients with mixed mania and 19 patients with pure mania. They found that the DST non-suppression rate was elevated in both manic and mixed states, but was higher in mixed-state patients. They also found that patients with mixed episodes displayed higher cortisol levels in plasma, CSF, and urine.

Some studies have noted significant thyroid abnormalities in bipolar disorder, such as elevated thyroxine (T_4) and free T_4 index in mania (Joyce 1991, Syra *et al.* 1991), and elevated thyroid stimulating hormone (TSH), decreased T_4, and thyroid antibodies in rapid cycling (Bauer *et al.* 1990). Our group has hypothesized that relative CNS thyroid hormone deficiency occurring in bipolar disorder might lead to mixed states as well as to rapid cycling, since both variants share affective lability, poor response to lithium, greater likelihood of response to antiepileptic mood stabilizers, and more common occurrence in women. Indeed, Zarate *et al.* (1997) reported that first-episode patients with mixed mania ($n = 15$) were more likely to have elevated TSH than patients with pure mania ($n = 57$) after controlling for age and gender. Similarly, Chang *et al.* (1998) found that the mean TSH was higher and the mean T_4 lower in 14 patients with mixed mania as compared to 23 patients with pure mania. By contrast, Joffe *et al.* (1994)

found no difference in the frequency of Grade II subclinical hypothyroidism or in mean thyroid hormone levels between mixed (n = 10) and non-mixed (n = 56) state patients in a cohort of 66 outpatients with bipolar disorder.

In studies of neurotransmitter systems, Post *et al.* (1989) found that acutely manic patients had higher CSF levels of norepinephrine than depressed or euthymic patients, and that, among manic patients, norepinephrine levels correlated with the degree of dysphoria, anger, and anxiety. Swann *et al.* (1994) compared patients with mixed mania, pure mania, and agitated depression and found that CSF 3-methoxy-4-hydroxyphenylglycol (MHPG) was significantly higher in mixed mania. However, they did not find significant differences between patients with mixed and pure mania (Swann *et al.* 1987). They also found that urinary norepinephrine excretion was higher in patients with mixed mania than with pure mania, which was higher than in patients with depressive episodes. These authors suggested that elevations in noradrenergic activity believed to characterize mania, may be most robust in mixed states. They also suggested that when the noradrenergic findings are taken together with the HPA findings, mixed mania combines biological abnormalities considered characteristic of mania and depression, which in turn implies that mania and depression are in fact superimposed in mixed states (Swann *et al.* 1993, 1994).

By contrast, Tandon *et al.* (1988) examined mean CSF homovanillic acid and 5-hydroxyindoleacetic acid in patients with mixed episodes, and found that levels were intermediate between those in patients with pure mania and patients with major depression. The authors concluded that mixed affective states were not a distinct entity, but rather a heterogeneous grouping with patients derived from manic and major depressive categories.

RESPONSE TO BIOLOGICAL TREATMENTS

Lithium

Case reports and case series have described the successful acute and long-term treatment of patients with various mixed states with lithium – alone or in combination with antipsychotics or clonazepam (Baastrup and Schou 1967, Carlson and Goodwin 1973, Kotin and Goodwin 1972, Evans and Nemeroff 1983). However, many studies suggest that mixed mania responds less well to lithium than does pure, euphoric mania (Cohen *et al.* 1988, Himmelhoch and Garfinkel 1986, Himmelhoch *et al.* 1976, Murphy and Beigel 1974, Prien *et al.* 1988, Secunda *et al.* 1985, 1987, Swann *et al.* 1986, 1997). For example, Secunda *et al.* (1987) found that 10 (90.9%) of 11 patients with pure mania responded favourably to lithium treatment as compared to only two (28.6%) of seven patients with mixed mania (p = 0.01). Prien *et al.* (1988) reported that 25 (36%) of 69 patients with mild to severe mixed mania responded to lithium, antipsychotic, lithium plus antipsychotic, or

lithium plus antidepressant compared with 20 (59%) of 34 patients with pure mania ($p < 0.001$). More recently, Swarm *et al.* (1997) investigated the relationship between depressive symptoms and treatment response in 179 hospitalized bipolar I patients with an acute manic episode randomized to receive lithium, valproate, or placebo (ratio 1:2:1). Depressive symptoms (defined as the presence of at least two depressive symptoms during mania) were associated with a poor response to lithium, whereas pure mania (defined as less than two depressive symptoms) was associated with favourable lithium response. By contrast, presence of depressive symptoms had no significant effect on valproate response.

Long-term studies suggest prophylactic treatment with lithium may also be less effective in mixed mania than in pure mania. Himmelhoch *et al.* (1976) reported that patients with mixed mania responded less well to psychopharmacological treatment than patients with pure mania at follow-ups ranging from 9 months to 5 years. Prien *et al.* (1988) conducted a double-blind prophylactic study of lithium, imipramine, and the combination in three subgroups of acutely manic patients, including 34 patients with pure mania, 46 patients with mixed mania with mild depression (defined as a HRSD score of 7–14) and 23 patients with mixed mania with moderate to severe depression (defined as a HRSD score ≥ 15). After initial stabilization of the acute episode the different treatments were begun. Many patients dropped out before entering the long-term preventative phase. Those who did enter included 20 patients with pure mania, 16 with mixed mania with mild depression, and nine with mixed mania with moderate to severe depression. Overall, lithium and the combination of imipramine and lithium were significantly more effective than imipramine alone in preventing recurrences. Patients with pure mania responded significantly better to both lithium and the combination than did patients in the mixed groups. By contrast, of the mixed patients, five (63%) of eight treated with lithium alone, and nine (90%) of 10 treated with the combination experienced recurrences, with an overall recurrence rate for all 18 patients of 82%. Thus, the combination of lithium and imipramine provided no advantage over treatment with lithium alone in the mixed patients, in whom both treatments provided poor protection against recurrences.

Valproate

Valproate has also been reported to be effective in mixed episodes, both in open-label studies and in controlled comparisons with placebo and lithium. For example, Calabrese and Delucchi (1990) studied 55 patients with rapid-cycling bipolar disorder in an open, prospective trial of valproate as both monotherapy and as an adjunctive medication. They found that all of the patients in the subgroup with mixed episodes experienced marked responses to valproate both acutely ($n = 13$) and prophylactically ($n = 12$).

Regarding double-blind studies, Freeman *et al.* (1992) and Clothier *et al.* (1992) compared lithium and valproate in 27 bipolar patients with acute mania and found them to be equally effective. In addition, favourable antimanic response to valproate was associated with high pretreatment depression scores. By contrast, in a double-blind, placebo-controlled study of valproate in 36 bipolar patients with acute mania (Pope *et al.* 1991), favourable antimanic response not associated with measures of depression or dysphoria – suggesting valproate is equally efficacious in mixed and pure mania (McElroy *et al.* 1991). Indeed, in a larger double-blind, placebo-controlled comparison of valproate versus lithium in the treatment of 179 patients with mania, depressive symptoms during mania had no significant effect on antimanic response to valproate, were associated with a poor antimanic response to lithium, and were associated with a better antimanic response to valproate than to lithium (Swann *et al.* 1997).

Carbamazepine

Patients with mixed states have also been reported to respond to carbamazepine, although the literature is not as extensive as it is for valproate or lithium. For example, Himmelhoch and Garfinkel (1986) reported that 21 (46%) of 46 lithium-resistant patients (80% of whom had mixed mania) responded to "anticonvulsant-based therapy", which usually involved carbamazepine. In a double-blind, placebo-controlled study of carbamazepine in 19 acutely manic patients, the 12 patients who responded "tended to be more dysphoric" than the seven patients who did not respond ($p < 0.10$) (Post *et al.* 1987). Also, the final degree of improvement with carbamazepine did correlate positively with the initial degree of anxiety ($p < 0.05$).

ECT

Electroconvulsive therapy (ECT) has repeatedly been reported to be an effective treatment for various mixed states, including mixed mania, mixed depression, and agitated depression (Dilsaver *et al.* 1993, Evans and Nemeroff 1983, Koukopoulos *et al.* 1992). In a randomized comparison of ECT versus lithium in 34 patients with acute mania, Small *et al.* (1988) found that the group receiving ECT did significantly better at weeks 6, 7, and 8. The strongest predictor of clinical outcome at the end of week 8 was baseline ratings of depression during mania, with depressive symptoms ultimately worsening in the group treated with lithium and improving in the group receiving ECT.

Antipsychotics

Open reports suggest standard and novel antipsychotics may be effective in treating various mixed states, including mixed mania, mixed depression,

and agitated depression (Koukopoulos *et al.* 1992, Suppes *et al.* 1992). In a recent double-blind, placebo-controlled, 4-week study of olanzapine in 115 inpatients with DSM-IV bipolar I disorder with an acute manic or mixed episode, olanzapine was superior to placebo in reducing manic symptoms. Mixed patients responded as well to olanzapine as did pure patients. In addition, patients with prominent depressive symptoms at baseline (defined as a HAMD-21 score ≥ 20) displayed statistically significant improvement in their HAMD scores with olanzapine treatment compared with placebo-treated patients (Tohen *et al.* 1999).

Antidepressants

In the only controlled study of an antidepressant in mixed mania, lithium alone, imipramine alone, and lithium in combination with imipramine were compared in the treatment of 25 mixed-state patients (16 of whom had mania with mild depression and nine of whom had mania with moderate or severe depression) (Prien *et al.* 1988). Five of the eight lithium-treated patients, all seven imipramine-treated patients, and nine of the 10 combination-treated patients experienced a recurrence. Imipramine treatment was thus associated with a greater risk of recurrence. Consistent with these findings, other investigators have reported that antidepressants may induce or exacerbate mixed bipolar states. Akiskal and Mallya (1987) described 25 patients referred for treatment-resistant depression who displayed subacute or chronic mixed states apparently induced by tricyclic antidepressants. These states were characterized by "unrelenting dysphoria/irascibility, severe agitation, refractory anxiety, unendurable sexual excitement, intractable insomnia, suicidal obsessions and impulses, and 'histrionic' demeanor – yet genuine expressions of intense suffering". They improved with antidepressant discontinuation and treatment with lithium or carbamazepine with or without low-dose antipsychotics. Koukopoulos *et al.* (1992) similarly reported 45 patients with bipolar disorder who experienced a "mixed depressive syndrome" with depressive and manic symptoms meeting DSM-IIIR criteria for major depression but not for mania, and who deteriorated when treated with antidepressants – displaying increased agitation, insomnia, and, in some, suicidal impulses. Patients responded to low-dose antipsychotics, lithium, antiepileptics, and ECT. Of note, it remains unclear whether mixed states are more or less likely to deteriorate than pure manias when exposed to antidepressants.

Other agents

Uncontrolled data in the form of case reports and case series suggest that gabapentin (McElroy *et al.* 1997), lamotrigine (Bowden *et al.* 1999), topira-

mate (McElroy *et al.* in press), and clonidine (Kontaxikis *et al.* 1989) may be helpful in some patients with mixed states.

SUMMARY OF TREATMENT RESPONSE DATA

In summary, substantial data suggest lithium may be less effective in the short- and possibly long-term treatment of mixed mania than it is in pure mania. Valproate, ECT, and possibly atypical antipsychotics (especially clozapine and olanzapine) may be more effective for these patients, though further comparative studies are needed. Of note, Bowden (1995) has argued that the relatively poor response of patients with mixed mania to lithium may be due to the limited spectrum of efficacy of lithium rather than the treatment refractoriness of mixed episodes *per se*. By contrast, Dilsaver *et al.* (1993) argued that depressive mania is a more virulent form of bipolar disorder, based on their results that demonstrated poorer response to antimanic agents in general, including valproate and carbamazepine as well as lithium. The treatment of mixed depressive states has received less attention, but antidepressant agents may exacerbate these conditions, and antimanic and mood-stabilizing agents are often necessary (either alone, in combination, or with antidepressaants) for optimal response.

DISCUSSION

Although long recognized, bipolar mixed states remain understudied and incompletely understood. Indeed, there remains debate as to what actually constitutes a mixed state and what mixed states represent. Specifically, investigators have variously speculated that mixed states might represent stage-related or severe forms of mania and depression, transitional states between manic and depressive episodes, as well as affective states distinct from pure mania and pure (retarded) depression. Indeed, different studies suggest that mixed states may be all of these things – in different patients or in the same patient at different times (McElroy *et al.* 1992).

Is mixed mania simply severe mania? In their study documenting three stages of mania, Carlson and Goodwin (1973) prospectively observed that, as manic episodes became more severe over time, they also became more dysphoric. In addition, patients with the most severe (stage III) mania did not differ regarding outcome and lithium response from those with less severe (stage II) mania. The notion that mixed mania is a stage-related form of mania – mania at its peak severity – is further supported by findings that depression, anger, and hostility during mania correlate positively with the overall severity of the manic episode in some studies (Kotin and Goodwin 1972, Post *et al.* 1989). Viewing mixed mania simply as severe mania, however, does not account for two important observations. First,

many studies (Cohen *et al.* 1988, Dell'Osso *et al* 1991, Himmelhoch *et al.* 1976, Prien *et al.* 1988, Secunda *et al* 1987) have found that the presence or degree of depression during mania does not correlate with ratings of overall manic severity. Second, patients have been reported to experience mixed hypomania, or hypomania with prominent depressive symptoms (Akiskal and Mallya 1987, Bauer *et al.* 1994, Nunn 1979), as well as mixed depression, or major depression with hypomanic symptoms (Koukopoulos *et al.* 1992). Thus, although mixed mania may include the most severely ill acutely manic patients, a wide range of severity in manic (as well as depressive) symptoms can be present.

Himmelhoch *et al.* (1976) proposed that mixed states represent patients getting "trapped" in the switch process – the transition from depression to mania or from mania to depression. Indeed, in a study of switches into and out of mania in 75 patients with bipolar disorder, Sitaram *et al.* (1978) found that 35 patients displayed 89 "rapid" switches (occurring in 24 hours or less) whereas 14 patients displayed 27 "slow" switches (occurring over periods of 2–6 days) – suggesting that the switch process can be protracted. This hypothesis is consistent with the continuum model of bipolar disorder (Court 1972), which suggests that mania and depression are pathophysiologically similar but quantitatively different states that exist along a severity continuum where depression represents mild to moderate illness, mania represents severe illness, and mixed states represent intermediate or transitional forms. However, Swann *et al.* (1993) have argued that mixed mania is not simply an intermediate state because the severity of mania in patients with mixed episodes may be less than, equal to, or greater than that of patients with pure manic episodes. Moreover, in their longitudinal study of the switch process, Bunney *et al.* (1972a,b,c) observed the most severe degree of depression during mania in patients with "normal" transitions from depression to mania – after the switch had occurred and the patient had become acutely manic. These findings, combined with observations that patients can experience isolated mixed episodes – either as an initial episode or later in the course of illness without preceding or subsequent mood episodes – support the notion that at least some mixed states are not transitional states. Indeed, Kraepelin distinguished mixed states occurring as "independent attacks" from those occurring as transitional forms. Moreover, Berner's group (1983) has identified stable versus unstable mixed states, and Cassano *et al.* (1983) have distinguished "pure mixed states" in which the "entire episode is one of mixed symptomatology" and which can be chronic, from the "typically short-lived transitional phenomena between manic and retarded depressive states".

It has also been proposed that mixed states represent affective states distinct from pure mania and pure depression. One possibility, suggested by Musalek *et al.* (1987) and consistent with a "tripolar model" of bipolar disorder, is that mixed states represent "a third independent mood quality,

separate from manic and depressive mood changes". If this were the case, mixed states might have a pathophysiology entirely distinct from mania and depression. Alternatively, in a "bipolar model", if the pathophysiological processes causing, mania and depression are truly separate, mixed states might represent these processes occurring simultaneously to varying degrees, perhaps in different regions of the central nervous system (e.g. hypothalamic–pituitary–adrenal-axis cortisol overactivity and limbic system noradrenergic overactivity).

Another possibility is that mixed states represent heterogeneous conditions with numerous aetiologies – reflecting, for example, dual heredities (the inheritance; of two or more illnesses such as bipolar, disorder and a depressive disorder), or the possibility that mania and depression can be modified by secondary factors (e.g. neurological abnormalities or disease, substance abuse or dependence, premorbid temperament, personality disorder, or antidepressant treatment). For example, Akiskal *et al.* (1998) proposed that mixed states occur when mood episodes arise from or are superimposed upon temperaments of opposite polarity (e.g. mixed mania from mania superimposed upon depressive or cyclothymic temperament, and mixed depression from major depression superimposed upon hyperthymic temperament).

Recognizing mixed states as separate from pure manic and depressive states has important clinical and theoretical implications. First, mixed states may be more common than initially appreciated, especially when broadly defined. Second, awareness of their varied presentations would aid in the proper diagnosis and treatment of bipolar disorder. Third, risk factors for the development of mixed states in certain bipolar patients might be identified, such as female sex, family or personal history of depression, premorbid depressive temperament, neuropsychiatric injury or disorder, exposure to antidepressants, alcohol and drug abuse, and young age. Fourth, bipolar disorder with mixed states (especially mixed mania) might display a more malignant course of illness and have a greater risk for suicide and poorer treatment, response (at least to lithium) than bipolar disorder without mixed states.

Regarding theoretical implications, if mixed states prove to be distinct from mania and depression, bidimensional or triangular models might be more appropriate than bipolar or continuum models to explain their occurrence. As reviewed in this chapter, an increasing number of investigators have suggested that mixed states might be better assessed with dimensional along with categorical systems that describe the degree of co-occurring manic and depressive symptoms or "mixity". Indeed, similar to cyclicity, and possibly related to it by representing an extreme form, "mixity" may represent an important dimension or spectrum of bipolar disorder in its own right (Akiskal *et al.* 1998, Bauer *et al.* 1994, McElroy *et al.* 1995). For research, purposes, therefore, dimensional and categorical measures of

depressive symptoms (e.g. MADRS, HRSD, and number of specified depressive symptoms, respectively) in studies of mania, and, by contrast, dimensional and categorical measures of manic symptoms (e.g. YMRS and a number of specified manic symptoms, respectively) in studies of bipolar depression, should be included so that mixed states can be adequately assessed. In addition, operational definitions of mixed states in current psychiatric classification systems will need to be substantially modified to more accurately reflect their true phenomenology. Lastly, theoretical explanations of the pathophysiology of bipolar disorder must account for the existence of mixed states and their distinctions from pure manic and pure depressive states.

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Chapter four

Rapid-cycling bipolar disorder

Joseph R. Calabrese, Daniel J. Rapport,
Robert L. Findling, Melvin D. Shelton
and Susan E. Kimmel

EARLY OBSERVATIONS

Emil Kraepelin first described the phenomenon of frequent cycling in "manic depressive insanity" in 1913 in his landmark textbook (Kraepelin 1913). Although he never used the term "rapid cycling" to describe the course of patients who cycled frequently, he meticulously documented that a significant subgroup of patients with bipolar disorder exhibited episode frequencies in excess of four per year. Through what might be the earliest use of the method of retrospective and prospective life charting, Kraepelin documented episode frequency and duration, but not amplitude (see Figure 1). In his survey of the general course of "manic depressive insanity" he described the "colouring" and frequency of attacks in 899 patients with "manic depressive insanity". Unfortunately, he never reported on the prevalence of rapid cycling in this cohort. These early observations led Kraepelin to conclude that bipolar disorder was accompanied by periodic cycling separated by symptom-free well intervals early in the course of the illness, whereas schizophrenia was more a stable disease marked by few if any remissions as well as a degenerative course. More recently, Dunner and Fieve (1974) first coined the term "rapid cycling" in a landmark paper which summarized longitudinal data designed to evaluate clinical factors associated with lithium prophylaxis failure. Koukopoulos (1980) replicated and extended the findings of Dunner and Fieve in a longitudinal study of the course of 434 patients with bipolar disorder. Both of these early reports suggested for the first time that patients with rapid cycling do not do well on lithium.

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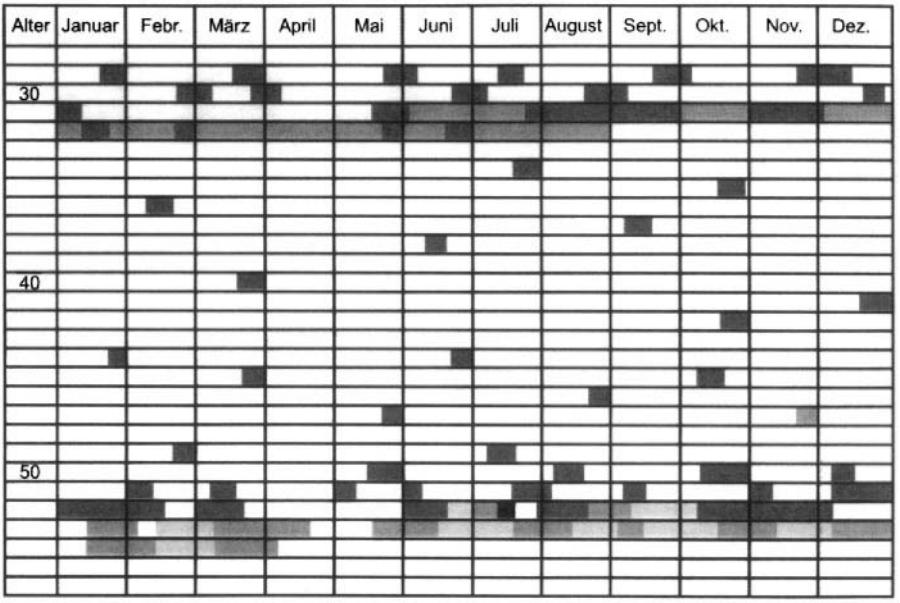

Figure 1 Kraeplin's use of life charting to document rapid cycling.

PHENOMENOLOGY

The definition of rapid cycling most commonly employed describes the phenomenon as being a course modifier and is predicated for the most part on the Dunner and Fieve conceptualization of the phenomenon:

1. Four or more episodes of depression, mania, or hypomania in the previous 12 months.
2. Patients need not have an intervening euthymic interval for a mania and a depression to be counted as two episodes.
3. Numbers of episodes were tabulated, rather than numbers of cycles; for example, two cycles in which manic episodes are biphasically coupled with depressions followed by euthymic intervals would count as four episodes and satisfy criteria for rapid cycling.
4. Episodes are demarcated by a switch to a mood state of opposite polarity or by a period of relative remission lasting 2 months (DSM IV 1994). Therefore, consecutive episodes with the same polarity must be separated by a period of relative remission lasting two months.

Although the original conceptualization of rapid cycling is not reflected in the Research Diagnostic Criteria (RDC) (Feighner *et al.* 1972), it is included as a course specifier in the 4th edition of the *Diagnostic and Statistical Manual of the American Psychiatric Association* (1994), "at least 4 episodes of a mood

disturbance in the previous 12 months that meet criteria for a manic episode, a hypomanic episode, or a major depressive episode". Episodes are demarcated by a switch to a mood state of opposite polarity (e.g. depressive episode to manic episode) or by a full or partial remission lasting at least 2 months. Neither the DSM-IIIR nor RDC required a minimum duration of the interepisode symptom-free euthymic interval before mood episodes could be counted separately. Instead, older nomenclatures defined the minimum duration of the symptomatic period:

DSM-IIIR: depression (14 days), mania (unspecified), and hypomanic(unspecified).
RDC: depression (definite 14 days, probable 7–13 days), mania (7 days), hypomania (definite 7 days, probable 2–6 days).
DSM-IV: depression (14 days), mania (7 days), hypomania (at least 4 days).

Prolonged single episodes accompanied by intermittent fluctuations within the mood state, i.e. cycling above or below baseline, due to changes in medication doses or levels, are counted as one episode. For example, patients who have one long period of mania followed by a short period of hypomania due to the transient use of neuroleptics or benzodiazepines, followed by a return to mania are counted as having only one episode.

The research conducted during the last 25 years of the 20th century appears to have focused on the extensions of Kraepelin's notions about the prognostic relevance of the recurrent nature of bipolar disorder.

DEMOGRAPHICS

The phenomenon of rapid cycling has been most commonly used to refer to frequent cycling in patients with bipolar disorder. However, rapid cycling is believed to exist in patients with recurrent major depression (Arana *et al.* 1989, Tay and Dunner 1992), but with a very low prevalence; Coryell *et al.* noted that only one of 919 patients with various types of major affective disorders exhibited rapid cycling (1992). The prevalence of rapid cycling in general populations of patients with bipolar disorder has been noted to be 13.6 (Maj *et al.* 1994), 18.5% (Coryell *et al.* 1992), 19% (Koukopoulos *et al.* 1980), 20% (Dunner and Fieve 1976), and 24.2% (Tondo *et al.* 1998). It has been reported to be as low as 4.3% in homogeneous populations patients with bipolar I disorder and as high as 31% in bipolar II disorder.

Coryell *et al.* reported on the first large-scale study of the phenomenology of rapid cycling in 1992. They noted that of 919 patients with major affective disorders who completed at least 1 year of a 5-year, semiannual follow-up, 18.5% of 243 bipolar patients developed rapid cycling during the first year but only one patient with a unipolar course did so. Of those rapid cyclers followed for the 5 years ($n = 39$), one met criteria for rapid cycling in all of

the subsequent 4 years, 18% continued to cycle rapidly in the second year but not in the remaining 3 years, and 64% had no rapid cycling after the first year. Rapid cycling bipolar disorder was more commonly observed in females. Family study data revealed no evidence that rapid cycling breeds true. This important study concluded that rapid cycling is transient, non-familial, and predicts a poor prognosis only over the short term. However, this study did not control for or standardize treatment, interviews only took place at 6-month intervals during the 5-year follow-up period, and prospective daily life charting methodology was not employed. During the same year, Shen compared a group of 51 patients with rapid cycling bipolar disorder to 51 patients with non-rapid cycling bipolar disorder (1992). It was noted that the rapid cycling group had more premorbid psychosocial stresses and were more likely to be type II.

As a result of a meta-analysis performed by Bauer and colleagues, the validity of rapid cycling as a course modifier was demonstrated in 1994, and was included in the fourth revision of the DSM in that same year. Validity was supported by observed differences in gender, prospectively assessed outcome and, perhaps, social class between rapid cycling and non-rapid cycling patients. The relationship of gender to episode frequency supports the cutoff of four or more episodes per year.

In the same year, Maj and colleagues (1994) compared 37 patients with rapid cycling bipolar disorder to 74 non-rapid cycling patients. These patients were followed monthly over 2–5 years. Patients with rapid cycling were older, were ill longer, were not over-represented in women, and had no increased frequency of hypothyroidism. Of the patients referred to their centre, they noted a 13.6% prevalence of rapid cycling. Rapid cycling persisted during the prospective study period ($n = 37$), decreasing only to 59% in year 1, 44% in year 2, 44% in year 3, 42% in year 4, and 35% in year 5. This is in marked contrast to the results of the Coryell *et al.* study, which was uncontrolled and not specifically designed to assess the phenomenology of rapid cycling. In the non-rapid cycling control group ($n = 74$), the prevalence of rapid cycling during the five years of follow-up increased overall from 0% at baseline to 8%, 9%, 2%, 4%, and 2%, respectively. The authors concluded that the course specifier of rapid cycling has practical relevance in that it identifies a subgroup of patients with a high recurrence rate. They noted its predictive value might be enhanced by the requirement of pole switching. Since no external validator was found, they concluded it was likely that rapid cycling represented one extreme of a continuum of episode frequency.

Tondo and colleagues have recently performed a meta-analysis of 10 studies to more carefully determine if rapid cycling was more common in 498 women (1998), as was previously suggested by some but not all prior studies. Results were inconclusive, but seemed to suggest that rapid cycling was only moderately more common in bipolar women than men. The

overall prevalence of rapid cycling was 24.2%. Women and men, respectively, represented 71.7% (357/498) and 28.3 (141/498) of rapid cycling cases (a 2.53-fold difference), but rapid cycling occurred in only 29.6% of women and 16.5% of men. This 1.78-fold difference was highly significant when all available data were pooled. However, significant sex differences in the risk of rapid cycling course were found in only six of 10 studies.

It is widely recognized that the age of onset of a mood disorder predicts the probability of relapse (Zis and Goodwin 1979). Patients with an age of onset between 20 and 29 have a 20% probability of relapsing within 24 months; those with onset between 30 and 39 have a 50% chance of relapsing, and those with onset at 50 or older have an 80% chance. Recent data now suggest that age of onset also predicts time to development of rapid cycling. It has been demonstrated that early-onset bipolar disorder (onset before age 26) matures into a pattern of rapid cycling more quickly that late-onset bipolar disorder (26 years or older). These new data suggest that early- and late-onset bipolar disorder are distinct illness subtypes with different courses and responses to treatment. Fujiwara and colleagues (1998), from the Okayama University, recently compared 14 patients with early onset to 21 patients with late onset, and concluded that those with earlier onsets tended to have rapid cycling at an early stage, and a good response to carbamazepine. Those with later onsets tended to have relatively long latency until the appearance of rapid cycling, and a good response to lithium. Antidepressants were more effective in the later-onset group, but tended to induce episode acceleration. Lithium's antimanic properties were better in the late-onset group, but did not maintain a prophylactic effect in either group.

Anecdotal reports suggest that rapid cycling does exist in patients who have their age of onset over the age of 60 years, but large-scale comparative studies have not been carried out (Gnam and Flint 1993, Nakamura and Kinoshita 1994, Camus *et al.* 1997, Schneider and Wilcox 1998).

FAMILY HISTORY/GENETICS

Family studies of rapid cycling bipolar disorder show no difference in family loading for bipolar disorder as compared with non-rapid cycling patients, nor does rapid cycling cluster in families of rapid cyclers. Nurnberg and colleagues (1988) first evaluated the inheritance of rapid cycling. Twenty-nine out of 195 bipolar/episodic schizoaffective patients were judged to be rapid cyclers (15%). The age-corrected risk of major affective disorder was 23.5% in 179 relatives of rapid cyclers and 31% in 189 relatives of matched non-rapid cyclers, suggesting that rapid cycling is not genetic and does not aggregate within families; this was replicated by Coryell and colleagues (1992) and Lish and colleagues (1993). Coryell and colleagues

collected information through family history and family study methods for 268 relatives of 45 rapid cyclers and 1273 relatives of bipolar non-rapid cyclers. More extensive data were obtained for 111 relatives of rapid cyclers and 397 relatives of non-rapid cyclers who were also re-evaluated prospectively and at 6 years after their initial interview. Neither data-sets revealed evidence suggesting that rapid cycling had bred true in their cohort. Lish and colleagues (1993) used the Family History Research Diagnostic Criteria to interview 165 rapid cyclers, non-rapid cyclers, or recurrent unipolar depressive disorder about the psychiatric history of 812 adult first-degree relatives. Rapid cyclers were younger and more likely to be female than non-rapid cyclers, but the relatives of rapid cyclers did not differ significantly from those of non-rapid cyclers in the prevalence of bipolar disorder, unipolar disorder, rapid cycling bipolar, or substance abuse. However, there was a non-significant trend for the relative of rapid cycling bipolar patients, as compared with those of non-rapid cycling patients, to have more substance abuse. These three studies appear to convincingly argue against any specific inheritance of rapid cycling as a discrete course modifier. However, it remains a possibility that early-onset rapid cycling, as opposed to late-onset, might be discretely inherited.

Only very recently have genetic abnormalities begun to be examined in rapid cycling. One anecdotal report has noted the presence of the same chromosomal aberration, a pericentric inversion of chromosome 9, in a bipolar II father and daughter (McCandless *et al.* 1998). The same group of investigators first demonstrated an association between ultradian rapid cycling and low activity of catechol-*O*-methyltransferase, and extended this finding to bipolar patients with either a current or a lifetime history of rapid cycling (Kirov *et al.* 1998). They have hypothesized that variation in the COMT gene modifies episode frequency. Concurrently, Veit and colleagues (1998) presented new data suggesting that catechol-*O*-methyl transferase activity is subject to variability in humans, that this activity is associated with episode frequency, and that low activity is primarily due to a G–A transition at codon 158. Psychiatric patients with psychiatric illness in velo-cardio-facial syndrome were studied, a genetic condition due to a microdeletion of chromosome 22q11, which includes the COMT gene. Of eight patients studied, 100% were found to have $\mathrm{COMT}^{\mathrm{met}}$ polymorphism on the complementary chromosome 22. They hypothesized that since the blockade of catecholamine re-uptake by TCAs and the blocking of breakdown by MAOIs have been associated with the induction of mania, homozygosity for COMT 158^{met} predisposes to rapid cycling, and possibly also represents a risk factor in the use of antidepressants. This study examined the frequency of COMT 158^{met} in 60 rapid cyclers; of the 60 ultra-rapid cyclers enrolled, four had been genotyped at the time of this publication, and all four were homozygous for COMT 158^{met}, the low-activity allele,

supporting the hypothesis that the presence of this allele may alter the course of bipolar disorder.

COMORBIDITY

An extensive literature exists on the presence of thyroid dysfunction in patients with bipolar rapid cycling. Some (Cho *et al.* 1979, Cowdry *et al.* 1983, Bauer *et al.* 1990, Kusalic 1992, McKeon *et al.* 1992) but not most (Joffe *et al.* 1988, Nurnberg *et al.* 1988, Wehr *et al.* 1988, Bartalena *et al.* 1990, Coryell *et al.* 1992, Shen *et al.* 1992, Cole *et al.* 1993, Maj *et al.* 1994, Oomen *et al.* 1996, Post *et al.* 1997) studies suggest that rapid cycling is associated with an underlying thyroid abnormality. Usually (Khouzam *et al.* 1991), the observed abnormality of thyroid dysfunction has been in the direction of decreased end-organ function. Herz first proposed that rhythmic disorders of mood might be caused by the removal of the thyroid gland (Herz 1964). Twenty-two recently thyroidectomized patients were examined for evidence of psychiatric complications in the Frederiksberg Hospital, Copenhagen, Denmark. Ten exhibited post-surgical psychiatric symptoms in the absence of any family psychiatric history. The authors described this as the "endocrine psycho-syndrome" and specifically noted that six patients exhibited temporary attacks of depression soon after the surgery. Cho and colleagues (1979) first demonstrated that the prevalence of lithium-induced hypothyroidism was much higher in rapid cyclers (31%) than in non-rapid cyclers. This was replicated by Cowdry *et al.* (1983), who noted overt hypothyroidism in 50.7% of 24 rapid cyclers and in none of 19 non-rapid cyclers. Elevated TSH levels were present in 92% of the rapid cyclers and 32% of the non-rapid cyclers. Five years later the same group (Wehr *et al.* 1988) refuted their earlier finding, reporting that thyroid dysfunction was no more common in rapid cyclers than in non-rapid cyclers. Bauer and colleagues (1990) have carried out the most thorough examination of thyroid function, reporting a spectrum of thyroid abnormalities in rapid cycling. They have also begun a systematic examination of the potential mood-stabilizing properties of thyroid supplementation, when used in augmentation of conventional mood stabilizers. Of 30 patients with bipolar rapid cycling studied prospectively for the presence of thyroid failure, 23% had grade I hypothyroidism (decreased FTIs with overt signs and symptoms), 27% had grade II (normal FTI, elevated TSH, and a single sign/symptom), and 10% had grade III (everything is normal but an augmented TSH response to TRH). A median and modal frequency of 24 episodes per year with a maximal frequency of two episodes per day suggests that episode counting was done with criteria inconsistent with the DSM IV.

It is clear that there is an increase in the prevalence of alcohol and drug abuse in patients with bipolar disorder (Regier *et al.* 1990). Whether rapid

cyclers have an increased prevalence of alcohol and drug abuse comorbidity compared to non-rapid cyclers has not been explored. Whether patients with bipolar disorder and comorbid alcohol or drug abuse/dependence have an increased prevalence of rapid cycling has likewise not been explored. However, preliminary data suggest that bipolar patients with comorbid alcohol and/or drug abuse/dependence cycle frequently, consistently experiencing twice as many lifetime hospitalizations (Keller *et al.* 1986, Sonne *et al* 1994, Brady *et al.* 1991, Haywood *et al.* 1995).

Other manifestations of comorbidity in rapid-cyclers has not yet been systematically studied. However, anecdotal reports have associated the onset of rapid cycling with neurological events or states such as strokes (Berthier 1992), subarachnoid haemorrhages (Blackwell 1991), and profound mental retardation with periodic aggressive acting-out behaviour (Glue 1989, Lowry and Sovner 1992).

SUICIDE ATTEMPTS AND PROGNOSIS

There are two reports that have evaluated the prevalence of suicide attempts in patients with rapid-cycling bipolar disorder, and both yielded unanticipated findings. Wu and Dunner (1993) carried out a retrospective chart review, in which they compared the prevalence of suicide attempts in rapid cyclers and non-rapid cyclers. One hundred patients with bipolar rapid cycling (33% of whom did not meet DSM-IV minimum duration criteria) were compared to 120 rapid cyclers. No differences were found. In the previously cited study by Coryell and colleagues (1992), 39 rapid cyclers were followed for 5 years and compared to 208 non-rapid cyclers. Only one patient met criteria for rapid cycling in all of the subsequent 4 years, 18% continued to cycle rapidly in the second year but not in the remaining 3 years, and 64% had no rapid cycling after the first year. The negative impact of rapid cycling on clinical outcome did not appear to extend into years 3, 4 or 5, and the number of suicide gestures did not differ between the two groups. In contrast to clinical opinion these two studies suggest that rapid cycling does not result in an increased prevalence of suicide attempts or a worsening of long-term prognosis. This is in contrast to the findings of Okuma (1993), who reported that even a distant lifetime history of rapid cycling worsens long-term prognosis and, in particular, worsens response to treatment with either carbamazepine and/or lithium. Methodological problems complicate the extent to which the findings from these reports can be generalized, as these studies tended to be retrospective, uncontrolled, and typically did not employ life charting methodology to quantify episode frequency.

PHARMACOTHERAPY

Lithium

In an attempt to elucidate predictors of response to lithium in bipolar disorder, Dunner and Fieve carried out a placebo-controlled double-blind maintenance study in a general cohort of 55 patients (Dunner and Fieve 1974); 20% were rapid cyclers and 80% were non-rapid cyclers. Rapid cyclers were disproportionately represented in the lithium failure group. Of the 11 patients with rapid cycling, 82% had failed lithium. Of the 44 non-rapid cyclers, 41% had failed lithium. The criteria for lithium failure were that patients were hospitalized, required treatment for depression or mania, or that mood symptoms as documented by ratings scales were sufficient to warrant a diagnosis of mild depression or hypomania/mania persistent for at least 2 weeks. Koukopoulos replicated and extended the findings of Dunner and Fieve in a study of the longitudinal course of 434 bipolar patients (Koukopoulos *et al.* 1980). Mania was followed by depression 28% of the time, depression followed by mania 25%, circular cycling with less than four episodes per year 19%, and circular cycling with four or more episodes per year in 20%. Of those with more than four episodes per year, there were 61 women and 26 men, and 82% had bipolar II disorder and 18% bipolar I. The depressions were usually severe, whereas the highs were mild to moderate. The durations of the depressions were 2–3 months, and were more prolonged than the hypomanias. In 20 patients the diease took the rapid-cycling course from the very beginning, whereas in the other 67 it started with a course that took 1–40 years to establish rapid cycling. Of the 294 patients who received continuous lithium, 65 were rapid cyclers; 50 of these received lithium for more than 1 year. Prophylaxis was poor in 72%, partial in 12%, and good in only 16%. During depressions, 44 patients received antidepressant drugs. Koukopoulos persuaded 21 of these to endure their depressions without the help of antidepressants, allowing them anxiolytics if absolutely necessary. Of the 21, 71% reached stabilization immediately after the end of the untreated depression or after a few milder and shorter episodes; four improved partially and two stayed unchanged. These early reports indicated that rapid cycling was present in about 20% of patients in a tertiary-care setting, more likely to be seen in females, more common in bipolar II disorder, and associated with lithium non-response.

Maj and colleagues (1998) have also reported on the effect of lithium therapy in patients with rapid-cycling bipolar disorder. A general cohort of 402 patients with bipolar disorder was treated with lithium and prospectively followed over a 5-year period. Eleven per cent were lost to follow-up, 28% had their lithium discontinued, and 38% had at least one recurrence. Of those relapsing, 10% had more than one episode (group C), 29% had more than one episode on lithium but a 50% decrease in days of

hospitalization compared to the prior two years (group B), and 23% no episodes on lithium (group A). Significant differences were observed between these three groups. There were no rapid cyclers in group A, 27% in group B, and 26.3% in group C. In contrast to the Tondo *et al.* study (1998), the study cohort included complex patients with other concomitant psychiatric disorders, alcohol or drug abuse, concomitant physical diseases, and permitted the concomitant use of other psychiatric drugs, including anticonvulsants. The authors concluded that, for patients who actually stay on lithium for several years, there is a drastic reduction of the mean number of days spent in the hospital, but noted that the presence of rapid cycling predicted poor prophylaxis. In addition, they noted that this variable could not be considered a true predictor of lithium failure as it actually predicted a poor outcome independent of treatment. This study did not control for anticonvulsant use, and for this reason the extent to which rapid cycling is a specific predictor of lithium failure remains unclear. Liu and colleagues (1989) then performed a study involving 18 patients with rapid cycling affective disorders who were followed for 1.5–4.5 years. Ten patients in this open study experienced complete remissions and, consistent with the data of Koukopoulos *et al.,* the patients who relapsed into depression responded to lithium, but only after the discontinuation of antidepressant medications.

Tondo and colleagues (1998) have also reported on the effect of lithium therapy in patients with rapid-cycling bipolar disorder. Frequency and duration of affective episodes and hospitalizations in a general cohort of patients with bipolar disorder were compared during the 8.38 years prior to lithium and the 6.35 years on lithium maintenance. Overall, 50% of bipolar patients relapsed in 3 years, 36% relapsed in 12 months, and interepisode duration increased from 8 months to 35 months. Patients with bipolar I disorder exhibited a 50% relapse rate in 17 months and interepisode durations increased from 8 to 17 months. Patients with bipolar II disorder exhibited a 50% relapse rate in 100 months and interepisode durations increased from 8 to 100 months. In the entire cohort of 317 lithium-responders, 15% exhibited rapid cycling. Of the 129 patients with bipolar II disorder, 31% were rapid cyclers as compared to only 4.3% of 188 patients with bipolar I; rapid cycling was 6 times more common in bipolar II disorder. The authors conclude that lithium maintenance yields striking long-term reductions in depressive as well as manic morbidity in both subtypes, with greater overall benefits in type II patients and with earlier treatments. The authors note that those patients who were enrolled and had rapid cycling, responded well to lithium prophylaxis. Of note, however, was the fact that this was a study of long-term outcome in a cohort of lithium-responsive patients. The study excluded patients who had been exposed to antidepressant or antipsychotic drugs for more than 3 months, those receiving long-term anticonvulsant treatment, and those abusing alcohol or drugs.

We believe the extent to which rapid cycling predicts non-response to lithium remains unclear, and that an urgent need exists for controlled studies that can help to clarify this controversial issue. We are currently conducting a series of double-blind, placebo-controlled studies in patients with rapid-cycling bipolar I and II disorder that will compare lithium to divalproex monotherapy, as well as the combination of lithium and divalproex concurrently administered.

Carbamazepine

Early reports by Post and colleagues (1987) suggested that rapid cycling might be a predictor of positive outcome to treatment with carbamazepine. Later findings, including those of Post's laboratory, have been contradictory (Joyce 1988, Okuma 1993, Denicoff *et al.* 1997).

Joyce first reported on the efficacy of carbamazepine in 18 patients with bipolar rapid cycling who underwent an open trial. All but two had failed lithium. Of the 18, 12 stayed on carbamazepine for 6 months. Two had a complete remission on carbamazepine alone, two responded to lithium plus carbamazepine, three had slight improvement, and five had no benefit. The author concluded that, while carbamazepine is effective for some rapid cyclers, the majority need other treatments. Later, Okuma carried out a retrospective study of 215 patients with bipolar disorder who received more than 2 years of treatment with carbamazepine or lithium. It was noted that 78% of non-rapid cyclers experienced moderate to marked improvement with carbamazepine prophylaxis, as compared to only 39% of those with rapid cycling. The same was also true for the lithium-treated group, which showed that 59% of the non-rapid cyclers responded, compared to only 25% of rapid cyclers. More recently, Denicoff and colleagues (1997) have studied 52 outpatients with bipolar disorder employing random assignment to a double-blind design for an intended 1 year of treatment with lithium or carbamazepine, a crossover to the opposite drug in the second year, and then a third year on the combination. *Post-hoc* analyses were carried out on those with rapid cycling, and showed that 56% of those receiving the combination of lithium and carbamazepine experienced moderate to marked improvement, as compared to only 19% for those on carbamazepine and 28% of those on lithium. Four of nine patients who responded to the combination did not respond to either monotherapy, suggesting that efficacy is not simply synergistic. Using a slightly different design, DiConstanzo and Schifano (1991) retrospectively examined outcome after 1, 2, and 5 years for 16 rapid cyclers given lithium alone or the combination of lithium and carbamazepine. The combination of lithium and carbamazepine was more effective than lithium alone. Of note is that none of these studies prospectively evaluated treatment outcome in a homogeneous cohort of rapid cyclers while controlling for treatment.

Valproate

In addition to studies evaluating the acute and prophylactic efficacy of valproate in classic bipolar disorder, there are now data from six published open trials that have assessed the spectrum of efficacy of valproate in 147 rapid cyclers. Forty-six patients were evaluated as part of mixed study populations (Puzynski and Klosiewicz 1984, Emrich *et al.* 1985, Herridge and Pope 1985, Klosiewicz 1985, McElroy *et al.* 1988) and 101 in a study primarily designed to assess the spectrum of efficacy of valproate in rapid-cycling bipolar I and II disorder (Calabrese and Delucchi 1990, Calabrese *et al.* 1993). Overall, 76 were studied with valproate monotherapy and 71 with valproate prescribed in combination with other psychotropic medications.

In the largest of these studies, 101 patients (59% either lithium-resistant or intolerant, 60 women and 41 men; mean $\pm$ SD age, 41.2 $\pm$ 14 years) received valproate in a prospective, naturalistic, open-label, 17.2 month trial (range 8.9–46 months) designed to evaluate the phenomenology of rapid cycling and its spectrum of response to valproate. The data suggested that valproate had marked acute and prophylactic antimanic efficacy, but only poor-to-moderate antidepressant properties. This study was both compromised and advantaged by its open, naturalistic, prospective, uncontrolled, longitudinal design. While not generating controlled-outcome data in one particular cell with formal rating scales, it produced both acute and prophylactic data regarding the management of mania and depression in a very complex, treatment-resistant, chaotic patient population.

A controlled randomized trial was begun in 1995 in an attempt to replicated these open-label findings. This trial has been designed to compare the efficacy of double-blinded lithium monotherapy to valproate monotherapy in a homogeneous cohort of 60 rapid cyclers (NIMH RO1 MH-50165). The primary objective of this study is to test the hypothesis that valproate monotherapy is more effective than lithium monotherapy in the prophylactic outpatient management of hypomania and mania in rapid cycling bipolar disorder. It is a modified random assignment, single-centre, 20-month, double-blind, parallel group comparison of divalproex and lithium. Bipolar type I and II patient subtypes undergo separate random allocation series to each of the two treatment groups. The primary efficacy variable for this study is time to first hypomanic or manic relapse, during maintenance monotherapy as defined by Research Diagnostic Criteria.

A second controlled study has also begun and is designed to compare the efficacy of lithium monotherapy to the combination of lithium plus divalproex in patients who not only have bipolar rapid cycling bipolar disorder, but are also currently abusing or dependent on alcohol, cannabis, and/or cocaine. It is a modified random assignment, 6-month, double-blind, parallel group comparison of lithium monotherapy to the concurrent admin-

istration of lithium and divalproex for the prophylactic outpatient management of hypomania/mania in 30 rapid cyclers with comorbid substance abuse. The primary objective of this study is to test the hypothesis that the combination of lithium plus divalproex is more effective than lithium monotherapy in the prophylactic management of hypomania and mania. The primary efficacy variable for this study is also time to first hypomanic or manic relapse during maintenance therapy. An important dependent variable for this study will be substance use, as measured by the Addiction Severity Index as well as the Time Line Follow Back procedure.

Lamotrigine

A series of open clinical reports evaluating bipolar patients suggest that lamotrigine possesses a broad spectrum of therapeutic activity in this disorder, including use in rapid cycling and mixed states. In 14 clinical reports involving 207 patients with bipolar disorder (66 with rapid cycling), lamotrigine was observed to possess moderate to marked efficacy in depression, hypomania, and mixed states; efficacy in more severe and/or hospitalized mania was unclear. In the largest of these studies the spectrum of activity of lamotrigine was examined in a 48-week, open-label, prospective trial in 75 patients with either bipolar I or II disorder (Calabrese *et al.* 1999a, Bowden *et al.* 1999). Lamotrigine was used as add-on therapy ($n = 60$) or monotherapy ($n = 15$) in patients presenting in depressed, hypomanic, manic, or mixed states. Of the 41 patients presenting depressed, 48% exhibited marked response, and 20% moderate response on the 17-item Hamilton Depression Rating Scale (HAM-D). Of the 31 presenting hypomanic, manic, or mixed, 81% exhibited a marked response and 3% a moderate response on the Mania Rating Scale. The magnitude of overall observed improvement was large, with the depressives exhibiting a 42% decrease from baseline HAM-D scores, and hypomanic/manic/mixed patients a 74% decrease from baseline MRS scores. *Post-hoc* analyses have been conducted on those 41 rapid cyclers and the 34 non-rapid cyclers. Improvement from baseline to last visit was significant among both subgroups for both depressive and manic symptoms. For patients entering the study in a depressive episode, improvement in depressive symptoms was equivalent in the two groups. Among patients entering the study in a manic, mixed, or hypomanic episode, those with rapid cycling improved less in manic symptoms than did non-rapid cycling patients. Among rapid cyclers with initial mild-to-moderate manic symptom severity, improvement was comparable to that in non-rapid cyclers; however, the subset of rapid cyclers with severe initial manic symptoms showed little improvement in mania. These findings suggest the spectrum of efficacy of lamotrigine may complement that of lithium and valproate.

A series of controlled studies has been initiated to evaluate the efficacy and safety of lamotrigine in various phases of bipolar I and II disorder. The first of these studies has been completed. It evaluated the efficacy and safety of two doses of lamotrigine compared with placebo in the treatment of a major depressive episode in patients with bipolar I disorder. Outpatients with bipolar I disorder experiencing a major depressive episode (n = 195) received lamotrigine (50 or 200 mg/day) or placebo as monotherapy for 7 weeks. Lamotrigine was shown to have significant antidepressant efficacy in bipolar I depression, with clinical improvement evident as early as the third week of treatment; switch rates on neither dose of lamotrigine exceeded that of placebo (Calabrese *et al.* 1999b). In addition, a very recent study of lamotrigine has shown this drug to be superior to placebo in the prevention of episodes of depression and hypomania in patients with rapid cycling bipolar disorder when studied over six months (Calabrese *et al.* 2000).

Thyroid supplementation

Stancer and Persad (1982) first reported on the potential efficacy of levothyroxine in patients with rapid-cycling bipolar disorder. In five of seven patients with treatment-refractory bipolar disorder, hypermetabolic doses of levothyroxine produced remissions. Subsequently, Bauer and Whybrow (1990) gave 11 patients with treatment-refractory bipolar rapid cycling open-label augmentation with high-dose levothyroxine. Improvement in depressive symptoms was seen in 10 of 11 patients. Improvement in manic symptoms was observed in five of seven patients who were hypomanic or manic. Four patients underwent double-blind placebo substitution and, of these, three relapsed into either depression or cycling. Treatment did not depend on previous thyroid status and adverse events were minimal.

OTHER MEDICATIONS AND MODALITIES

A series of predominantly open-label preliminary reports have evaluated the efficacy of clozapine (Calabrese *et al.* 1991, 1996, Suppes *et al.* 1994, Frye *et al.* 1996, Novae 1998), risperidone (Jacobsen 1995, Vieta *et al.* 1998, Novae 1998), and olanzapine (Sanger *et al.* 1998) in rapid cyclers. These data suggest this class of antipsychotic medications may have specific mood-stabilizing properties, particularly in the management of mania and mixed states. Nimodipine is the first calcium channel-blocker which has been both anecdotally (Goodnick 1995) and systematically (Passaglia *et al.* 1998) studied in patients with refractory mood disorders. Passaglia and colleagues from the National Institute of Mental Health evaluated the efficacy of nimodipine in 30 patients with treatment-refractory affective illness,

employing a placebo/nimodipine/placebo crossover design. Ten patients showed a moderate to marked response to double-blinded nimodipine monotherapy and those who did well had ultradian rapid cycling. In two reports, totalling 23 patients, electroconvulsive therapy has been used to acutely treat rapid cycling (Berman and Wolpert 1987) as well as a maintenance therapy (Vanelle *et al.* 1994). In the latter report, 22 patients with treatment-refractory unipolar and bipolar disorders experienced moderate to marked response from maintenance electroconvulsive therapy administered over 18 months. Bipolar rapid cycling and delusional depression appeared to be predictors of positive response.

Wehr and Goodwin (1979) first demonstrated that maintenance use of the tricyclic antidepressants (TCA) induced an acceleration of episode frequency in five female rapid cyclers. A shortening of cycle duration (total number of days in each consecutive pair of manic and depressive phase) was demonstrated by use of a crossover design (placebo > TCA > placebo > TCA) while continuing all other medications. Cycle lengths on TCA, 33 ± 14 days, were about one-fourth of those on placebo, 127 ± 50 days. Every cycle length without TCAs was more than four standard deviations greater than those with TCA. Consistent with the above data, Koukopoulos and colleagues (1980) have recommended that the discontinuation of TCAs be considered early in the treatment of rapid-cycling bipolar disorder. Later, Wehr and colleagues (1988) studied 51 patients with rapid cycling affective disorders and observed that the rapid cycling was associated with the continuation of antidepressant medication in 51%.

Tondo and colleagues (1990) have recently observed that patients with spontaneous rapid cycling relapse more quickly than those with antidepressant-induced rapid cycling after the discontinuation of lithium. This finding suggests that subjects with spontaneous rapid cycling before lithium tend to return to that course after the discontinuation of lithium, while those with an induced rapid cycling course tend to return to the course displayed prior to induction. The authors concluded that antidepressants do increase the frequency of affective episodes and do induce rapid cycling. More recently, Altshuler and colleagues (1995) have applied life charting methodology to the study of antidepressant-induced mania and episode acceleration in 51 patients with treatment-refractory bipolar disorder. Their data suggest that one-third of patients with treatment-refractory bipolar disorder experience antidepressant-induced mania, that 25% experience antidepressant-induced cycle acceleration, and that antidepressant-induced mania may be a marker for increased vulnerability to antidepressant-induced cycle acceleration. Antidepressant-induced cycle acceleration (but not antidepressant-induced mania) appeared to be associated with a younger age at first treatment and more likely to occur in women with bipolar II disorder.

Rapid-cycling bipolar disorder has also been noted to respond to treatment with clorgyline (Potter *et al.* 1982), clonidine (Alary and Andersson

1988), sleep deprivation (Benjamin and Zohar 1992), primidone (Brown *et al.* 1993), acetazolamide (Hayes 1994), choline bitartrate (Stoll *et al.* 1996), and topiramate (Marcotte 1998). Studies have recently been published that begin to evaluate the role of behavioural interventions as adjuncts to pharmacotherapy in the treatment of patients with rapid-cycling bipolar disorder. A cohort of 15 rapid-cycling outpatients were studied prospectively for 3 months at the National Institute of Mental Health to determine if behavioural interventions affected the diurnal rhythm associated with switching (cycling from hypomania to depression, or depression to hypomania). Feldam-Naim and colleagues (1997) determined that patients were more likely to switch from depression into mania/hypomania during daytime and from mania/hypomania into depression during nighttime. They concluded that the use of light or activity during depression, and the use of induced-sleep or exposure to darkness during mania/hypomania might be therapeutic. This initial hypothesis was confirmed by Wehr and colleagues (1998) in a case study of one patient who was studied over several years. Using the patient's regular sleep routine as a baseline, the subject was then asked to remain at bed rest in the dark for long periods (10–14 hours each night). Twice-daily self ratings, once-weekly observer ratings, and wrist activity monitoring were used to assess mood. His rapid cycling stabilized during the long nightly periods of enforced bed rest in the dark. The authors conclude that fostering sleep by scheduling regular nightly periods of enforced bed rest in the dark may help to prevent mania and stabilize mood in patients with rapid cycling.

RAPID-CYCLING BIPOLAR DISORDER IN CHILDREN AND ADOLESCENTS

Prototypic forms of adult bipolar disorder (those that are characterized by distinct, prolonged mood states and inter-episodic periods of euthymia) have been described in children and adolescents for decades. However, in recent years there has been a growing interest in the atypical presentations in this age group. Biederman and colleagues have described cohorts of severely impaired children who meet cross-sectional symptom criteria for mania. These children and adolescents appear to have chronic presentations accompanied by irritability, dysphoria, and symptoms suggestive of attention deficit disorder (Biederman *et al.* 1995, Geller *et al.* 1995). Although these children are believed to meet criteria for bipolar disorder, they frequently do not present with periods of elation or euphoria and may not have distinct, sustained, periodic mood episodes. Geller and colleagues (1995) have also suggested that patients who develop bipolar disorder during childhood and adolescence have a different course from the prototypic one seen in adults. These investigators have hypothesized that children

and adolescents with bipolar disorder frequently present with mixed states, dysphoric manias or hypomanias, chronic and continuous cycling, hyperactivity, and brief episodes not always meeting minimum duration criteria.

The prevalence of rapid cycling in children and adolescents has not been systematically determined, but reports have ranged from 6% to 80% (Carlson 1998). We have recently begun a 12-month, double-blind, controlled trial designed to compare the maintenance efficacy of lithium to divalproex in children and adolescents who meet DSM-IV criteria for bipolar I disorder documented through a semi-structured diagnostic interview in addition to a clinical assessment performed by a child psychiatrist. Of 24 patients (mean age, 11.2 years, range, 5–17) enrolled, the prevalence of rapid cycling meeting DSM-IV criteria is 67% (Findling and Calabrese, unpublished data).

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Chapter five

Bipolar schizoaffective disorders

Andreas Marneros, Arno Deister and Anke Rohde

POLYMORPHISM AND BIPOLARITY IN SCHIZOAFFECTIVE DISORDERS

One of the most important questions since the very beginning of scientific psychiatry is: What kind of illness should be diagnosed in a patient having first a schizophrenic episode but some months later a depressive episode, or a manic episode followed by a schizodepressive or a schizomanic episode? As early as in 1863, Karl Kahlbaum integrated the longitudinal polymorphous psychotic disorders into one type, i.e. "vesania typica circularis". According to Kahlbaum not only the cross-sectional psychopathological symptomatology is important for the diagnosis, but also the longitudinal aspect. Almost 100 years later Kurt Schneider demanded, for the diagnosis of schizoaffective disorders (according to his nomenclature the "cases-in-between"), not only the concurrent occurrence of schizophrenic and affective symptomatology but also the longitudinal changes from schizophrenic to affective episodes and vice-versa (Schneider 1950, Marneros 1989a,c, 1999, Marneros *et al.* 1986, 1991). Some modern authors, however, speak of a "false diagnosis" when one kind of episode is followed by another (e.g. Horgan 1981, Mukherjee *et al.* 1983). Based on our longitudinal findings we define two types of schizoaffective disorders:

(a) *"Concurrent",* characterized by the coincidence of schizophrenic and affective episodes.
(b) *"Sequential",* characterized by the longitudinal change from schizophrenic to affective episodes and vice-versa (Marneros *et al.* 1986, 1988c, 1989a, 1991).

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 111–125.

The longitudinal investigation of *monomorphous* (having, during a long period of time, only the same type of episode) and *polymorphous* (having various types of episodes) schizoaffective disorders over a period of 25 years in the Cologne Study showed the following results:

1. The majority of schizoaffective disorders (70.3%) were polymorphous (Marneros *et al.* 1988a,b,c, 1989a,b,c, 1991), i.e. during the course more than one type of episode occurred: schizophrenic, schizodepressive, schizomanic, manic, depressive and mixed). Less than one-third of the patients (29.7%) had a monomorphous course, with only one type of episode during the whole course.
2. Independently of the type of the initial episode, all other types of schizophrenic, schizodepressive, schizomanic, schizoaffective mixed and all types of affective episodes may occur.
3. In the majority of polymorphous schizoaffective disorders the first change occurred as early as the second episode (63.4%).
4. In patients with polymorphous schizoaffective disorders the first change occurred on average 7.5 years after the first manifestation; in 72% of cases within the first 5 years.
5. Comparison between monomorphous and polymorphous schizoaffective disorders showed no significant differences in relevant sociodemographic premorbid features or features regarding course, patterns and outcome.

A special group within the polymorphous schizoaffective disorders is formed by patients having a change from depressive (or schizodepressive) into manic (or schizomanic) or mixed symptomatology and vice-versa: *the bipolar schizoaffective disorders.*

In the 1980s the question arose of whether schizoaffective disorders can be dichotomized into unipolar and bipolar disorders, in the same way as affective disorders. This question has been answered with a clear "yes". It has been found that the differences between unipolar and bipolar schizoaffective disorders are similar to those between unipolar and bipolar affective disorders (Marneros 1989d,e, 1999, Marneros *et al.* 1990c,d,e, 1991).

The simple categorization of the schizoaffective disorders into schizodepression and schizomania according to cross-sectional criteria has proved inadequate and insufficient both for clinical and for research purposes. Comparative studies of cross-sectionally diagnosed schizodepression and schizomania therefore have only limited value. By classifying the schizoaffective disorders into unipolar and bipolar types, however, we take some longitudinal features into account.

Based on the findings of the Cologne Study in which the longitudinal course and outcome (follow-up for more than 25 years) of 101 schizoaffective, 106 affective and 148 schizophrenic patients were compared (Marneros *et al.* 1986, 1988a,b,c, 1990a,b,c, 1991, 1995, Marneros and Tsuang 1986, 1990), we will attempt to answer three questions:

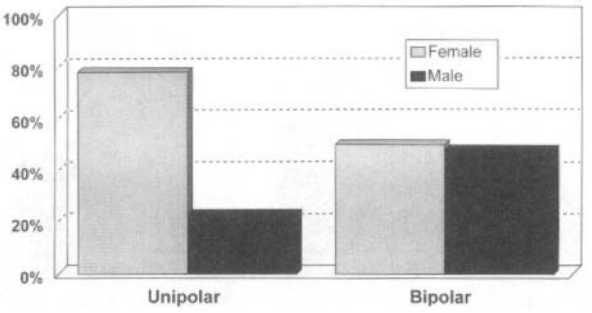

Figure 1 Schizoaffective disorders: sex distribution ($n = 72$).

1. What are the differences between unipolar and bipolar schizoaffective disorders?
2. Are there any similarities between unipolar affective and unipolar schizoaffective or between bipolar affective and bipolar schizoaffective disorders?
3. What are the unipolar and bipolar schizoaffective disorders?

DIFFERENCES BETWEEN UNIPOLAR AND BIPOLAR SCHIZOAFFECTIVE DISORDERS

Differences in sociodemographic and premorbid features

Sex distribution

In the group of unipolar schizoaffective disorders females are significantly more frequent than males, whereas in the group of bipolar schizoaffective disorders the distribution of the two genders is almost equal (Figure 1).

Educational level

The educational level is higher in patients with bipolar schizoaffective disorders than in those with unipolar schizoaffective disorders. As a consequence, a higher occupational status is more frequently represented in the group of bipolar patients.

Premorbid personality

In the group of unipolar schizoaffective disorders an accumulation of personalities with obsessoid, asthenic and low self-confidence traits can be observed. In the group of the bipolar schizoaffective disorders, personalities with sthenic features and high self-confidence are more frequent. No significant differences between unipolar and bipolar schizoaffective patients

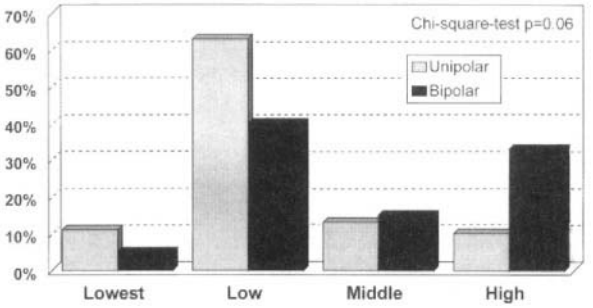

Figure 2 Schizoaffective disorders: educational level ($n = 72$).

Table 1 Schizoaffective disorders: premorbid personality

	Unipolar (n = 36)	*Bipolar* (n = 33)	*Total* (n = 69)	*p*
Obsessoid	39%	15%	28%	0.008**[a]
Sthenic/high-self-confident	14%	46%	29%	
Asthenic/low-self-confident	47%	39%	44%	

**$p < 0.01$; [a]chi-square test.

could be found with regard to the following sociobiographic variables: broken home, life events, stable heterosexual partnership before onset, social contacts, family history of mental disorders. However, bipolar schizoaffective patients became ill earlier than unipolar schizoaffective patients.

Differences in longitudinal course

We found that the course of bipolar schizoaffective disorders differs significantly from that of unipolar schizoaffective disorders. Patients with bipolar schizoaffective disorders have significantly more episodes, a higher annual frequency of episodes, more cycles and a higher annual frequency of cycles than unipolar schizoaffective disorders. Therefore, the polyphasic course of bipolar schizoaffective disorders is the most frequent type of course (see Figure 3). The cycles in bipolar schizoaffective disorders are usually shorter than in unipolar schizoaffective disorders (see Figure 4).

Regarding long-term outcome we could find no relevant differences between unipolar and bipolar schizoaffective disorders.

We assessed the long-term outcome with various instruments: for instance GAS (Global Assessment Schedule), DAS (Disability Assessment Schedule from the WHO), PIRS (Psychological Impairment Rating Scale, also from the WHO) and others. We found no significant differences. Obviously,

Table 2 Schizoaffective disorders: course I

	Unipolar (n = 36)	*Bipolar* (n = 33)	*p*
Number of episodes			
Median	3	6	0.007**[a]
Arithmetic mean	4.33+	6.88+	
Geometric mean	3.36+	5.46+	
Standard deviation	3.41+	4.36+	
Minimum value	1	1	
Maximum value	16	18	
Arithmetic mean of logarithmically transformed values	1.213+	1.670+	
Annual frequency of episodes			
Median	0.12+	0.28+	0.000**[a]
Arithmetic mean	0.16+	0.35+	
Geometric mean	0.13+	0.26+	
Standard deviation	0.11+	0.27+	
Minimum value	0.03+	0.03+	
Maximum value	0.48+	1.42+	
Arithmetic mean of logarithmically transformed values	−2.044+	−1.354+	

**$p < 0.01$; [a]*t*-test; [b]Mann–Whitney *U*-test.

however, the long-term outcome is dependent on the number and frequency of episodes: the more frequent the episodes, the more unfavourable the long-term outcome. Usually patients with bipolar schizoaffective disorders relapse more frequently than unipolars, have more episodes and then perhaps a more unfavourable outcome. However, this seems to be a function not of the bipolarity but of the number of episodes.

SIMILARITIES AND DIFFERENCES BETWEEN UNIPOLAR AFFECTIVE AND UNIPOLAR SCHIZOAFFECTIVE DISORDERS AND BETWEEN BIPOLAR AFFECTIVE AND BIPOLAR SCHIZOAFFECTFVE DISORDERS

With regard to *sociodemographic data,* differences exist between unipolar and bipolar affective disorders in sex distribution, age at onset and premorbid personality (Marneros *et al.* 1990c,d,e, 1991, Marneros 1999). However, we found exactly the same differences between the unipolar and bipolar schizoaffective disorders (Marneros *et al.* 1991).

With regard to *long-term course,* unipolar and bipolar affective disorders differ in number of episodes, annual frequency of episodes, number of

Table 3 Schizoaffective disorders: course II

	Unipolar (n = 36)	*Bipolar* (n = 33)	*p*
Number of cycles			
Mean	2	6	0.002**[a]
Arithmetic mean	3.87+	6.44+	
Geometric mean	2.89+	5.18+	
Standard deviation	3.38+	4.15+	
Minimum value	1	1	
Maximum value	15	17	
Arithmetic mean of logarithmically transformed values	1.062+	1.645+	
Annual frequency of cycles			
Mean	0.25+	0.48+	0.011*[a]
Arithmetic mean	0.34+	0.51+	
Geometric mean	0.23+	0.40+	
Standard deviation	0.32+	0.33+	
Minimum value	0.05+	0.09+	
Maximum value	1.33+	1.33+	
Arithmetic mean of logarithmically transformed values	−1.467+	−0.924+	

*$p < 0.05$; **$p < 0.01$; [a]*t*-test; [b]Mann–Whitney *U*-test.

cycles, annual frequency of cycles and average cycle length. Exactly the same differences exist between the unipolar and bipolar schizoaffective disorders. We could find no differences, however, concerning *long-term outcome,* neither between unipolar and bipolar affective disorders nor between unipolar and bipolar schizoaffective disorders (if we consider only the same number of episodes).

Comparison of *bipolar affective* and *bipolar schizoaffective disorders* showed no differences in any important sociodemographic and premorbid features (Marneros *et al.* 1991) (see Table 5). As Table 6 shows, there were also no differences in any essential aspects of the long-term course. Differences concerning the long-term outcome were found (Table 7), however, in that the affective type of bipolar disorders shows a more favourable outcome than the schizoaffective bipolar disorders. The same difference was found between unipolar affective and unipolar schizoaffective disorders (Marneros *et al.* 1991).

There are no differences between the two groups concerning sociodemographic and premorbid features and no differences in the long-term course. Yet there are differences in long-term outcome: unipolar affective disorders have a more favourable outcome than unipolar schizoaffective disorders.

Table 4 Schizoaffective disorders: length of cycles and episodes (months)

	Unipolar (n = *31*)	*Bipolar* (n = *32*)	*p**
Average cycle length (months)			
Mean	45.50+	26.07+	0.033*[a]
Arithmetic mean	74.07+	40.21+	
Geometric mean	35.59+	22.52+	
Standard deviation	62.15	33.49	
Minimum value	9.58+	8.25+	
Maximum value	227.75+	136.00+	
Arithmetic mean of logarithmically transformed values	3.572+	3.115+	
Average length of episodes per patient (months)			
Mean	2.42+	1.75+	0.084[a]
Arithmetic mean	2.77+	2.09+	
Geometric mean	1.89+	1.47+	
Standard deviation	2.18+	1.34+	
Minimum value	0.72+	0.37+	
Maximum value	12.00+	7.30+	
Arithmetic mean of logarithmically transformed values	0.638+	0.385+	

*$p < 0.05$; [a]*t*-test.

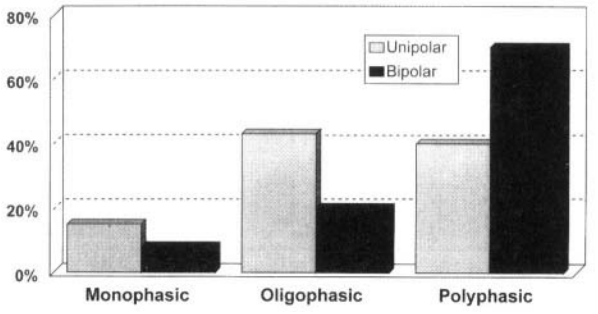

Figure 3 Schizoaffective disorders: course ($n = 72$).

WHAT ARE THE UNIPOLAR AND BIPOLAR SCHIZOAFFECTIVE DISORDERS?

Our data revealed evidence that not only the presence of schizomanic or mixed schizomanic-depressive episodes qualifies for the diagnosis of a bipolar schizoaffective disorder. Our data support the assumption that, in addition to the concurrent type of schizoaffective disorders, a sequential

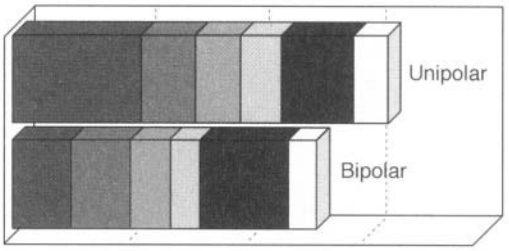

Figure 4 Schizoaffective disorders: length of cycle ($n = 72$).

type exists, characterized by longitudinal changes between schizophrenic and affective episodes.

Of course some of us believe there is a kind of comorbidity between schizophrenia and mania, or between schizophrenia and major depression. We realize that the concept of comorbidity is convenient to answer all difficult questions of psychiatry; in this case, however, the concept has to be supported by operational data. However, our data showed no difference between the concurrent and sequential types of schizoaffective disorders – on any possible level.

It may be true, then, that human beings as well as mental disorders are not a "one-day butterfly" or a "one-night butterfly" but a continuity. Perhaps we cannot explain everything with the facile answer of comorbidity, but perhaps some questions can be answered, at least partially, with reference to continuity and longitudinality.

BIPOLAR SCHIZOAFFECTIVE DISORDER: PRESENT STATE AND FUTURE

Recent research has confirmed former assumptions that schizoaffective disorders occupy a position between affective and schizophrenic disorders regarding relevant sociodemographic and premorbid features as well as patterns of course, outcome, treatment response and prophylaxis (Angst 1986c, 1989, Angst *et al.* 1980, Deister *et al.* 1990, Marneros *et al.* 1988a-c, 1989a-f, 1991, Maj 1985, Maj and Perris 1985; see also various contributions in Marneros 1989a and in Marneros and Tsuang 1986, 1990 as well as Marneros *et al.* 1995).

It seems certain that schizoaffective disorders are not identical with schizophrenic disorders, although in some individual cases the schizodominance is clear. It can also be said that there are some significant differences between schizoaffective and affective disorders in spite of strong similarities (contributions in Marneros and Tsuang 1990 and Marneros 1999).

It also seems certain that unipolar affective disorders differ significantly from bipolar affective ones, especially with regard to some relevant socio-

Table 5 Premorbid and sociodemographic data (Marneros *et al.* 1990c)

	Schizoaffective bipolar (n = *56*)	*Affective bipolar* (n = *30*)	
Educational level			$p = 0.456^a$
Lowest level	3.6%	0.0%	
Low level	42.9%	50.0%	
Middle level	19.6%	10.0%	
High level	33.9%	40.0%	
Occupation at onset of illness			$p = 0.471^a$
Unemployed	1.8%	3.3%	
Housewife	19.6%	23.3%	
Unskilled worker	10.7%	10.0%	
Skilled worker	14.3%	3.3%	
White collar worker	17.9%	33.3%	
Top white collar worker	14.3%	6.7%	
In training	21.4%	20.0%	
Stable heterosexual partnership before onset (>6 months)			
Total	64.3%	66.7%	$p = 0.825^a$
Patients older than 25 years	93.8%	76.2%	$p = 0.152^a$
Female patients >25 years	87.5%	78.6%	$p = 0.870^a$
Male patients >25 years	100.0%	71.4%	$p = 0.152^a$
Married at onset			
Total	53.6%	56.7%	$p = 0.783^a$
Patients older than 25 years	81.3%	61.9%	$p = 0.118^a$
Female patients >25 years	75.0%	57.1%	$p = 0.301^a$
Male patients >25 years	87.5%	71.4%	$p = 0.349^a$
Premorbid personality (global categories)			$p = 0.089^a$
Obsessoid (typus melancholicus)	15.1%	26.7%	
Asthenic/low self-confidence	47.2%	23.3%	
Sthenic/high self-confidence	37.7%	50.0%	
Premorbid social interactions			$p = 0.093^a$
Tendency to isolation	26.8%	44.8%	
No tendency to isolation	73.2%	55.2%	
Mental illness in the family	66.1%	63.3%	$p = 0.800^a$
Broken home situation	39.3%	26.7%	$p = 0.242^a$
Life events			
Before first episode	50.0%	46.7%	$p = 0.786^a$
At least once during course	85.7%	80.0%	$p = 0.706^a$
Episodes with life events	28.8%	33.5%	$p = 0.246^a$
Season of birth			$p = 0.770^a$
Spring (March to May)	21.4%	30.0%	
Summer (June to August)	21.4%	23.3%	
Autumn (September to November)	21.4%	20.0%	
Winter (December to February)	35.7%	26.7%	

[a]Chi-square test.

Table 6 Long-term outcome and social consequences of the illness (Marneros *et al.* 1990c)

	Schizoaffective bipolar (n = 56)	*Affective bipolar* (n = 30)	
Global Assessment Scale			$p = 0.391$[a]
No difficulties (score 91–100)	46.4%	66.7%	
Slight difficulties (score 71–90)	14.3%	10.0%	
Moderate difficulties (score 51–70)	19.6%	13.3%	
Severe difficulties (score 31–50)	14.3%	10.0%	
Very severe difficulties (score 0–30)	5.4%	0.0%	
Arithmetic mean	75.2	85.1	$p = 0.069$[b]
Median	82.5	95.0	$p = 0.128$[c]
Standard deviation	25.4	20.5	
Disability Assessment Schedule			$p = 0.008$[a]
Excellent adjustment (score 0)	48.2%	66.7%	
Very good adjustment (score 1)	14.3%	13.3%	
Good adjustment (score 2)	30.4%	3.3%	
Fair adjustment (score 3)	0.0%	10.0%	
Poor adjustment (score 4)	7.1%	6.7%	
Very poor adjustment (score 5)	0.0%	0.0%	
Living situation at end of observation time	(n = 50)	(n = 26)	$p = 0.053$[a]
Mental illness without impact on autarky	72.0%	88.5%	
Mental illness with impact on autarky	28.0%	7.7%	
Permanently hospitalized	0.0%	3.8%	
Downward occupational drift (without housewives)	(n = 38)	(n = 24)	
	52.6%	29.2%	$p = 0.070$[a]
Downward social drift (without housewives)	(n = 38)	(n = 21)	
	26.3%	28.6%	$p = 0.852$[a]
Premature retirement (because of mental illness)	(n = 38)	(n = 24)	
	31.6%	25.0%	$p = 0.578$[a]
Achievement of the expected social development	(n = 56)	(n = 30)	
	64.3%	76.7%	$p = 0.238$[a]

[a]Chi-square test; [b]*t*-test; [c]Mann–Whitney *U*-test.

demographic and premorbid data and some patterns of course (Angst 1978, 1980a, b, 1986a,b, Angst *et al.* 1973, Rohde *et al.* 1990, Winokur and Clayton 1967, Goodwin and Jamison 1990, Paykel 1992, Marneros 1999). Differences very similar to those between affective unipolar and affective bipolar patients were found between bipolar and unipolar schizoaffective patients

Table 7 Parameters of course (Marneros *et al.* 1990c)

	Schizoaffective bipolar (n = 56)	*Affective bipolar (n = 30)*	
Polyphasic course	75.0%	66.7%	$p = 0.411$[a]
Prodromal symptoms (>6 months)	14.3%	13.3%	$p = 0.838$[a]
Annual frequency of episodes			
Geometric mean	0.26	0.23	$p = 0.451$[d]
Median	0.30	0.21	$p = 0.214$[c]
Standard deviation	0.24	0.16	
Minimum value	0.03	0.10	
Maximum value	1.40	0.70	
Number of cycles			
Number of patients	52	29	
Geometric mean	5.2	3.8	$p = 0.056$[d]
Median	6.0	4.0	$p = 0.062$[c]
Standard deviation	4.3	3.6	
Minimum value	1	1	
Maximum value	18	15	
Annual frequency of cycles			
Number of patients	52	29	
Geometric mean	0.40	0.41	$p = 0.948$[d]
Median	0.47	0.38	$p = 0.965$[c]
Standard deviation	0.30	0.48	
Minimum value	0.07	0.10	
Maximum value	1.33	1.54	
Average length of episode (months)			
Geometric mean	1.5	1.9	$p = 0.106$[d]
Median	2.0	2.1	$p = 0.121$[c]
Standard deviation	1.2	1.6	
Minimum value	0.38	0.62	
Maximum value	7.3	8.4	
Average cycle length (months)			
Number of patients	52	29	
Geometric mean	21.3	19.3	$p = 0.563$[d]
Median	26.6	31.8	$p = 0.890$[c]
Standard deviation	33.6	34.1	
Minimum value	8.3	7.8	
Maximum value	164.3	119.8	
Activity of illness (years)			
Arithmetic mean	15.7	15.3	$p = 0.784$[b]
Median	14.5	14.0	$p = 0.784$[c]
Standard deviation	10.9	11.7	
Minimum value	0.0	1.0	
Maximum value	43.0	47.0	
Inactivity of illness (years)			
Number of patients	39	19	
Arithmetic mean	11.7	12.3	$p = 0.775$[b]
Median	10.0	10.0	$p = 0.485$[c]
Standard deviation	7.9	6.4	

[a]Chi-square test; [b]*t*-test; [c]Mann–Whitney *U*-test; [d]*t*-test (log-values).

(Angst 1986c, 1989, Dunner 1980, Perris 1982, Marneros *el al.* 1989a-c, 1991, 1999, Winokur *et al.* 1986, 1990).

It seems that even after creating two voluminous groups of unipolar and bipolar diseases, each including both affective and schizoaffective disorders, the main differences and similarities between unipolar and bipolar types remain unchanged (Marneros *et al.* 1990c,d,e, 1991, Marneros 1999). This finding gives further support to the assumption of the two distinct entities, namely unipolar and bipolar diseases, which, however, are phenomenologically and prognostically inhomogeneous.

Future research must isolate more precisely the reasons for the inhomogeneity of schizoaffective disorders, and discover whether the proportion of schizodominant cases in a sample could be responsible for the differences found between unipolar affective and unipolar schizoaffective disorders, on the one hand, and between bipolar affective and bipolar schizoaffective disorders, on the other. Perhaps, after excluding a schizodominant group, affective and schizoaffective disorders could be classified as two subtypes of a ″unipolar disorder″ or a ″bipolar disorder″. It remains to be investigated whether a schizodominant type of schizoaffective disorders represents a bridge between schizophrenia and bipolar and unipolar diseases (Angst 1986c, Kendell 1986, Marneros 1995). But ″schizodominance″ has to be defined precisely; this problem remains unsolved. As long as inhomogeneity exists, and the reasons for it are unclear, it is difficult to define a voluminous diagnostic category.

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Chapter six

Bipolar disorders during pregnancy, post partum and in menopause

Anke Rohde and Andreas Marneros

INTRODUCTION

It is well known that hormonal changes can result in changes of mood as well as several other psychic functions. Pregnancy, the post-partum period and menopause are associated with hormonal changes which occur frequently in women and seem to trigger the danger of psychic instability in different ways.

PREGNANCY

Because the first manifestation of bipolar illness during pregnancy is a rare occurrence, the literature on that topic is quite limited. However, a ″protective″ effect of hormonal changes associated with pregnancy has been discussed (Oates 1986). When bipolar disorders do occur in pregnancy, they usually constitute a relapse of a preexisting bipolar disorder, often following a discontinuation of prophylactic medication because of the pregnancy. Studies show that even with a history of bipolar affective illness, a relapse of the illness tends not to occur during pregnancy (Marks *et al.* 1992, McNeil *et al.* 1984) and the frequency of hospitalization is particularly low during pregnancy in patients with manic depressive illness (Lier *et al.* 1989). There are also case reports which show that patients with severe bipolar illness improved significantly during pregnancy (Sharma and Persad 1995).

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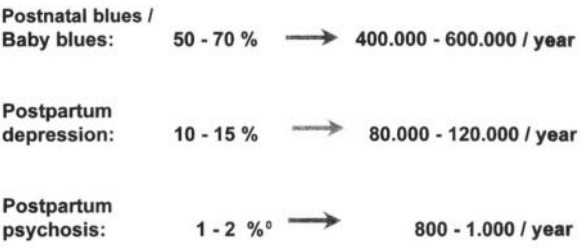

Figure 1 Frequency of post-partum disorders (approximately 800 000 deliveries/ year in Germany).

POST-PARTUM PERIOD AND PSYCHIATRIC DISORDERS

In contrast to pregnancy, the post-partum period seems to be a time of special vulnerability for the onset of psychiatric illness. Before the frequency of bipolar disorders in the post-partum period is discussed we define the three most important psychiatric post-partum disturbances:

1. The most frequently reported disturbance (found in 50–70% of all deliveries) is the *postnatal blues* or baby blues which occur between the third and fifth day after delivery. The main symptoms are affective lability, irritability and sleep disorders. Baby blues can be classified as a "physiological" consequence of the very abrupt hormonal changes after delivery. Treatment is not necessary.
2. *Post-partum depression* ranging from very mild respectively minor depression to major depression with psychotic symptoms, is more frequently reported (found in approximately 10–15% of all deliveries) and, in most cases, occurs within the first weeks or months after delivery.
3. *Post-partum psychosis* starts in the majority of cases within the first 2 weeks post partum in approximately one or two of every 1000 deliveries (Brockington and Cox-Roper 1988, Gitlin and Pasnau 1989, Kendell *et al.* 1987, Kumar 1994). Most bipolar disorders post partum belong to this last category.

When the frequency of these different types of disorders is calculated on the basis of approximately 800 000 deliveries per year in Germany, it becomes clear that compared to post-partum depression, post-partum psychosis is only a "minor" problem with regard to the total number of cases (see Figure 1).

Especially in regard to post-partum depression, it is well established that, in the majority of cases, psychological and social factors (for example, personality, role expectations, etc.), as well as hormonal factors play an important role. Here, especially, the interaction between oestrogen and the serotonin system is discussed. In contrast, hormonal changes (e.g. the major

decrease of oestrogen and progesterone after delivery) seem to play the most important role in bipolar disorders resp. post-partum psychoses. Here, the question of hypersensitivity of dopamine receptors is one of the targets of studies in that field (Wieck *et al.* 1991). Nevertheless, that psychological aspects may also have some influence can be shown by the fact that also "bipolar fathers" also have relapses of illness when their wives become pregnant and have children (Davenport 1982).

It is currently believed that affective disorders and post-partum psychoses have a multifactorial aetiology, and hormonal changes are only one of these factors. Also important are, among others, genetic disposition, sociobiographical parameters and psychological stress.

Psychiatric admissions after delivery

Kendell *et al.* (1987) carried out an epidemiological study by calculating the frequency of psychiatric admission using an obstetric register and a psychiatric register. It was discovered that for women with a history of manic depressive illness, manic or depressive, the risk of psychiatric admission in the puerperium was much higher than for those women with a history of schizophrenia or depressive neurosis. Within the first 30 days after childbirth the risk for psychiatric admissions was found to be 21.4% for women with bipolar manic-depressive illness and 13.3% for women with unipolar affective disorder. The risk for schizophrenia was calculated at 3.4% and the risk for "depressive neurosis" was calculated at 1.9%. Linking the Danish Medical Birth Register and the Danish Psychiatric Central Register, Terp and Mortensen (1998) found that although childbirth is indeed a strong risk factor for a first admission with psychosis the risk in general may be less than previously assumed. Compared with unipolar affective disorders the risk for admission was about twice as high for bipolar patients, whether for first admissions or for readmissions. Indeed, in cases of women with bipolar affective disorders, hospital admission took place immediately after delivery with a relative risk of 2.3 for readmissions and 6.82 for first admissions (day 2–28). In an earlier study, Stewart *et al.* (1991) showed that women with a history of bipolar disorder had more than a 20% risk of an affective episode following childbirth; Reich and Winokur (1970) and Davidson and Robertson (1985) found a 30% risk. Dean *et al.* (1989) even calculated the risk to be as high as 50%. Thus, a history of a bipolar disorder is a strong risk factor in post-partum psychosis. Therefore Stewart *et al.* (1989) discussed the necessity of prescribing a lithium prophylaxis prepartum or directly post-partum – a procedure which was found to be successful (see also Cohen *et al.* 1995) – but also might cause many problems with breastfeeding and the need to wean.

Diagnostic categories of post-partum psychosis

Emil Kraepelin, who also expressed his views on this topic in his textbook of psychiatry, also deserves to be mentioned. It was his opinion that about 14% of all mental disorders in female inpatients in mental asylums were a consequence of gestational functions such as pregnancy, delivery or lactation (Kraepelin 1903). He also made clear that, in his view, ″puerperal mania″ – an often-used general term for post-partum disorders in the late 1800s/early 1900s (i.e. Fuerstner 1875) – is not a disease entity, but rather a group of illnesses that may occur post partum. This opinion is still valid, or, ″valid again″, after a number of studies that unsuccessfully sought to find support for the hypothesis that puerperal disorders are a separate nosological entity (i.e. Hays and Douglass 1984). Kraepelin saw mostly manic or catatonic states of excitement, especially the latter, often during the course of dementia praecox and less frequently during infection delirium or exhaustion delirium (Kraepelin 1903) – an observation which is in accordance with modern findings. There are some researchers (e.g. Brockington and Kendell in England) who see manic or schizomanic illnesses as the main representation of psychotic disorders post partum (Brockington and Cox-Roper 1988, Kendell *et al.* 1987, Videbech and Gouliaev 1995). But there are other research groups – including our own – that have additionally found a significant number of paranoid hallucinatory schizophrenia, catatonic schizophrenia or schizophreniform disorders (Rohde and Marneros 1993) resp. ″unspecified functional psychoses″ (Klompenhouwer and van Hulst 1991).

Bipolar post-partum disorders in the Cologne Study

Some of the findings of the Cologne Study (a long-term study on schizophrenic, schizoaffective and affective disorders, Marneros *et al.* 1991) regarding post-partum disorders are presented here. Of a study population of 86 patients hospitalized between 1950 and 1979 because of a post-partum psychosis we were able to follow up on 61 patients and evaluate the whole course of their illness – on average 25.6 years (min. 12, max. 41 years). Included were only patients with an onset of illness within 6 weeks post partum and patients without any history of psychiatric illness or psychiatric symptoms during pregnancy.

Psychopathology and diagnosis

Table 1 shows that psychomotor and affective symptoms were present in nearly all patients, but formal thought disorders, delusions and hallucinations were also very frequent; 33% of the patients had first-rank symptoms of schizophrenia. Euphoria was present in only 19.7% of the post-partum

Table 1 Psychopathological symptoms (61 post-partum episodes)

	Percentage	*Percentage*
Disturbances of orientation		**24.6**
Attention disorders and disturbances of memory		**26.2**
Disorders of concentration	19.7	
Disorders of attention	6.6	
Formal thought disturbances		**70.5**
Incoherence	47.5	
Depressive rumination	16.4	
Flight of ideas	14.8	
Thought blocking	8.2	
Apprehension and obsession		**11.5**
Mistrust	8.2	
Delusions		**80.3**
Delusions of reference	34.4	
Delusions of persecution	32.8	
Religious delusions	14.8	
Delusions of grandeur	11.5	
Hypochondric delusions	8.2	
Other unspecified types of delusions	23.0	
Disturbances of perception		**62.3**
Illusions	34.4	
Auditory hallucinations	44.3	
Visual hallucinations	21.3	
Gustatory/olfactory hallucinations	8.2	
Disorders of experience of the self		**24.6**
Constraint of thought	6.6	
Constraint of volition	6.6	
Feeling somatically influenced	9.8	
Disturbances of affectivity		**93.4**
Free-floating anxiety	62.3	
Affective lability	31.1	
Depressive mood	47.5	
Bewilderment	24.6	
Internal restlessness	23.0	
Euphoria	19.7	
Puerilistic behaviour	18.0	
Decreased self-confidence	14.8	
Inappropriate affect	14.8	
Irritability	11.5	
Hopelessness	9.8	
Complaining	6.6	
Increased self-confidence	6.6	
Psychomotor disturbances		**98.4**
Agitation	57.4	
Catatonic excitement	47.5	
Logorrhoea	27.9	
Decreased drive	27.9	
Stereotypes	11.5	
Mannerism	9.8	
Other symptoms		
Suicidality	23.0	
Suicidal attempt	9.8	
Aggression	27.9	
Sleep disturbances	41.0	
Disturbances of behaviour	31.1	
Disturbances of perception	11.5	

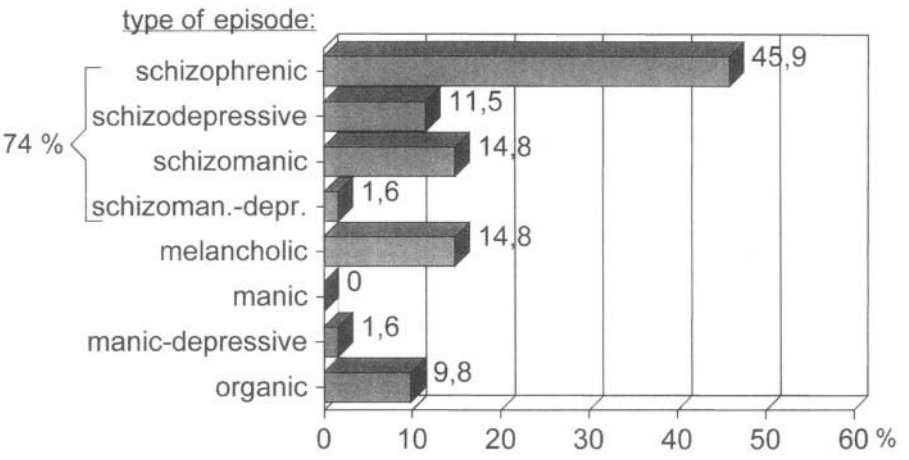

Figure 2 Cross-sectional diagnoses (61 post-partum episodes).

episodes and increased drive was present in only 22.1% of the episodes. Anxiety, depressive mood, affective lability, etc. were much more frequently reported (see Table 1). Delusions of grandiosity were found in 11.5% of the episodes of illness.

As a result of the psychopathological pictures the cross-sectional diagnosis was mainly "schizophrenic episode" (taken together, 74%), while schizomanic, schizomanic-depressive and pure manic episode with this diagnostic criteria added up to only 18% (Figure 2). The fact that this rather low frequency of bipolar disorders is not a result of the applied diagnostic criteria could be shown by a polydiagnostic approach, using also other criteria. Table 2 gives an overview of the ICD-10 diagnoses. In addition to delirium, schizophrenia and polymorphic psychoses, affective and schizoaffective disorders were diagnosed with the same frequency; 18% of the investigated post-partum episodes were classified as bipolar disorders.

The long-term course and relapse rate

The follow-up investigation took place 12–41 years after first manifestation (25.6 years on average after the post-partum episode). All recorded episodes during the course of the illness were evaluated, paying close attention to psychopathology, diagnosis and course.

Figure 3 shows not only the initial (i.e. cross-sectional) diagnosis, but also the longitudinal diagnosis with a major group of schizoaffective disorders. This is mainly done because several of the cases which were classified as schizophrenic episodes on first manifestation post partum, suffered from affective or schizoaffective episodes later during the course of the illness.

Table 2 ICD-10 diagnoses (61 psychoses post partum)

ICD-10 diagnosis		*No.*	*Percentage*
F 05	**Delirium**	**6**	**9.8**
F 20	**Schizophrenia**	**10**	**16.4**
F 20.0	Paranoid schizophrenia	6	9.8
F 20.2	Catatonic schizophrenia	4	6.6
F 23	**Acute transient psychotic disorders**	**18**	**29.5**
F 23.1	Acute polymorphic disorder with symptoms of schizophrenia	4	6.6
F 23.2	Acute schizophrenia-like disorder	14	23.0
F 25	**Schizoaffective disorder**	**8**	**14.8**
F 25.0	Schizomanic disorder	7	11.5
F 25.1	Schizodepressive disorder	1	1.6
F 25.2	Mixed schizoaffective disorder	1	1.6
F 3	**Affective disorders**	**11**	**18**
F 30.1	Manic episodes without psychotic symptoms	1	1.6
F 32.2	Severe depressive episode without psychotic symptoms	9	14.8
F 38.00	Manic-depressive mixed episode	1	1.6

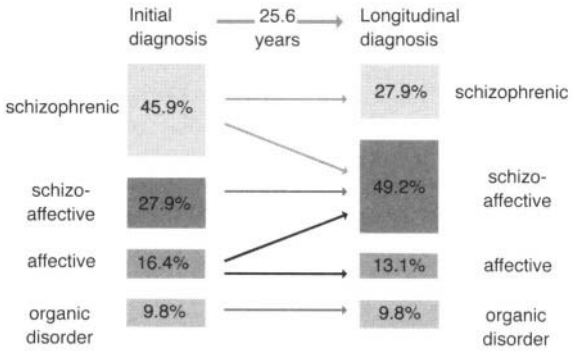

Figure 3 Longitudinal diagnosis (61 post-partum episodes).

In Table 3 the relapse rates of the major ICD-10 groups are shown. Everything is in the expected range but most interesting are the differences in post-partum relapses – here 25% for affective disorders, 38% for schizoaffective disorders and, very interestingly, only 9.5% for acute polymorphic psychosis, although they have the most subsequent deliveries. The relapse rate in the bipolar group (affective and schizoaffective disorders) was 82% compared to 69% for unipolar (affective and schizoaffective) disorders.

Table 3 Relapse rates (61 disorders with onset post partum)

ICD-10	Total (%)	Relapses (%)	Relapses / deliveries	Post-partum relapses (%)
F 05 ($n = 6$)	9.8	0.0	0/5	0.0
F 20 ($n = 10$)	16.4	90.0	1/3	33.3
F 23 ($n = 18$)	29.5	50.0	2/21	9.5
F 25 ($n = 16$)	26.2	68.8	3/8	37.5
F 30–38 ($n = 11$)	18.0	81.8	2/8	25.0

Schizoaffective disorders

We were able to compare the 30 cases of puerperal illness with the long-term diagnosis schizoaffective disorders with another group of 60 female schizoaffective patients from the Cologne Study on schizophrenic, schizo-affective and affective disorders, investigated using the same instruments and methods (Rohde and Marneros 1992). The majority of premorbid and sociodemographic variables, as well as course parameters, were similar in the two groups. Most of the few differences (i.e. in age of first manifestation, marital state at onset, presence of stable heterosexual relationship before onset, acuteness of onset, presence of live events) are closely connected with the inclusion and exclusion criteria applied for the puerperal disorders (exclusion of patients with preexisting illness or psychiatric symptoms during pregnancy, inclusion only if onset was within 6 weeks of parturition). The main difference in parameters regarding course was that schizoaffective disorders with onset post partum had initial schizomanic episodes more frequently than did the non-puerperal schizoaffective disorders, a finding which perhaps reflected the "pathoplastic" role of the puerperium on psychotic disorders (McNeil 1986). Regarding long-term outcome, some differences were found in favour of the schizoaffective post-partum group, but further investigation of these differences gave the strong impression that these differences are mainly an effect of selection – for instance, because schizoaffective patients with outcome in persisting alterations are less likely to be married or have children.

MENOPAUSE

The information on the effect of menopause as it relates to bipolar disorders is limited. Kraepelin (1903) found an increase in mental disorders in the climacteric period in women, although in his opinion the most important reason for this increase was the ageing itself and not the specific female changes that occur in hormonal processes. An increase in disorders was also found in male patients; however, it was a somewhat smaller increase.

There is no evidence that manifestation of bipolar disorders is increased after menopause compared with other periods of life. There are single case reports on first manifestation or re-manifestation of manic episodes after the start of a hormone replacement therapy (Young *et al.* 1997). There is also no proof or evidence that the frequency of major depression is higher after menopause. Therapeutic efficacy of oestrogen replacement therapy, as well as the influence of exogenous estrogens or progesterones on the course of bipolar illness is still controversial (Leibenluft 1996). Such evidence has up to now been found mainly in cases of minor depression.

The assumption of Kraepelin (1899) that the late-onset depression ("Involutionsmelancholie") is an autonomous type of depression was not supported by the investigation of his own pupil Dreyfus (1907), so Kraepelin revised his initial opinion (Kraepelin 1913). The investigations of Angst (1966) showed that the "Involutionsmelancholie" belongs to the group of "endogenous depression".

CONCLUSION

Finally, it can be said that major and minor depression and adjustment disorders form the majority of affective illness in pregnancy and after menopause, while the first manifestation of major psychiatric disorders (i.e. bipolar affective disorder) is rare. In contrast, the rate of first manifestation of illness, as well as first admission with a psychiatric disorder, is significantly increased after delivery. Especially in the case of pre-existing bipolar disorders, the post-partum relapse risk is increased. The research findings available up to now show clearly that no single cause can be found for the possible "protective" effect of pregnancy and the risk factor during the post-partum period. There is some evidence that the influence of gonadal hormones (i.e. oestrogens, progesterone) on the brain with the resulting effects on neurotransmitter systems might play an important role. However, further research in this field is necessary.

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Chapter seven

Adolescent-onset bipolar illness

Stan Kutcher

Bipolar disorder has long been understood to demonstrate onset during the adolescent years. Aretaeus of Cappadocia is reported to have described the incidence of bipolar illness as occurring "in those periods of life with which much heat and blood are associated, persons are most given to mania, mainly, those about puberty" (Adams 1856). Kraepelin identified a similar age of onset for the disorder, noting that the period of risk was in the 10–15 years following the onset of puberty (Kraepelin 1921). Recent data from large epidemiological catchment area studies have confirmed these previous observations (Burke *et al.* 1990, Weissman *et al.* 1988) and it is now relatively commonly understood that the onset of bipolar disorder may be largely in the adolescent and young-adult years, particularly when the first affective illness episode (which is often depression) is identified as the start of the illness (Kutcher *et al.* 1998, Kusumakar *et al.* in press).

More recently, increased interest in potential prepubertal manifestations of this disorder have arisen (Nottleman and Jansen 1998, Hechtman and Greenfield 1997, Geller and Laby 1995). At the core of this interest is the definition of child or very early-onset (prepubertal) bipolar illness. Some authors (Geller and Laby 1995, Wozniak *et al.* 1995) argue that non-cyclical mixed affective, behavioural and cognitive disturbance found in some severely dysfunctional children is a "developmentally" coloured manic (bipolar) illness. Others do not ascribe to this perspective, and demand a higher standard of evidence than that provided by proponents of the bipolar perspective (McLellan 1998, Carlson 1998). Still others categorize these multidimensionally impaired children as within the schizophrenic spectrum (Kumra *et al.* 1998). To date, however, the descriptions of non-episodic

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 139–152.

chronic and severe behavioural and affective disturbances in the prepubertium in the absence of data which substantiate genetic or familial loading for bipolar disorder, a course and outcome characteristic of bipolar disorder, evidence of patho-aetiological mechanisms specific to bipolar illness, or an unequivocal response to the pharmacotherapies known to be effective in bipolar disorder cannot be explained as a *form-fruste* of the illness. As Carlson has noted, "manic [symptoms] seem to function more as a barometer of severity of psychopathology, than for specifically defining youths with bipolar disorder" (Carlson 1995).

Currently, the diagnosis of early-onset bipolar disorder in teenagers is made using similar criteria to those of adults following the *Diagnostic and Statistical Manual IV* of the ICD-10 nomenclature. This approach to diagnosis is an evolution of considerations that have utilized a variety of different criteria developed from clinical evaluations modified over the last half-century (Weller *et al.* 1995, Paptheodoru and Kutcher 1996, McGlashan 1988). The developmental considerations pertinent to the issue of mood differentiation in young people have been introduced as modifications of "adult" criteria such that irritable mood and frequent affective driven outbursts can be considered. Functional impairment and absence of an alternative organic or substance-induced patho-aetiology completes the diagnostic ascertainment.

While the presence of a mania is necessary for a diagnosis of bipolar disorder, the onset of this illness should not be identified as the time of the first manic episode. Rather, it should be taken as the onset of the first affective episode. Evidence from a number of clinical studies of adolescent bipolar probands suggests that the depressive episode often precedes the first manic episode. Data available from a longitudinal study by Kutcher and colleagues of a bipolar I adolescent-onset population shows that the first depressive onset demonstrates a mean age of about 15½ years with the first manic episode occurring about 1 year later (Kutcher *et al.* 1998). While the depressive episodes are phenomenologically indistinguishable from major depressions described in adults the available evidence regarding manic episodes suggests that, in adolescents, the predominant symptoms are those of mixed affective states, rapid cycling and irritability (Kutcher *et al.* 1998, Paptheodoru and Kutcher 1996, McGlashan 1988). The "classic" grandiosity, while often clearly present, is usually not associated with euphoric states but rather with irritable states. Psychotic symptoms are common and may have in the past contributed to the misdiagnosis of the manic state as an acute psychosis of schizophreniform or schizophrenic type (Carlson *et al.* 1994, Joyce 1984). In the adolescent cohort the onset of a clinical depression which is sudden in nature, associated with psychomotor retardation, mood-incongruent psychotic symptoms and a "manic switch" with antidepressant medications may be predictive of a long-term bipolar course (Strober and Carlson 1982). The available evidence indicates

that early-onset bipolar disorder is not gender-specific with incidence and prevalence rates being roughly equal in males and females (Lewinsohn *et al.* 1995, Zarate and Tohen 1996).

While the lifetime prevalence of bipolar disorder approaches 1% the true prevalence of adolescent-onset bipolar illness is not yet clearly defined. Reports by Lewinshon *et al.* using epidemiological samples suggests that up to 1% of the adolescent population may meet diagnostic criteria for bipolar illness (Lewinsohn *et al.* 1995). Other investigators report lower figures (Zarate and Tohen 1996, Faedda *et al.* 1995). The presence of symptoms consistent with mood disregulation, dysphoric irritability and behavioural disinhibition occurs at higher rates. The relationship of these symptoms to the core disorder of bipolar illness, however, is not clear, and although some authors include this group in the bipolar diagnostic category, no substantial evidence exists that indicates clearly whether these symptoms are indeed either an early manifestation of bipolar illness, a prodrome of bipolar disorder or a milder variant of the illness itself (Carlson 1998, Faedda *et al.* 1995).

Recent years have seen an explosion in the tendency to "diagnose" states deemed to be "comorbid" with each other. Comorbidity in psychiatric disorders, however, can be classified as belonging to one of three very different descriptive conditions. The first would be a "true" or "valid" comorbidity. In this condition two or more clearly separate disorders occur concurrently. In this scenario there is no presumed patho-aetiological direction – that is, one disorder is no more likely to lead to the other and a common third disorder causing both others is not felt to be operant. The second comorbid condition is a developmental comorbidity. In this model one disorder leads to the development of another separate disorder while itself persisting. Thus, there is a longitudinal differentiation of the disorders and the second disturbance may either be patho-aetiologically related to the first or arise from the alterations in either the internal or external environment caused by the effect of the primary disorder. A third comorbid condition is that of "spurious" comorbidity. In this case comorbidity is simply a function of a diagnostic nomenclature in which symptom overlap amongst different conditions or syndrome threshold criteria amongst different conditions permits the assigning of multiple diagnosis when insufficient scientific evidence for their uniqueness exists. The available literature on early-onset bipolar disorder must be critically evaluated with these considerations regarding psychiatric "comorbidity" firmly in mind.

For example, a number of authors have described a high degree of "comorbidity" between bipolar mania and attention deficit hyperactivity disorder. Some of these authors (Wozniak *et al.* 1995 and West *et al.* 1996, for example) have tended to apply cross-sectional diagnostic criteria without critically evaluating the potential for "true", "developmental" or "spurious" comorbidity. Others have uncritically accepted these descriptive rela-

tions as evidence of "true" comorbidity. Unfortunately, the symptomatic overlap amongst these two diagnostic categories, either in the identified criteria for syndromal assignment or in the associated symptomatic complexes found within each disorder (secondary symptoms), will often permit an assignment of a "comorbid" diagnosis which is more a reflection of the method of description rather than the identification of two or more separate, yet concurrent entities (Carlson 1998). If ADHD and bipolar disorder were truly highly comorbid, as suggested by a number of investigators, longitudinal studies of ADHD children would be expected to identify high rates of bipolar illness onsetting over the life span. Such, however, is not the case. Furthermore, it would be expected that in the presence of "true comorbidity" between ADHD and bipolar disorder significantly increased rates of both illness would be found in first-degree relatives in adolescent probands suffering from either ADHD or bipolar illness. No replicated study has to date firmly demonstrated such an association (Biederman *et al.* 1998).

Furthermore, the presence of hyperactive-type symptoms, while they may be identified through a diagnostic process as present, may not be seen in multiple contexts, nor may they lead in and of themselves to functional impairment. Thus, external validation of syndromal diagnosis must be sought whenever a postulated comorbidity is observed. This is necessary because "spurious" comorbidity is likely to be state-dependent; that is, it is observed only at the time that a specific disorder is being manifest. For example, if a diagnosis of ADHD is only made concurrently with the diagnosis of bipolar disorder, and not independently from it, then the ADHD diagnosis could be considered to be dependent on the state of mania. Ideally, it should exist either prior to a manic episode, during any depressive episode, and during a period of time in which the bipolar disorder is in remission. One approach to this problem would be to examine the premorbid characteristics of early-onset bipolar probands to determine the prevalence of ADHD prior to illness onset. The available data to date show that when this approach is taken the prevalence of ADHD in an adolescent onset bipolar cohort was not significantly greater than that found in the population at large, especially when a prodromol period is excluded from analysis (Kutcher *et al.* 1998, Duffy *et al.* 1998, Quackenbush *et al.* 1996). At this point in time the most parsimonious perspective regarding the issue of comorbid ADHD and bipolar disorder would be to apply the Scottish legal term of "not proven", and to insist on further and more sophisticated evaluations.

Similar criticisms can be made of the described comorbidity between conduct disorder and bipolar illness. Again, the state-dependent features of a manic or hypomanic episode, with its attendant impulsivity, decreased judgement, overactivity and stimulus-seeking drives, can lead young people to disturbances in conduct that cross-sectionally and for short durations may meet criteria for conduct disorder. Those studies which have attempted

to differentiate state-dependent conduct disorder diagnosis from state-independent conduct disorder diagnoses have described that, in bipolar patients, a secondary conduct disorder – that is one which is of the "developmental" type of comorbidity – may most appropriately characterize the observed relationship (Kutcher *et al.* 1989).

Similar caveats extend to descriptions of comorbid substance and alcohol abuse and anxiety disorders. To date the data available are not comprehensive enough, nor are the available studies considerate enough to allow any firm conclusions about "true" comorbidity to be drawn.

Although the genetic basis of bipolar disorder is highly suggestive based on studies which include segregation, linkage, and association analyses (see Alda 1997) the genetic diathesis of this disorder has not been clearly characterized. Heredity factors as expressed in a family history of mood disorders have for over 80 years been argued to be one of the most, if not the most, important risk factor for the development of bipolar illness. A variety of family studies using either a bottom-up or top-down approach have shown high rates of familial risk for both bipolar and unipolar disorder in bipolar families (Duffy *et al.* 1997, Strober 1995). There is also a suggestion from available family studies that the process of genetic anticipation (the worsening of illness severity and earlier age of onset seen in successive generations) may be evident with bipolar disorder, as has been described for several medical neurological conditions and possibly for schizophrenia. Confirmatory evidence for this hypothesis, however, is at this time lacking.

The premorbid characteristics of early-onset bipolar probands has been of interest to psychiatrists since the time of Kraepelin, who reported a personality dimension of assertiveness or extroversion in clinical samples. Somewhat similar observations by other investigators have led to the suggestion that affective lability or cyclothymic and hyperthymic features may be premorbid "markers" for the onset of bipolar illness (Kusumakar *et al.* in press). These observations, however, cannot be appropriately evaluated in the absence of studies in which population-based samples of young people who showed these personality characteristics can be followed over time to determine whether or not these features are independent and attributable risk factors for the disorder. Similarly, the value of excessive mood lability or extreme affective dysregulation in young people as a predictor of bipolar mood disorder has not been established.

Of interest, however, are recent data described from studies of adolescent-onset bipolar I probands by Kutcher and colleagues (Kutcher *et al.* 1998) and from the children of bipolar probands by Duffy and colleagues (1998) which identify that in the premorbid state the majority of individuals who go on to demonstrate a bipolar illness show good to excellent premorbid academic achievement, positive work ethic and good peer relationships. Of further interest is that large numbers of these individuals have been identified as showing superior or exemplary achievement in one or more areas

including scholastic ability, athletics or the arts. These data suggest that, for a substantial number of early-onset bipolar probands, a premorbid history free from significant psychiatric disturbance is the norm.

The course and medium-term outcome of bipolar illness onsetting in adolescence has only recently been described. Kutcher and colleagues (1998), in a cohort study of adolescents with bipolar I disorder followed up for a mean duration of almost 5 years, described a chronic course with multiple hospitalizations for depression and mania (1.7 and 1.4 hospitalizations respectively over 4.6 years). Interepisode functioning was marked by significant improvement in acute-phase symptoms but fell short of premorbid levels.

In this group of patients optimized pharmacotherapy using a variety of different agents, including lithium, valproate, antipsychotics and others, had been utilized and, additionally, the vast majority of subjects had received a variety of individual, group and family psychotherapies as well as community case management and special education programming (Kutcher *et al.* 1998). In spite of these interventions, however, these remitted bipolar probands, when compared with unipolar depressed adolescents and bipolar controls, showed significantly more dysphoric symptoms at the time of evaluation and a variety of cognitive deficits. In particular, the Weschler Intelligence Scale for Children Revised showed full-scale IQ raw scores significantly less than either unipolars or controls in the bipolar group ($p < 0.001$). Similar findings held when the verbal subscale and the performance subscale were separately evaluated. When group differences greater than 10 percentile points were compared the bipolars scored significantly less well on a variety of indices including coding, symbol search, picture arrangement and processing speed index. Using the Wisconsin Card Sort test, the bipolar group showed significantly fewer categories completed and a greater tendency towards perseverative errors. These cognitive difficulties were not explained by type of medication or time of assessment. Premorbid data utilizing these indices were not available for comparison (Robertson *et al*. 1998a).

Premorbid academic information, however, was available for the bipolar group. This was obtained through an extensive review of the child academic and school records as outlined in Quackenbush *et al.* (1996). This showed the majority of bipolar probands during their premorbid functioning to be at or above grade level in both elementary and secondary academic achievement (Kutcher *et al.* 1998). However, at the time of assessment, a mean duration of 4.6 years following onset of the first manic episode, and during a state of illness remission the bipolar group scored significantly worse than both unipolar or normal controls in terms of their scholastic performance. Of these subjects old enough to have graduated from high school, only 58% of bipolars compared to 86% of unipolars and 92% of controls had achieved this goal. Overall academic lag (current grade versus expected

grade) was significantly greater for the bipolar group (Robertson *et al.* 1999a).

Analyses of academic achievement based on data from the Wide Range Achievement Test-R (WRAT-R) showed that in language functioning (spelling and reading) bipolar patients performed at or close to expected grade level and not significantly poorer than unipolar or normal controls. This was evident for both males and females alike. However, on the mathematics evaluations both male and female bipolar probands scored significantly worse than age- and sex-matched unipolars or normal controls. Mathematics achievement in the bipolars was far below current grade expectations and greater than 3 years below expected grade standard (Robertson *et al.* 1999a).

When analysis of attention difficulties was conducted in this population, the bipolar group did not show significantly poorer performance. Results from the Continuous Performance Test (CPT) showed that, in terms of overall processing speed, overall attentional variability, speed decrement over time, variability over time, commission errors, omission errors, response bias, and overall cognitive activation and arousal no significant group differences occurred. Eight controls ($n = 44$) and one unipolar ($n = 30$) subjects demonstrated CPT results consistent with scores found in ADHD subjects (Robertson *et al.* 1999b). These findings provide further support for the perspective that the described "comorbidity" between ADHD and bipolar illness (discussed above) is possibly an artifact of the manic state.

Peer relationships were noted to be problematic in the bipolar group. Evaluating the sample with the Social Adjustment Inventory for Children and Adolescents (SACIA) the bipolar group showed significantly more problems with peer relationships taken from a global level than unipolars or controls, and also showed significantly poorer satisfaction with their peer relationships. Bipolar probands reported significantly greater peer difficulties both in school and in extracurricular and recreational settings (Robertson *et al.* 1999a). Bird and colleagues conclude that, when it comes to peer relationships, the bipolar cohort was the "most significantly impoverished" (Bird *et al.* 1999).

In studies of family functioning, as a group, the bipolar probands when assessed using the Family Adaptation and Cohesion Scale did not show significant differences from controls with respect to their ratings of their relationships with either parent. Their reports of family adaptability and cohesion were within the United States national norms for the instrument (Robertson *et al.* 1998b). The bipolar group, however, did report significantly more difficulties in minor problems with parents and relationships with siblings (Robertson *et al.* 1998c). These data suggest that for bipolar youth the illness may not have a detrimental effect on sharing, affective, support and communication within the adolescent–parent dyad. Relationships with siblings, however, may be more problematic (Robertson *et al.* 1998b,c).

In terms of overall health the Duke Health Profile Evaluation identified that the bipolar group was significantly lower than the controls in terms of their self-ratings of mental health (Kutcher *et al.* data on file). Similarly, the bipolar group reported significantly greater symptoms of anxiety and depression than controls. This evidence of significantly increased subthreshold and subclinical symptomatology, even in the remitted state, was paralleled by data from the Symptoms Checklist – 58 in which youth with a bipolar disorder self-reported significantly more anxiety and depression than controls. Similar data using the Beck Depressive Inventory report the finding that even in a state of clinical remission bipolar probands suffer from a variety of significant but non-specific symptoms of dysphoria, anxiety, depression and distress, suggesting that their quality of life may be impaired by the ongoing process of the illness (Bird *et al.* 1999).

These data do not support a perspective that adolescent-onset bipolar onset disorder is a mild disturbance, or one in which the affective disturbance returns to premorbid levels during inter-episode functioning. On the contrary, the available long-term data clearly show for bipolar I disorder illness onsetting in adolescence a prognosis is that of a chronic disease with significant disturbances identified across a variety of areas of functioning, most specifically in terms of academic achievement, mathematical ability, peer relationships and sub-syndromal symptoms.

Treatment of bipolar disorder should be directed by this information. In particular, attention must be paid to the therapeutic relationship between clinician and patient, and to the importance of timely hospitalization for acute episodes of the illnesses. During outpatient treatment, specific attention should be paid to academic reintegration and the importance of bolstering peer relationships. In the classroom setting, a variety of practical interventions should be instituted to promote optional achievements. These are listed in Quackenbush *et al.* (1996). To date the importance of a peer-focused intervention has not been mirrored in treatment programmes. The clinical challenge is to avoid the regression of illness-based group treatment models while at the same time providing a secure non-judgemental peer environment. A study by Kutcher *et al.* of consumer evaluation of treatments in this sample of bipolar adolescents is consistent with these suggestions (Kutcher *et al.* in press). In this group the role of nurses, physicians, hospital, medications and psychoeducation were scored exceedingly highly. Self-help groups, family physicians, school counsellors, and self-help literature were not well received.

The goals of treating a young person with bipolar disorder should be the early identification of the disorder and early, affective intervention. These should be directed towards providing symptomatic relief, the prevention of deterioration and the promotion of healthy development with achievement of optimal functioning. For effective long-term treatment a strong foundation of trust and a positive interpersonal therapeutic relationship

between teen and clinician is necessary. In addition, the relationship between the clinician and patient must extend to the family as multiple family issues will arise given the impact of the disorder on family functioning. Psychoeducation is considered by most clinicians to be an essential component of treatment of the disorder, and includes information about the illness and about its treatment. At this point in time there are no specific published studies of the effectiveness of psychoeducation in adolescent-onset bipolar patients. The available adult data, however, show considerable support for the role of psychoeducation in reducing hospital admissions, and improving compliance with medication (Kusumakar *et al.* in press, Haxley *et al.* in press). A variety of psychological therapies including interpersonal, social rhythm and cognitive behaviour therapy can be applied by practising clinicians to young bipolar patients. Unfortunately, the evidence for the effectiveness of these interventions has yet to be demonstrated, although suggestive but sporadic evidence is available.

In the acute manic phase, pharmacotherapy and short-term hospitalization are the mainstays of intervention. Treatment with thymoleptic medication should be initiated soon after initial diagnosis and following baseline medical evaluation (Kutcher 1997a,b). Current data regarding the use of thymoleptics in adolescent bipolar patients suggest that in some individuals lithium may be a useful first-line agent. This may be particularly so in patients with mania who have had no previous episode of depression, in patients in whom mania is predominantly euphoric in its presentation and the presence of a positive response to lithium of a first-degree relative. One or more of these clinical features may lead the clinician to suggest lithium carbonate. Although the data are variable it is expected that 40–50% of adolescents with mania may respond to lithium treatment. Serum levels are generally targeted to fall between 0.8 and 1.1 mmol/L. Continuation lithium treatment is associated with symptomatic stability while discontinuation is associated with relapse (Strober *et al.* 1990).

Common adverse effects in adolescents include significant decrease of weight gain and of lithium acne. The effect of lithium on prophylaxis has been demonstrated in one naturalistic discontinuation study in which Strober *et al.* (1996) demonstrated that, on 18-month follow-up, over 90% of subjects who discontinued lithium relapsed compared to only about a third of subjects who continued to take their medication.

In the individual treated with long-term lithium, care must be taken to monitor thyroid and renal function. Usually it is recommended that this should occur at 6-month intervals (Kutcher 1997a). Lithium should not be prescribed to individuals who have significant impulsivity and high degrees of suicidality, as this medication can be lethal in overdose.

As many manic episodes in adolescents are of the mixed or rapid cycling type divalproate sodium/valproate is often chosen as the initial pharmacological treatment. A number of open studies have suggested that valproate

may be useful in treating the manic phase of the illness (Kusumakar *et al.* in press). At this point in time, however, no long-term prophylactic studies have been reported and therapeutic serum levels have not been established. One study, by Kusumakar and colleagues (in press) demonstrated, in a head-to-head comparison with lithium, that 60% of a valproate-treated group showed adequate episode suppression over long-term treatment compared to less than 30% of the lithium group. In spite of this, the vast majority (>80%) of both groups continued to exhibit subsyndromal symptoms and considerable dysfunction.

Although clinicians note that many teenagers often tolerate valproate better than lithium, weight gain is also a complicating factor with this treatment. A transient thrombocytopenia can occur, but this rarely warrants discontinuation of medication. A recent concern about polycystic ovary syndrome in young adolescent females treated with valproate suggests that in this group a careful evaluation of menstrual functioning is necessary at baseline and at particular intervals thereafter (Kusumakar *et al.* in press).

Although carbamazepine has been used in the treatment of adult mania, and to our knowledge has been reported in a small number of adolescents (Kutcher 1997a), the difficulties associated with its use (in particular its propensity for adverse haematological reactions, its multiple drug–drug interactions, its ability to autoinduce its own metabolism and the toxicity of its major metabolite) make this compound much less attractive for use as a first-line treatment in this population.

Recent preliminary studies suggest that lamotrigine, another anticonvulsant medication, may be of some utility in this population, particularly in the depressive phase of the disorder, but other anticonvulsants such as gabapentine, while theoretically of value, have not been appropriately evaluated (Kusumakar *et al.* in press). In a recent open study on a small number of adolescent girls with ultra-rapid cycling, Kusumakar and colleagues identified a positive response to topirmate augmentation of a primary mood stabilizer (Kusumakar *et al.* in press).

Antipsychotic medications may be of use either in the acute phase or to maintain mood stability in the long-term (Kutcher 1997a,b). Whenever possible the newer "atypical" agents should be utilized due to their decreased propensity to cause significant treatment-emergent adverse events in young people. However, these compounds are also not without their difficulties, and some of the adverse events that may affect compliance with treatment include excessive weight gain, particularly with olanzapine, and galactorhhoea with risperidone. Double-blind placebo-controlled studies of either of these compounds in adolescent bipolar illness are not available at the time of this writing.

In terms of depressive episodes associated with bipolar illness in young people no definitive studies in this population have been reported. The available evidence for the treatment of unipolar depression in teens suggests

that SSRI medications may be effective in ameliorating the symptoms of clinical depression in this population (Emslie *et al.* 1997). In an individual who presents with a depressive episode within the context of a bipolar longitudinal course initial therapeutic intervention would be to titrate upwards the dose of the thymoleptic medication, being guided by the emergence of adverse events. When the mood state does not respond to this intervention another reasonable alternative would be to add light therapy as described in an open study by Papatheodorou and Kutcher (1995). Twice-daily 10 000 lux administered over 2 weeks has been found to ameliorate the depressive symptoms when initiated early enough in the course. Alternatively, SSRI medications may be considered, but always with thymoleptic "cover".

Electroconvulsive therapy has been successfully used in this population (Kutcher and Robertson 1996). ECT should be considered as a treatment option in this group of adolescents in either a manic or depressive phase of the illness which is unresponsive or minimally responsive to optimal medication intervention, or in those teens who have significant suicidal/homicidal or catatonic symptoms that put them at serious life risk. In these cases the ECTs should be administered following the guidelines of the American Academy of Child and Adolescent Psychiatry (in preparation).

CONCLUSION

The adolescent years are a period of greatest risk for the onset of bipolar illness. The disorder, when it onsets in this age group, is a serious mental illness characterized by a long-term chronic course with significant morbidity across a variety of interpersonal, social, cognitive, academic and vocational domains. Effective early identification and treatment are necessary, and a coordinated approach combining pharmacotherapy and a variety of psychosocial interventions, particularly educational strategies, is necessary.

Acknowledgements

This work was supported in part by grants from the Canadian Psychiatric Research Foundation, Queen Elizabeth II Health Sciences Research Trust, and the Designated Mental Health Research Fund – Province of Nova Scotia. Thanks to Heather Robertson, Diane Bird and Dr Vivek Kusumakar for the co-investigation and collaboration on a variety of the projects described in this chapter. Appreciation to Linda Ford for manuscript preparation.

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Chapter eight

Bipolar disorder in old age

Kenneth I. Shulman and Nathan Herrmann

MANIA IN OLD AGE: IMPLICATIONS FOR CLASSIFICATION, PATHOGENESIS AND TREATMENT

The study of mania in old age affords some unique research opportunities such as the capacity to study the life course of bipolar disorder. Given that the mean age of onset of bipolar disorder is 21 years (Kessler *et al.* 1997), identifying a cohort of bipolars in late life potentially provides a retrospective view of some 50 years or greater of this disorder. Kraepelin (1921) emphasized the longitudinal view of major mental disorders and used this perspective to differentiate manic-depressive illness from dementia praecox. Can we further refine our nosology and classification system by studying an elderly cohort? Can we identify distinct subtypes on the basis of long-term clinical course? What are the implications for treatment?

The second major opportunity, provided by elderly bipolar probands, is the exploitation of the extended lifetime exposure of first- and second-degree relatives. Genetic factors can be explored both by history and direct examination. One has available for scrutiny the entire life course of parents, aunts, uncles and most siblings. Children of elderly probands are often in their 50s and 60s, and even some grandchildren have reached the mean age of onset of bipolar disorder at 21 years. Such opportunities for examining the familial pattern of illness and direct genetic examination should not be missed.

Finally, the elderly provide a high prevalence of neurological comorbidity (Shulman 1997, Shulman and Singh 1999) Recent advances in neuroimaging now afford new opportunities to characterize the nature and location of brain lesions (Steffens and Krishnan 1998). Can this area of investigation cast light on the pathogenesis of bipolar disorders in younger adults in whom brain pathology is less overt and most likely related to subtle neuro-

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 153–174.

physiological changes? The presence of comorbid neurological conditions associated with mania in late life has contributed to the uncertainty and, indeed, confusion surrounding the diagnostic classification of mood disorders in old age. The available evidence from epidemiological/clinical and neuropathological studies will be critically reviewed and directions for future research identified.

CLASSIFICATION

Following Kraepelin's (1921) identification of manic-depressive insanity, others have distinguished between bipolar and unipolar disorders based largely on familial patterns of inheritance (Leonhard *et al.* 1962, Perris 1966, Angst 1966, Winokur *et al.* 1969). Next evolved the concept of secondary mood disorders elaborated by the St Louis group (Robins and Guze 1972) in which the focus was on major depression considered to be "secondary" or directly related to a comorbid medical or psychiatric condition. This notion was extended to manic syndromes by Krauthammer and Klerman (1978) who proposed the term "secondary mania" for manic syndromes closely associated temporally with systemic medical or neurological conditions. Secondary mania was also associated with a negative family history, no prior history of mood disorder and was considered distinct from delirium. DSM-IV (American Psychiatric Association 1994) translates this concept into the category of "mood disorder due to a medical condition". The underlying presumption is that "the disturbance is the direct physiologic consequence of a general medical condition". Herein lies the dilemma in old age. Given the high prevalence of comorbid medical conditions in geriatric patients who also take multiple medications, when is mania a "direct consequence" and when is it simply a comorbid condition (Shulman and Herrmann 1999). Keeping in mind the fact that the vast majority of elderly patients who suffer from serious medical and neurological conditions do not develop manic or even hypomanic symptoms, how do we conclude that mania is a "direct physiologic consequence" when it does occur in such patients? Similarly, the DSM-IV category of "substance-induced mood disorder" is problematic in an elderly population. An aetiological relationship is assumed by temporal association (manic symptoms developing within a month of intoxication or withdrawal) or simply by the presumption of a causative relationship on the part of the examiner.

Finally, Akiskal's notion of a "bipolar" spectrum may be a better fit with the complex factors identified in late-life mania (Akiskal 1983). The bipolar spectrum that involves temperament and the notion of affective vulnerability may be more useful in understanding why such a small minority of cerebral lesions in old age result in a manic syndrome. These difficult diagnostic and nosological issues are fundamentally linked to our under-

standing of the nature of manic syndromes. Moreover, our management and treatment decisions follow closely on the heels of these important conceptual challenges.

EPIDEMIOLOGY

Both prevalence and incidence rates for mania and bipolar disorders in old age show considerable variability within the literature (Chen *el al.* 1998). Marked differences exist between rates for published hospital admissions and community prevalence of bipolar disorder (Shulman and Herrmann 1999). From a community perspective, initial findings from the Epidemiologic Catchment Area (ECA) study revealed no cases of mania in the community out of almost 1000 elderly patients who were interviewed (Kramer *et al.* 1985). Methodological concerns are significant as manic patients are less likely to consent to be interviewed, and bipolar I patients are much more likely to be hospitalized, especially in old age given the increase in frailty and vulnerability of such individuals. Subsequent ECA data for mania in the community reveal a decrease in prevalence from 1.4% in the young adult population to a minuscule 0.1% in those 65 and over living in the community. In contrast, the "treated prevalence" rates for elderly psychiatric inpatients has been reported between 4.7% and 9.0% (Chen *et al.* 1998). An earlier study by Spar *et al.* (1979) noted that only four out of 14 elderly inpatients who carried a diagnosis of bipolar disorder were known to suffer from this condition prior to their admission. Misdiagnosis was based on a variety of psychotic features that had preceded the hospitalization. Available data suggest that an average annual rate of eight elderly patients with mania are treated on inpatient psychogeriatric units (Shulman *et al.* 1992, Yassa *et al.* 1988). Elderly manic patients represent about 12% of mood disorders treated on such inpatient units with a 2:1 female preponderance (Yassa *et al.* 1988). Unfortunately, there are no data available on the treated prevalence of mania in outpatient settings or community geriatric psychiatry services.

In contrast to community prevalence, the first admission rates to psychiatric inpatients for mania have revealed an increase at the extremes of old age (Spicer *et al.* 1973, Eagles and Whalley 1985). A recent Finnish study shows that almost 20% of manic patients admitted were over the age of 60, with the highest 1-year incidence occurring in the 50–59 age group for males and the 40–49 age group for females (Rasanen *et al.* 1998). The original hypothesis by Spicer *et al.* (1973), that the increased incidence for first admissions for mania in late life was associated with the development of dementia, has not been substantiated by other studies (Broadhead and Jacoby 1990, Shulman and Post 1980).

AGE AT ONSET AND CLINICAL COURSE

Two recent studies have focused on age at onset as a heuristically useful distinction in understanding bipolar disorders in old age (Wylie *et al.* 1999, Young and Klerman 1992). Depending on a number of methodological issues, including the cutoff for "elderly bipolar" and inclusion of those with secondary mania or neurological disease, the mean age of a first mood episode among elderly bipolars varies from less than 30 years up to 57 years (Chen *et al.* 1998). For those studies that used a late-onset cutoff of 60 years or more, the mean age at onset of mood disorder ranged from 42 to 57 years while the mean age at onset of mania ranged from age 51 to 60 years (Chen *et al.* 1998).

Using "mixed-age" studies of hospitalized manic patients, the average age at onset is approximately 30 years (Goodwin and Jamison 1990, Tohen *et al.* 1990). However, in community-based samples such as the US National Comorbidity Study (Kessler *et al.* 1997) the mean age at onset was 21 years, similar to the earlier ECA study of Weissman *et al.* (1988). Given this very early onset in the general population, it is most striking that, in studies of hospitalized elderly manic patients, very few had developed mania before the age of 40 (Snowdon 1991, Shulman *et al.* 1992). Where have all the young bipolars gone? Certainly, one possibility is that more effective treatment with mood stabilizers over the past few decades has significantly reduced the "treated prevalence" of mania in late life. Others have suggested that the illness may burn out after many years (Winokur 1975). Still others suggest that the higher mortality rate among younger bipolar patients from natural causes, as well as suicide, may be responsible for the lower prevalence in late life (Snowdon 1991, Weeke and Vaeth 1986). A long-term follow-up of bipolars has indeed shown a higher suicide rate (Tsuang 1978). In contrast, in a study of elderly hospitalized manic patients, only one committed suicide after an average 6-year follow-up (Shulman *et al.* 1992).

Keeping in mind the conclusion of Perris (1966) that the diagnosis of unipolar depression could be made on the basis of three consecutive depressive episodes, findings in old age suggest a re-consideration of this direction. Generally, about half of index elderly bipolar patients who have been hospitalized experience depression as their first mood disorder (Stone 1989, Broadhead and Jacoby 1990, Snowdon 1991, Shulman *et al.* 1992). On average the mean age at onset of their depression is in middle age, just under 50 years. Most striking amongst these elderly bipolars, however, is the very long latency (15 years on average) before mania becomes manifest (Shulman and Post 1980). About one-quarter of these patients experience a delay of at least 25 years, ranging as high as 47 years between the first depressive episode and the onset of mania. In most studies, half of the elderly bipolars whose first episode was depression went on to experience at least three distinct depressive episodes prior to first mania (Shulman and Post 1980,

Stone 1989, Broadhead and Jacoby 1990, Snowdon 1991). This apparent "conversion" to bipolarity after many years of recurrent depressions is most likely related to the concept of secondary mania associated with coarse neurological disorders elaborated below.

While the majority of bipolar patients pursue a clinical course that is characterized by both depressive and manic episodes, a small subset of approximately 12% meet strict criteria for unipolar mania (Shulman and Tohen 1994). These criteria included at least three distinct manic episodes without evidence of major depression for a minimum of 10 years from the time of first hospitalization for mania. Shulman and Tohen (1994) note that the subgroup of unipolar manics experienced an age at onset significantly lower (mean 41 years) compared to "bipolar" elderly patients who had a mean onset of 65 years. Thus, elderly unipolar manic patients are amongst the very few elderly bipolars whose illness begins early in life. This difference suggests that there may be variations in genetic vulnerability and pathogenesis between these subgroups that merit further investigation. Emphasis should be placed on the fact that this involves a study of hospitalized patients only. Data on a community-based sample of elderly bipolars are lacking.

Three studies have provided data on long-term clinical outcome in elderly bipolars (Berrios and Bakshi 1991, Dhingra and Rabins 1991, Shulman *et al.* 1992), Two of the studies provided follow-up data for a mean of 6 years and used a group of elderly depressives as a comparison group (Dhingra and Rabins 1991, Shulman *et al.* 1992). In contrast to the original study of the natural history of mental disorder (Roth 1955) mania in old age seems to have a better prognosis. For those patients who were still alive, 72% were considered symptom-free and 80% were living independently (Dhingra and Rabins 1991). The same study, however, found that 34% of the original cohort had died at follow-up and almost one-third of the patients who were examined directly at follow-up had experienced a significant decline in cognition. This was reflected by a score less that 24 on the Mini Mental State Examination (MMSE). Mortality rates in the Shulman *et al.* (1992) study revealed that 50% of the elderly manic patients had died at mean 6-year follow-up compared to only 20% of an age- and sex-matched comparison group of unipolar depressives.

Using a naturalistic cross-sectional analysis, Berrios and Bakshi (1991) determined that manic symptoms compared to depressive symptoms were less likely to respond to treatment. Manic symptoms are also associated with cognitive dysfunction and cerebrovascular disease, and produced persistent behavioural and psychosocial disturbances. They suggest that the poor outcome of manic symptoms is associated with delirium (Lipowski 1980).

Several studies that have examined age at onset related to family history in first-degree relatives have produced inconsistent results based on inade-

quate methodologies (Shulman and Herrmann 1999, Chen *et al.* 1998). As noted earlier, the extended exposure of first-degree relatives in elderly bipolar probands increases the likelihood of positive findings for parents, siblings and children. These familial vulnerabilities and genetic patterns of inheritance have not been adequately exploited to date and require further investigation. The wide range in proportion of elderly probands with a positive family history of mood disorder in first-degree relatives (24–51%) is a reflection of the inconsistent methodologies (Broadhead and Jacoby 1990, Glasser and Rabins 1984, Shulman *et al.* 1992, Snowdon 1991, Stone 1989). In Stone's review (1989) an earlier age of onset was associated with a positive family history while other studies have found that the presence of neurological disorders produces a lower but still significant familial predisposition in the range of 30% (Snowdon 1991, Shulman *et al.* 1992). The lowest prevalence of familial predisposition seems to occur in those elderly bipolars who have a very late onset of mania associated with neurological disorders, namely a secondary mania (Tohen *et al.* 1994). In general, it appears that genetic factors play a less prominent role in elderly bipolars, especially those with comorbid neurological disorders. Nonetheless, a special affective vulnerability appears to be necessary for that small proportion of neurologically impaired elderly patients who develop manic syndromes.

CLINICAL FEATURES

Systematic analysis of the clinical features of mania in old age suggest that the presentation is similar to mixed-age populations but with lesser intensity (Broadhead and Jacoby 1990). Age carries a negative or low association with a number of factors on the Mania Rating Scale (MRS) including the "activity–energy" score, sexual interest, religiosity, initiating and making plans (Young 1997). While depressive episodes in elderly bipolar patients have been poorly studied (Young 1997), earlier clinical impressions suggested a higher prevalence of mixed episodes (Post 1982). This requires further assessment.

Cognitive impairment is a consistent finding in most studies of geriatric mania (Shulman 1997). Yet the original speculation by Spicer *et al.* (1973), that mania in late life was a forerunner of dementia, has not been substantiated by other outcome studies (Shulman *et al.* 1992). Cognitive dysfunction in old age as well as in mixed-age populations does not remit as in depressive pseudo-dementia, suggesting it is not simply an attentional deficit (Savard *et al.* 1980, Dhingra and Rabins 1991). When compared to depressed elderly, manic patients have been found to be more cognitively impaired with higher Hachinski scores consistent with an underlying cerebrovascular pathology (Berrios and Bakshi 1991).

NEUROLOGICAL COMORBIDITY AND THE DIAGNOSTIC GREY ZONE

Particular difficulties surround our understanding and diagnostic labelling of patients who develop manic syndromes in the context of clinically or even radiologically detectable brain lesions. The psychiatric literature has been largely influenced by the concept of secondary mania elaborated by Krauthammer and Klerman (1978). This term is used to describe mania associated with a wide variety of cerebral–organic and medical pathologies. The emphasis is on the relative lack of familial predisposition and prior psychiatric history in contrast to "primary bipolar disorders" that are associated with a much stronger genetic predisposition and no obvious structural neuropathology. A number of recent reviews summarize the multiplicity of medical and neurological conditions associated with this disorder (Strakowski *et al.* 1994, Verdoux and Bourgeois 1995, Carroll *et al.* 1996). The literature consists largely of individual case reports and relatively small case series.

In parallel to the psychiatric literature is a robust neurological literature that uses the term "disinhibition syndrome" to describe a very similar clinical condition to that of mania (Starkstein and Robinson 1997). The neurological literature reveals a consistent finding of a predominance of right hemisphere lesions in association with disinhibition syndromes as well as secondary mania (Starkstein *et al.* 1990, Steffens and Krishnan 1998). Earlier work on the phenomenon of pathological laughing and crying supports this localization. Left-sided brain lesions tend to produce pathological crying while right-sided lesions produce pathological laughing (Sackeim *et al.* 1982).

Lesions associated with these syndromes are heterogeneous in nature, including head injuries (Jorge *et al.* 1993), a variety of endocrine conditions (Sweet 1990, Lee *et al.* 1991, Ur *et al* 1992), epilepsy (Carroll *et al.* 1996) and HIV (Lyketsos *et al.* 1993). However, predominating in frequency are right-sided cerebrovascular lesions (Cummings 1993, Fawcett 1991, Carroll *et al.* 1996, Jampala and Abrams 1983, Robinson *et al.* 1988). One case of mania occurring after cardiac surgery had even been preceded by a right-sided cerebrovascular accident (Isles and Orrell 1991). Further support for the significance of neurological comorbidity in mania in late life comes from a retrospective cohort study that compared elderly bipolars to a sex- and age-matched group of unipolar depressives (Shulman *et al.* 1992). More that one-third of the manic group had evidence of heterogeneous neurological disorders compared to only 8% of the depressives. Table 1 documents the nature of these disorders and their relationship to age at onset and family history. While genetic factors tend to be less prominent in late-onset disorders (Mendlewicz *et al.* 1972) these elderly bipolar patients have a 50% prevalence of mood disorder in first-degree relatives (Shulman *et al.* 1992).

Table 1 Demographic and clinical data for 18 elderly patients with mania and neurological disorders at index hospitalization

Patient	*Sex*	*Family history of affective disorder*	*Age at onset of affective disorder (years)*	*Age at first manic episode (years)*	*Neurological disorder*
1	Male	Negative	82	82	Chronic alcoholism, peripheral neuropathy
2	Female	Positive	20	20	Frontal lobotomy, bilateral encephalomalacia
3	Female	Negative	50	50	Chronic alcoholism, dementia
4	Female	Negative	67	67	Chronic alcoholism, seizures/delirium
5	Male	Negative	69	70	Chronic alcoholism, blackouts/delirium
6	Male	Negative	68	68	Cerebral contusions
7	Female	Positive	41	46	Parkinson's disease
8	Female	Negative	39	43	Right cerebral infarct
9	Female	Negative	83	83	Multiple cerebral infarcts
10	Female	Negative	43	58	Encephalopathy/neuroleptic malignant syndrome
11	Male	Negative	58	58	Closed head injury
12	Male	Negative	80	80	Recurrent cerebral contusions (boxing), lacunar infarct
13	Female	Positive	71	71	Left cerebral haemorrhage 20 years before onset of affective disorder
14	Female	Positive	39	39	Cerebral infarct
15	Male	Positive	84	85	Dementia
16	Male	Negative	76	76	Embolic cerebral infarct, mild dementia
17	Female	Negative	19	19	Right capsular necrosis, cerebral vasculitis (rheumatoid)
18	Female	Positive	68	68	Parkinson's disease

From Shulman KI *et al.* 1992.

A fortiori, in very late-onset first episode mania, 10 of 14 patients had comorbid neurological disorders; largely cerebral infarctions (Tohen *et al.* 1994). In follow-up (mean 4.5 years) five of the six men with mania died.

NEUROIMAGING AND BRAIN LOCALIZATION

A compelling case has been made for the existence of a clinically significant brain circuit responsible for disinhibition syndromes as well as secondary mania (Starkstein and Robinson 1997). The orbito-frontal circuit (OFC) includes connections to the frontal lobes that modulate psychomotor and motivational behaviour; limbic connections that modulate emotional drive; and the hypothalamus, amygdala and brain stem nuclei that modulate instinctive behaviours. Thus, lesions of the inferior and frontal aspects of the brain impact on these connections, thus accounting for the psychomotor, emotional and instinctive symptoms of secondary mania. Similarly, the diagnostic term "frontal lobe dementia" includes elements of disinhibition associated with decreased metabolic activity in the orbito-frontal circuit (Starkstein *et al.* 1994).

Neuroimaging research has helped to elucidate the nature, more so than the location, of brain lesions (Shulman 1997). These findings include a preponderance of subcortical hyperintensities, decreased cerebral blood flow and evidence of silent cerebral infarctions. An increase in subcortical (basal ganglia) hyperintensities has been found in elderly manics, largely in the inferior half of the frontal lobe (McDonald *et al.* 1991, Woods *et al.* 1995). The relationship to cerebrovascular disease is strengthened by the associated risk factors such as hypertension, cardiovascular disease and diabetes mellitus.

Late-onset mania is associated with a higher prevalence of silent cerebral infarctions (Kobayashi *et al.* 1991, Fujikawa *et al.* 1995). This association is true even compared to age-matched depressives, resulting in a prevalence of >20% of silent cerebral infarctions in mania over the age of 60. Cerebral blood flow studies suggest that a specific decrease is evident in the right basal temporal cortex (Migliorelli *et al.* 1993). All of the findings support a concept of "vascular mania" not dissimilar to the evolving concept of "vascular depression" in old age, as elaborated by Alexopoulos *et al.* (1997).

PROPOSED SUBTYPES

Based on the review of the literature on bipolar disorder and mania in old age, it would appear that four distinct subtypes emerge, all of which require corroboration through further systematic research. We would propose the following distinct subtypes:

1. Early-onset bipolars who remain symptomatic into old age (primary bipolar disorder).
2. Middle-aged depressives who "convert" to mania later in life after a long latency and multiple depressive episodes.
3. Unipolar mania which tends to have an early age at onset and continued episodes into old age.
4. Late-onset mania associated with neurological disorders (secondary mania, disinhibition syndromes).

MANAGEMENT OF MANIA IN OLD AGE

What implications might these proposed subtypes have for the management of mania in late life? Does ageing itself have any effect on treatment? Unfortunately, these questions cannot be answered with a truly evidence-based approach. Despite the prevalence, morbidity and mortality reviewed above, there are no randomized controlled studies of treatment in an elderly manic population. Clinicians have therefore had to rely on clinical guidelines designed for younger populations. This approach, however, is potentially hazardous as a result of pharmacokinetic and pharmacodynamic changes that occur in older populations (Herrmann *et al.* 1997, Naranjo *et al.* 1995).

Pharmacokinetic changes that occur with ageing include effects on absorption, volume of distribution, hepatic metabolism and renal clearance. Pharmacodynamic changes may include changes in receptor sensitivity, increased monoamine oxidase levels and decreased cholinergic function. All these factors, associated with frequent concomitant medical illnesses and their treatments, increase the risk of adverse events and drug interactions (Naranjo *et al.* 1995). Furthermore, if the aetiology of certain types of late-onset mania differs compared with younger populations (e.g. those associated with neurological disorders), it is possible these patients may not benefit from, or tolerate, standard treatment approaches.

Given these caveats, management will be reviewed beginning with a discussion of assessment, general approaches to treatment and a brief review of the guidelines published for the treatment of younger manic patients. The studies on the treatment of elderly manics will then be reviewed, emphasizing the modifications necessary to treat this population.

The management of elderly manics begins with a thorough medical and psychiatric assessment to rule out medical conditions, medications, or other psychiatric diagnoses such as dementia and delirium, that may present with manic symptoms. The history and physical examination should emphasize the search for localizing neurological signs and symptoms. This includes documenting a history of head injury, cerebrovascular disease and risk factors, and careful examination for movement disorders. Routine labo-

ratory investigations are necessary for assessment and differential diagnosis as well as providing baseline values for treatment with mood-stabilizing medications. Most guidelines for younger patients make no recommendations for neuroimaging. In contrast, neuroimaging has been described as "essential" for elderly manics (Van Gerpen *et al.* 1999). Depending upon the severity of symptoms, hospitalizations may be necessary to protect the patient from self-harm or socially and financially damaging behaviours. Establishing a therapeutic alliance is essential as these patients will require lengthy follow-up. There are no studies of psychotherapy or psychoeducational approaches with elderly manic patients; however, these interventions should lead to improved compliance with medication and possibly improved social functioning and understanding of the illness (Bauer and McBride 1996).

Management can be divided into acute and maintenance treatment (American Psychiatric Association 1994, Canadian Network for Mood and Anxiety Treatments 1997, Frances *et al.* 1996, Kusumakar and Yatham 1997). Guidelines for younger patients have continued to endorse the use of lithium carbonate or valproate as first-line therapy for acute mania. ECT can be considered for patients with severe symptoms or life-threatening behaviour. Benzodiazepines are recommended for insomnia and agitation, while neuroleptics may be required for psychotic symptoms. Both benzodiazepines and neuroleptics should be tapered and discontinued after remission of acute symptoms. For patients who have not responded following 2–3 weeks of therapy at appropriate dosages and serum levels substituting or adding another mood stabilizer (lithium, valproate or carbamazepine) is recommended. This recommendation, however, may be a particular problem in older patients as polypharmacy is a concern. While adding another mood stabilizer may sometimes be necessary, substitution should be attempted first. If the patient remains only partially improved, or is a non-responder, further substitution or addition of other mood stabilizers should be considered. Other options recommended at this stage would include the use of novel mood stabilizers (example lamotrigine, gabapentin, calcium channel blockers), the use of clozapine, or ECT. For patients who present with mixed affective symptoms, recommendations have generally favoured the use of anticonvulsants such as valproate or carbamazepine as first-line therapy, rather than lithium. Similarly, for patients who present with rapid cycling, therapy usually begins with valproate or carbamazepine, adding the other agent or lithium for partial or non-responders. Avoiding antidepressants and insuring normal thyroid function in this population has also been recommended.

For maintenance therapy, guidelines are unclear whether long-term maintenance should be initiated after a single manic episode or after two episodes. Several controlled trials have documented lithium's value as a prophylactic agent (Sharma *et al.* 1997). Studies suggest that prophylaxis

with lithium should occur at similar dosages and serum levels as acute treatment, since lower levels (less than 0.6 mmol/L) are associated with an increased risk of relapse (Gelenberg *et al.* 1989). The efficacy of valproate and carbamazepine for maintenance therapy has also been demonstrated in controlled trials (Sharma *et al.* 1997).

Bipolar patients on maintenance therapy should be followed at least every 6 months with regular monitoring of serum levels and appropriate laboratory investigations. It is unclear how long maintenance therapy should be maintained, though there is increasing evidence that abrupt discontinuation of mood stabilizers, especially lithium, is associated with high relapse rates within several months, even after many years of mood stability (Suppes *et al.* 1993). Similarly, elderly patients on mood stabilizers may be at a high risk for relapse and may require ongoing maintenance therapy "for life". Recommendations suggest that, when discontinuation is necessary, it should occur extremely slowly and medications should be tapered over a period of at least 1 month (Suppes *et al.* 1993).

MOOD STABILIZERS IN THE ELDERLY

Lithium carbonate

While there are several uncontrolled naturalistic and retrospective case series that suggest lithium is equally effective in the elderly compared with younger populations, there are no randomized controlled trials of its use for acute mania or maintenance therapy in late life (Himmelhoch *et al.* 1980, Schaffer and Garvey 1984, Shulman and Post 1980, van der Velde 1970, Chen *et al.* 1999). Lithium remains one of the most commonly used mood stabilizers in the elderly, and some studies suggest that the prevalence of lithium use is even higher in elderly populations compared with younger ones (Head and Dening 1998).

Despite evidence for its effectiveness and widespread use, lithium, must be used cautiously in older patients. Lithium is eliminated by the kidneys and normal-age associated declines in creatinine clearance and glomerular filtration rates will affect its pharmacokinetics. Furthermore, lithium levels will increase with age as a result of decreased volume of distribution (Chapron *et al.* 1982, Hardy *et al.* 1987). Hardy *et al.* (1987) studied the kinetics of lithium in nine elderly patients and documented clearance of approximately one-half that of younger patients, as well as significant intra-individual variations. Lithium was eliminated more slowly from a smaller volume of distribution compared to younger individuals. Based on these pharmacoketic data, these authors recommend that geriatric patients may require one-third to one-half less lithium than younger adults, and that this could be administered as a single daily dose. Similar results were noted in a study of young, middle-aged and elderly patients where the latter required

36% less lithium to reach similar serum levels compared with the younger patients (Greil *et al.* 1985).

Besides these pharmacokinetic changes the elderly may also be more sensitive to lithium from a pharmacodynamic perspective. Studies have noted increased adverse reactions and toxicity at serum levels considered normal in younger adults (Murray *et al.* 1983, Roose *et al.* 1979, Smith and Helms 1982). However, the tolerability of lithium in the elderly remains controversial. In a retrospective study of 114 elderly outpatients treated with lithium, 61% experienced side-effects at some point in their therapy but this translated into only one side-effect for every 10 years of lithium use (Holroyd and Rabins 1994). Other studies have supported the conclusion that lithium is safe and well tolerated in the elderly (Parker *et al.* 1994). A recent small randomized study of adjunctive lithium prophylaxis in an elderly medical-psychiatric population, however, raised some concern (Stoudemire *et al.* 1998). This study of depressed patients found that 76% (13/17) of patients randomized to receive lithium were unable to tolerate it because of side-effects such as gastrointestinal disturbances and tremor. Possible explanations for this poor tolerability may be related to the specific patient characteristics (medically ill, depressed patients) or the effects of polypharmacy, as lithium was added to antidepressants in this study.

Because of the pharmacokinetic and pharmacodynamic changes noted above, recommendations for the elderly have often included the use of lower dosages and serum levels (0.5–0.8 mmol/L) (Glasser and Rabins 1984). Not all authors agree with this recommendation as there is some suggestion that higher levels are associated with better outcome (Young 1996). For example, in a recent retrospective study comparing lithium with valproate, 30 elderly manics were treated with lithium (Chen *et al.* 1999). Serum levels greater or equal to 0.8 mmol/L were associated with greater improvement compared to patients whose serum levels were lower. Sixty-seven per cent of patients were rated as improved overall on lithium therapy, with a higher percentage (82%) improving with serum levels between 0.8–1.3 mmol/L. While these results appear impressive, the study was retrospective and excluded patients with any evidence of "secondary mania", particularly neurological illness. No information was provided on tolerability or the percentages of patients who could not tolerate the higher serum levels. Given the significant medical comorbidity and frequent co-occurrence of neurological disease in late-life mania, it is not surprising that many authors still recommend lower serum levels, as levels greater than or equal to 1.0 mmol/L have frequently been associated with toxicity (Shulman and Herrmann in press, Van Gerpen *et al.* 1999).

Adverse effects of lithium include impact on the central nervous system, gastrointestinal, cardiovascular, endocrine and renal systems. The elderly may be more susceptible to impaired cognition and delirium (Himmelhoch *et al.* 1980, Schaffer and Garvey 1984), with evidence of neurotoxicity that

can last for weeks following discontinuation and undetectable serum levels (Nambudiri *et al.* 1991). Lithium can also induce tremor, worsening of Parkinsonian tremor and spontaneous extrapyramidal symptoms. It is unclear whether gastrointestinal effects such as irritation and nausea, or renal effects such as reduced tubular concentrating effects and nephrogenic diabetes insipidus, are more common in the elderly. While it is unclear whether the elderly are more susceptible to lithium-induced hypothyroidism, a recent community study noted that 32% of a group of 148 elderly people were on thyroid replacement or had elevated TSH levels (Head and Dening 1998). The elderly may be at higher risk for cardiovascular events because of preexisting sinus node disease and the concomitant use of cardiovascular medications (Roose *et al.* 1979). There are also numerous medications used more frequently in the elderly that can interact with lithium (Finley *et al.* 1995). Thiazide diuretics can decrease lithium clearance by 25%, increasing serum levels of lithium and potentially leading to toxicity. Angiotensin-converting enzyme (ACE) inhibitors will also increase serum lithium levels, though reports of the effects of calcium channel blockers and loop diuretics are less conclusive. Certain non-steroidal anti-inflammatory drugs, such as indomethacin, will increase lithium concentrations, and other anti-inflammatories, such as acetylsalicylic acid (ASA) and sulindac, may be safer alternatives as they do not appear to have this effect (Herrmann *et al.* 1997).

Valproate

Given concerns about lithium's tolerability and potential for drug interactions in the elderly, recent attention has been focused on the use of anticonvulsants as mood stabilizers. While there are no data to support the contention, some authors have even suggested that older age is a relative contraindication to lithium therapy and a specific indication for therapy with carbamazepine or valproate (Gerner and Stanton 1992). Several early case reports (McFarland *et al.* 1990, Risinger *et al.* 1994) and recent larger case series (Kando *et al.* 1996, Noaghiul *et al.* 1998, Chen *et al.* 1999, Mordecai *et al.* 1999) suggest that valproic acid is effective and well tolerated in the elderly. In one study 90% of 21 elderly manic patients were rated as very much or much improved, with only two patients who experienced significant adverse reactions, such as sedation, which responded to dose reduction (Noaghiul *et al.* 1998). The average dose of divalproex sodium used in the study was 1400 mg/day with an average valproate level of 72 mg/L. There was no relationship between serum levels and outcome, even though the mean serum level achieved in this study was within the recommended range suggested by studies with younger patients (45–125 mg/L) (Bowden *et al.* 1996). In another retrospective study of 29 elderly manics treated with valproate, 38% demonstrated improvement compared to 67% of 30 patients

treated with lithium (Chen *el al.* 1999). In this study, serum levels of valproate were correlated with response but only when a "tighter" range of serum levels was employed (65–90 mg/L). Eighteen per cent of patients with levels between 45 and 65 mg/L improved, compared with 75% of patients with levels between 65 and 90 mg/L. This study also suggested that lithium was more effective for classic mania, while response rates for mixed mania were similar for both lithium and valproate. Case reports have suggested that valproate is effective for the treatment of elderly rapid cycling bipolars as monotherapy (Gnam and Flint 1993) or in combination with lithium carbonate (Schneider and Wilcox 1998).

Studies in elderly manics and patients with dementia suggest that valproate is extremely well tolerated (Herrmann 1998, Porsteinsson *et al.* 1997). Side-effects have included sedation and gastrointestinal disturbances. The latter, including anorexia, nausea and vomiting, can be lessened with use of divalproex sodium. In a recent pharmacoepidemiological study with a mixed-aged patient sample, treatment with divalproex was significantly less likely to cause gastrointestinal side-effects, specifically anorexia, nausea, vomiting and dyspepsia, compared with valproic acid (Zarate *et al.* 1999). Valproate is highly protein-bound and a weak inhibitor of cytochrome P450 2D6. It can inhibit the metabolism of tricyclic antidepressants and displace diazepam from protein-binding sites, increasing plasma concentrations and potentially leading to adverse events (Janicak 1993). Compared with the other commonly used anticonvulsant carbamazepine, valproate is generally considered better tolerated and less likely to cause drug interactions.

Carbamazepine

While carbamazepine has been demonstrated to be safe and effective in young manic patients for acute management and prophylaxis, there are only a small number of case reports (Kellner and Neher 1991, Schneier and Kahn 1990) and no controlled trials of its use in the elderly. Recommendations for use in elderly patients have generally suggested maintaining relatively low serum levels, as levels above 9 μg/ml may be associated with an increased risk of side-effects (Young 1996). Carbamazepine is a potent inducer of cytochrome P450 2D6 and is highly protein-bound, making it a significant concern for potential drug interactions (Janicak 1993). Medications commonly used in the elderly, including calcium channel blockers, erythromycin, cimetidine and fluoxetine, can increase plasma levels of carbamazepine, while carbamazepine can decrease plasma concentrations and half-lives of warfarin, theophylline, haloperidol and alprazolam. Despite the concerns about tolerability and the potential for drug interactions, a recent study of carbamazepine for the treatment of agitated, frail, demented patients suggests it can be well tolerated in the elderly (Tariot *et al.* 1998).

OTHER TREATMENTS

There is a small amount of preliminary data on a variety of other mood stabilizers and adjunctive treatments for elderly manics. In one case report the anticonvulsant gabapentin was used successfully to treat an elderly female with bipolar disorder intolerant of lithium and valproate (Sheldon *et al.* 1998). Elderly patients were also included in two recent case series utilizing gabapentin (Ghaemi *et al.* 1998, Cabras *et al.* 1999). While response by age was not noted, in one of these studies, which included 22 mixed-aged patients, the oldest subject, an 82-year-old patient, was the only subject who discontinued treatment early because of inadequate response (an increase of hypomanic and agitated symptoms) (Cabras *et al.* 1999). Another anticonvulsant with potential mood-stabilizing effects is lamotrigine. In a single case report, lamotrigine was added to divalproex to successfully treat an elderly rapid cycling bipolar patient (Kusumakar and Yatham 1997). Some elderly patients were also treated in an open-label study of lamotrigine in treatment-refractory bipolar patients (Calabrese *et al.* 1999). There is a single case report of a 66-year-old manic patient treated successfully with a calcium channel blocker, verapamil (Gash *et al.* 1992).

Neuroleptics and benzodiazepines are commonly used as adjuncts in the treatment of elderly bipolars (Sajatovic *et al.* 1996). Elderly patients are particularly susceptible to side-effects from typical neuroleptics such as anticholinergic effects, orthostatic hypotension and extrapyramidal symptoms, including a dramatically higher incidence of tardive dyskinesia compared with younger patients (Naranjo *et al.* 1995). As a result there is some suggestion that clinicians are more cautious with their use, and fewer elderly patients are discharged on these medications (Broadhead and Jacoby 1990). The atypical neuroleptics such as risperidone, olanzapine and quetiapine are better tolerated in the elderly and cause much less extrapyramidal symptoms including tardive dyskinesia (Jeste *et al.* 1999). Given emerging data suggesting they also have anti-manic and mood-stabilizing effects (Tohen *et al.* 1999), these drugs will probably be used more frequently for elderly manics. Shulman *et al.* (1997) successfully treated three elderly manic patients with clozapine who had been previously non-responsive to lithium and valproate. Finally, ECT has also been reported to be effective and well tolerated in elderly manic patients (Mukherjee *et al.* 1994).

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Chapter nine

Temperament and personality types in bipolar patients: a historical review

Jules Angst

INTRODUCTION

A historical review of the temperament/personality of manic and bipolar patients remains to be written, whereas there are many such reviews of bipolar illness and of mood disorders (Schüle 1878, Ritti 1894, Mendel 1881, Pilcz 1901, Schott 1903, Birnbaum 1928, Lewis 1934, Fischer-Homberger 1968, Huber 1985, Berrios 1988, Berrios and Beer 1992, 1995, Perris 1992, Pichot 1995, Porter 1995, Haustgen 1995, Angst 1998).

This chapter will focus on significant moments in the development of the *concepts of the temperament/personality of manic and bipolar patients,* concepts which have changed considerably since they were first described nearly 2000 years ago. Some caution is necessary in dealing with these concepts: the meanings of basic terms such as melancholia and mania have changed considerably in the course of two millennia; the meaning of any association that may have been described, as for example between the melancholic and the sanguine temperaments and melancholia and mania will not necessarily correspond to present-day concepts; lastly, we cannot be certain – despite our assumptions – that the authors have been describing the same phenomena.

As regards the sources of this chapter, for the nineteenth and twentieth centuries the original French, German and English texts were used; access to the Greek and Latin sources was through the English translations. As far as possible I have retained the authors′ own terminology.

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 175–199.

For reasons of space this review could not take into account the full extent of modern research and theories on the personality of bipolar patients; it concentrates on the developments that currently appear to be the most significant and most promising. For more exhaustive accounts of developments in the field, the reader is referred to the reviews of von Zerssen (1993, 1996 and 1999b) on personality and affective or functional disorders in general.

TEMPERAMENT SINCE ANTIQUITY

A clear and comprehensive description of *the early concept of temperament* was given recently by Kagan *et al.* 1994:

"The Greeks and Romans believed that a balance among the four humours of yellow and black bile, blood, and phlegm, present in all persons, created an opposition within each of two pairs of bodily qualities: warm versus cool and dry versus moist. Gale n derived nine temperaments from the four humours; in the ideal personality, the complementary characteristics of warm-cool and dry-moist were exquisitely balanced. In the remaining four types, one pair of qualities dominated the complementary pair, for example, warm and moist dominated cool and dry. These latter four were the temperamental categories Galen called melancholic, sanguine, choleric, and phlegmatic. ..."

Sharpe's (1964) introduction to and translation of the medical writings of Isidore of Seville (AD 560–636), who in the early Middle Ages described the humoural theory in detail, reveals the surprisingly modern nature of *the ancient concept of temperaments:* it *is in fact a dynamic concept,* the humours were formed and renewed daily, and as Sharpe notes "the bodily constitution is determined by the proportions in which these elemental qualities are mixed, the *temperamentum.* Health consists in a harmony of these elements, and excess or defect in one or more of these qualities produces disease" (p. 24) (for a graphic representation of Isidore of Seville's description of the humoural concept see Figure 1). From a modern perspective, Greenwood (1943), cited in Sharpe 1964, notes that for Galen every human temperament could be represented by a point in a plane the position of which was determined by its coordinates. As Greenwood stresses "Galen did not, of course, express this geometrically but verbally and verbosely". Clearly the concept was – in today's terms – *dimensional.* But as Greenwood points out, Galen's successors ignored his insistence on continuity and picked out "typical" temperaments. As a result "Galen's insistence on continuity was forgotten by clinicians".

As Kagan observes, in the nineteenth century the term *character* – a much more *static* concept – was used to describe the distinctive behavioural styles, while temperament referred to the variation in emotional reactivity. *Today, temperament* conventionally refers to stable behavioural and emotional reac-

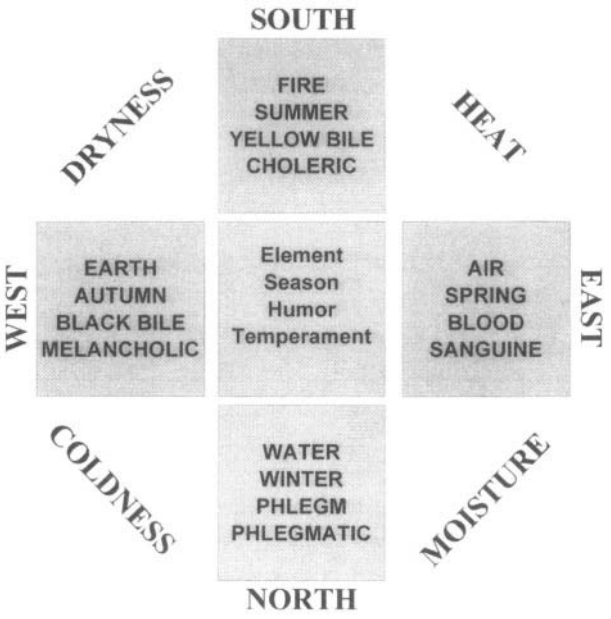

Figure 1 Schema of the four elements and their distribution in the world, year, human body and its temperaments, quarters of the globe and prevailing winds according to Isidore of Seville (from Sharpe 1964, with the permission of the American Philosophical Society).

tions that appear early and are influenced in part by genetic constitution (Kagan *et al.* 1994, pp. 40–2).

MELANCHOLIA AND MANIA IN ANTIQUITY

Melancholia as described by Hippocrates was a consequence of black bile (produced in the spleen) and was predominantly a somatic or even polysomatic disorder, which could concomitantly also create psychological effects; if the latter were at all dominant, then it meant insanity; nevertheless some loose connection with today's depression may well have been present (Starobinski 1960).

The term *mania* had complex connotations; in Plato's writings it meant wrath, fury, mental excitement and thought; "for Plato there was both an abnormal variety of mania as rage and a god-inspired variety of revelatory mania, which empowered one to make prophecies" (Stone 1997, p. 9).

The terms melancholia and mania as used in Antiquity were not congruent with today's concepts (Jeliffe 1911, Ackerknecht 1957, Fischer-Homberger 1968, Berrios 1988, Berrios and Beer 1992); both terms were much broader and included all functional psychoses, i.e. schizophrenia and

partially also organic psychoses (Marneros 1999). They did however include today's depression and mania; but for instance agitated depression would probably have been regarded as mania; because agitation and excitement were elements of mania.

Aretaeus of Cappadocia (*c.* AD 30–90) developed an original concept of mania and melancholia (Huber 1985) and explicitly described the association of melancholia and mania in the same individual (an association described centuries later by Mead (1673–1732) and Chiarugi (1753–1820)), but no "manic-melancholic" disorder emerged from these observations (see also Angst and Marneros 2000, Marneros and Angst in this book). More specifically, Aretaeus taught that mental disease had its origins in the head or abdomen and that both melancholy and mania were different expressions of the same malady: "it appears to me that melancholy is the commencement and a part of mania" (transl. Adams 1856, p. 299). Aretaeus departed from humoural theory, however, favouring instead descriptive terms:

"Those prone to the disease are such as are naturally passionate, irritable, of active habits, of an easy, disposition, joyous, puerile: likewise those whose disposition inclines to the opposite condition, namely, such as are sluggish, sorrowful, slow to learn, but patient in labour, and who when they learn anything soon forget it; those likewise are more prone to melancholy who have formerly been in a mad condition" (trans. Adams 1859, p. 301).

Aretaeus may be seen to presage contemporary continuum theories of personality (Stone 1992, p. 13).

NINETEENTH-CENTURY VIEWS OF TEMPERAMENT, MANIA AND MELANCHOLIA

In the first half of the nineteenth century the terms mania and melancholia still encompassed all kinds of mental disorders (including schizophrenia, intoxications and brain disorder); in parallel the concept of temperaments inherited from Antiquity was still in use. We find, for instance, Esquirol (1838, vol. 1, p. 39) noting that choleric and sanguine temperaments predispose to mania. Esquirol described manic patients as being highly sensitive, lively, irritable, angry, enthusiastic and risk-taking, and some as suffering from sleep problems, somnambulism, hysterical fits and epileptic convulsions. The ancient concepts were also still alive in Kahlbaum (1878), who considered that the melancholic temperament could be compared to melancholia and the sanguine to mania (p. 1129).

When Griesinger (1861) compiled his textbook, no clear classification of mental disorders had yet emerged; Zeller's *Unitarian degeneration theory* (1837) still dominated the field. Griesinger's discussion of the causation of mental illness thus rejected the concept of temperaments outright (p. 165 referring also to Gall, Georget and Lotze). Griesinger believed in general

(unspecific) constitutional factors predisposing to mental disorder, namely irritable weakness (pp. 55, 163) (corresponding to today's neuroticism) and psychic pain (painful, depressive, negative affect) (pp. 163, 213). For Griesinger the basic disturbance of mania was psychomotor in nature (p. 276), expressed as being unbound, free and exaggerated. Griesinger's concept of mania was a broad one, which included non-affective psychoses; thus transitions from melancholia to mania were possible. Griesinger distinguished between emotional disorders (*Gemüthsleiden*), melancholia, mania and depression on the one hand and madness (*Wahnsinn*) (p. 57) on the other.

Circular insanity (bipolar disorder) and cyclothymia

The modern classification of mood disorders emerged a century and a half ago with Jean-Pierre Falret (1851) who created (*folie circulaire*) *bipolar disorder* and with Baillarger 1854 (*folie à double forme*), both marking the beginning of a promising development.

Falret's description of *folie circulaire* enabled the detection of its mild forms: his son, Jules Falret (1866, 1878, 1897), clearly identified the *attenuated types of folie circulaire* (Jeliffe 1911) and provided detailed descriptions of personalities recognizable in present-day terms as hyperthymics (hypomanics) and mild depressives within the norm. They continued to live the life of the community, or the family, without needing to be treated as sick. Such cases were considered to represent the mildest and most frequently overlooked phase of *folie circulaire* (Jeliffe p. 664). Hecker (1898) described them as cyclothymics following the classification of Kahlbaum (1882).

The contribution of Kahlbaum (1863) to modern psychiatric classification was decisive, because of his distinction between remitting and non-remitting forms of mood disorders. Kahlbaum's classification system, based on close clinical observation, is terminologically extremely complex. For our purposes it is Kahlbaum's. 1882 concept of *true mood disorder* (*echte Gemütskrankeit*), influenced by the concepts of J-P. Falret and Baillarger, which is of great interest. True mood disorders consists of dysthymia (Flemming 1844), *hyperthymia and cyclothymia* (these last two terms are Kahlbaum's creation), which correspond to today's depression, mania and bipolar disorder. He considered milder cases to be very common.

Hecker, Kahlbaum's pupil and son-in-law, described (1871, 1877, and 1898) cyclothymia as a mild circular disorder, which was rarely recognized as a disorder at all and in its mild stages was considered to be normal. Hecker also noted the *creative powers* of cyclothymics. These mild forms of circular disorder correspond to some extent to Kraepelin's hypomania and to Schüle's mania mitis or mania mitissima (Jeliffe p. 667).

In France cyclothymia received much attention from Deny (1908, 1909) and his pupil Kahn (1909); they extended the term to cover not only the

mild forms of manic-depressive intensity (MDI) but also a special morbid predisposition, all of which were considered to be highly inheritable (Lewis the cyclothymic constitution 1934, p. 26). The cyclothymic constitution was assumed to be the expression of an imbalance in the individual's moral sensitivity, usually starting in adolescence and characterized by a permanent, basic disorder of the affective sphere, which could take a circular or intermittent course. The milder forms of cyclothymia were described as being almost normal psychological conditions (Kahn 1909, pp. 12, 19, 239). Ballet (1902) had gone even further, hypothesizing that circularity might be a characteristic of the normal functioning of the nervous system, which was merely magnified and amplified during periods of pathological change. Löwenfeld's circular neurasthenia was subsumed by Kahn to cyclothymia.

In the twentieth century the term cyclothymia has been used in three ways: (1) for manic-depressive disorder (Schneider 1967, Weitbrecht 1968); (2) for mild grades of manic-depressive disorders; and (3) for constitutional features and personalities, characteristic of bipolars. Several authors have used the second concept (Hecker 1871, Hoche 1897).

The potentially productive development of research on bipolar disorder initiated by Falret was halted by Kraepelin's problematic but widely accepted Unitarian concept of MDI. It was not until the 1960s that Falret's concept was revived (Angst 1966, Perris 1966, Winokur *et al.* 1969). As a consequence of the conceptual diagnostic changes introduced by Kraepelin, systematic research on the temperament or personality of patients suffering from bipolar disorder was delayed for 60 years.

Emil Kraepelin: manic-depressive insanity and disposition/fundamental states

The year 1899 saw the birth of Kraepelin's immensely influential concept of *manic-depressive insanity (MDI),* and until 1920 all research on bipolar disorder was dominated by Kraepelin's authority.

In a later development of his thinking, Kraepelin (1913) clearly also held a dimensional view of MDI, including the mildest forms of characteristic mood changes, which he considered to be pre-stages of the disorder and as transitions to the individual dispositions. Kraepelin posited that MDI had *a general psychopathic basis* (p. 1237) in the form of *four personal dispositions:* the *depressive* disposition ("constitutional mood disturbance"), the *manic* disposition (Specht (1905) and Nitsche (1910) – what Kraepelin had earlier called "constitutional excitement"), the *irritable* disposition (regarded by Kraepelin as a mixture of the depressive and manic) and the *cyclothymic* disposition referring in this context to Wilmanns' (1906) work.

For Kraepelin all four dispositions represented premorbid characteristics, and, although Kraepelin did not consider MDI to be heterogeneous, he did not preclude the existence of subgroups (p. 1993). In fact, in his empirical

Table 1 Disposition and subtypes of MDI (from Kraepelin (1913), p. 1366

Disposition	*Depressives*	*Manics*	*Combined*
Depressive (%)	64.2 (45)	8.3 (17)	27.5 (28)
Manic (%)	35.6 (45)	23.3 (17)	41.1 (28)
Irritable (%)	45.5 (45)	24.4 (17)	30.1 (28)
Cyclothymic (%)	35.3 (45)	11.7 (17)	53.0 (28)

Figures in parentheses are estimated expected values.
von Zerssen 1999, personal communication.

approach Kraepelin came very close to distinguishing between mania, depression and bipolar subgroups.

Kraepelin cross-tabulated the four personality dispositions with the depressive, manic and combined groups of mood disorder in order to test for the heterogeneity of MDI (Table 1). He found that 53% of patients with a cyclothmic disposition belonged to the combined group and 64.2% of patients with a depressive disposition were also depressed; the manic and the irritable dispositions were more frequently identified in manic patients. Kraepelin did not believe that the depressed group had any special nosological status, because one-third of those with a depressive disposition were diagnosed as falling into the manic or combined groups. Kraepelin also found that 35.6% of his patients with a manic disposition suffered from depression; the same was true for 35.3% of those with a cyclothymic disposition and 45.5% with an irritable disposition (p. 1366). On the basis of these inconsistent findings Kraepelin decided to stand by his Unitarian concept of MDI. However, given the estimated expected values (which were not available to Kraepelin), one could also assume heterogeneity.

It is worth pointing out that Kraepelin never used the term temperament, either in its ancient or its modern sense, in this context. Referring to Reiss (1910), he posited an inner relationship between the different forms of disposition and MDI (p. 1310), a hypothesis that he based on their familial co-occurrence and the observation that they could develop into MDI. He also stressed the existence of *fundamental states (Grundzustände),* which often (37%, p. 1303) characterized the intervals between episodes, subsuming to these fundamental states the above four dispositions which frequently preceded the manifest disorder (p. 1304). It is clear that Kraepelin's concept was *Unitarian,* embracing disposition, fundamental states and manifest clinical forms of MDI (p. 1183). In view of the many and various types of transition, Kraepelin concluded that these distinctions were artificial and arbitrary (p. 1237). He therefore had no difficulty in integrating Kahlbaum's cyclothymia as a mild form of MDI (p. 1349)

Under Kraepelin's encouragement, Rehm (1919) wrote a monograph on MDI, which was based on Kraepelin's patients in the Munich psychiatric

hospital. Discussing the constitution of patients suffering from MDI, Rehm distinguished five subtypes of personality (p. 31), which he removed from the group of psychopathies (today's personality disorders) and subsumed under MDI (p. 32). Rehm's constituents of personality were: temperament, character, sleep, diurnal changes, headache, etc, which he used to distinguish the following subtypes: (1) personalities showing marked changes between melancholia and mania (present-day cyclothmic personalities); (2) cases showing constitutional psychomotor agitation (present-day hyperthymic personalities); (3) depressive–anxious personalities; (4) manic and depressive personalities (present-day cyclothymic), predominantly irritable, angry and oppositional; and (5) the depressive–retarded. According to Rehm, such personalities could but did not necessarily develop into MDI. He further described three constitutionally based subtypes of MDI: manic, melancholic and cyclothymic, and allocated chronic mania to the first group (p. 115).

In present-day terms, Rehm's Types 1 and 4 personality and his cyclothymic constitution would correspond to cyclothymia, his Type 2 and manic constitution to hyperthymia and his Type 5 and melancholic constitution to the depressive or melancholic personality.

Describing the characteristic features of patients suffering from MDI, Kraepelin noted that some had since youth been extraordinary and agitated, exhibiting frequent inexplicable mood changes, whereas others were brooding, excessively pious, shy and quiet. Some were mentally subnormal and some manifested hysterical features (pp. 399–400). In this early description of personality Kraepelin did not distinguish between depressive and manic-depressive patients.

Reiss (1910) devoted an extensive article entitled: "Constitutional mood variants and manic-depressive insanity: Clinical investigations of the relationship between disposition and psychosis" (*Konstitutionelle Verstimmung und manisch-depressives Irresein. Klinische Untersuchungen über den Zusammenhang von Veranlagung und Psychose)* to the relationship between temperament, emotional reactions, character and manic-depressive insanity. He started from the finding that depressive temperaments were predominant in depressive patients (p. 384) and set out to investigate which temperament was characteristic of manic and circular patients. On the basis of 181 records he concluded that he had totally failed in his attempt to demonstrate a relationship between temperament and psychoses (p. 595); he saw this negative finding as fully confirming Kraepelin's concept. Nevertheless Reiss (1910) found that subjects with a more cheerful disposition suffered more from manic states, while those with a depressive disposition suffered more from depressive states (p. 600).

The later Kraepelin (1913) saw Reiss' results as a clear demonstration of a relationship between personal characteristics (*Eigenart*) and the clinical form of the disorder, if not already as an expression of the disorder itself.

In this sense he thought it not improbable that an irritable disposition could be considered as a pre-stage of manic-depressive insanity (p. 1993)

Cyclothymia and hyperthymia as a mild form of manic-depressive insanity

Wilmanns′ monograph (1906) The mild cases of manic-depressive insanity (cyclothymia) (*Die leichten Fälle des manisch-depressiven Irreseins (Zyklothymie) und ihre Beziehungen zu Störungen der Verdauungsorgane*) stressed that such cases were too mild to be considered an apparent disorder; without knowledge of MDI they would completely escape recognition. Wilmanns′ mild cases included *cyclothymics* as described by Hecker (1877, 1898). In some cases Wilmanns also observed childhood enuresis, pavor nocturnus, cramps, etc. He found no evidence of low intelligence; indeed the intelligence of such individuals was above average and often associated with creative talents (poetry and music). In personality they were sensitive and showed a sense of delicacy (*feinfühlig*) (p. 768). Wilmanns observed no antisocial features in their previous history. Oversensitivity made them vulnerable to subtle changes in their environment that often went unnoticed by others. It is clear from the above that Wilmanns′ concept assumed there to be a continuum between cyclothymia and manic-depressive illness. Wilmanns′ list of features of mild hypomania would correspond to modern hyperthymia (pp. 776, 779); he describes such subjects as lively, talkative, irritable, liking to be at the centre of attention, fast in taking decisions and taking an active role, showing a very happy mood, good psychological and physical well-being, being fresh and strong, sure of themselves, curious, socially active, needing little sleep, and not experiencing tiredness. He found them to have increased efficiency without any loss of quality in their work, to be generous and lacking in any sense of being abnormal or sick. Like Kahlbaum and Hecker, Wilmanns also drew a clear distinction between hyperthymia, dysthymia and cyclothymia (p. 779).

Cyclothymia is described in Stransky′s (1911) masterly monograph on MDI as a mild form of MDI, which in some cases involved no further alteration of the subject′s personality and which was indistinguishable from the norm. Stransky reports reputable authors as holding the view that such cases were very mild forms of MDI (Wilmanns, Römheld and Ziehen); he also refers to the contemporary controversy (Oppenheim, Sollier, Dunin, Löwenfeld, Friedmann, Oddo, Markus) over whether cyclothymia ought not rather to be considered as a form of constitutional mood change, as a variant of psychopathic degeneration or, within the framework of the dichotomy psychoses/neuroses, as a neurosis (pp. 80–1). Stransky also refers to a further variant of MDI, *chronic mild mania,* considered by some authors to be a psychopathic variant, and by Kraepelin (1899) to be a chronic constitutional excitement.

The early Jung (1904) recorded in detail a number of cases of manic mood changes (*manische Verstimmung*), patients characterized by a stable submanic complex of symptoms, which had mostly developed in youth and lasted many years without remission. Jung found that exacerbations could occur in the course of their disorder and saw the social restlessness and social problems, the alcoholism, delinquency, and what he termed the "moral insanity" characterizing these patients as submanic symptoms. The symptoms described by Jung would correspond to today's *hyperthymia or very mild mania.*

In parallel with this clinical empirical work on cyclothymia and hyperthymia, there was, at the beginning of this century, considerable background controversy over the relationship between temperament or character and psychoses, the main protagonists being Tiling (1904) and Neisser (1905). Tiling considered the individual disposition (temperament/character/individual personality) or *Anlage* to be the sole factor in determining the constellation of symptoms (*Symptombilder*) and their course. He believed in purely psychological connections, rejecting anatomical hypotheses. In contrast, Neisser refused all psychological explanations of the psychoses, although he admitted their influence in the case of personality disorders.

REBIRTH OF TEMPERAMENT

In 1921 Kretschmer published his influential work on physique and character in relation to schizophrenia and manic-depressive disorder. Kretschmer upheld Kraepelin's Unitarian concept of MDI but extended cyclothymia to include depressive, syntonic, hypomanic–hyperthymic changes of mood (Marneros *et al.* 1992). Kretschmer saw psychoses as intersections in a network of physical and characterological constitutional relationships and regarded psychoses as no more than the accentuation of normal subtypes of *temperament* (p. 91).

Kretschmer developed two continua from personality subtypes to psychotic subtypes, one applying to MDI (cyclothymic–cycloid–manic-depressive) and one to schizophrenia (schizothymic–schizoid–schizophrenic). Referring explicitly to the work of Hoffmann (1921) (see below), Kretschmer stressed that the temperamental subtypes could often better be observed in close relatives than in patients (p. 89). Among manic-depressive patients three subtypes of temperament were found most frequently: (1) social, kind-hearted, friendly and warm-hearted; (2) cheerful, humorous, lively and fiery; (3) quiet, calm, taking things to heart (*schwernehmend*) and tenderhearted (*weich*). These correspond to his cyclothymic–cycloid, hypomanic and depressive temperaments.

Kretschmer defined *constitution* as the outcome of all the inherited individual features, *character* as the sum total of reaction patterns developed over

a person's lifetime through the interaction of nature and nurture (pp.184–5) and *temperament* as a heuristic term designating the biologically determined part of the mind, which correlates via humour with body build. This concept, which does not seem far from Galen's *chymoi* or "humours" as the basis of temperament, has been strongly criticized on various grounds, which have been summarized by von Zerssen and Akiskal (1998).

Hoffmann (1921) published an extensive monograph detailing the findings of the investigations that, with Gaupp and Rüdin's encouragement, he had conducted into the offspring of patients with mood disorders. Among relatives Hoffmann frequently observed not only secondary cases of depressive, manic and cycloid psychopathies but also mild pre-stages of MDI, e.g. hypomanic and depressive temperaments and cyclothymia (p. 114). Hoffmann concluded that they all shared the genetic disposition to MDI. On this basis he also raised the question whether MDI might not be *heterogeneous,* coming very close to distinguishing between depression, bipolar disorder (circular disorder, cycloid constitution) and cyclothymic temperament (p. 195). However, his doubts had no immediate impact. As von Zerssen and Pössl (1990) wrote: "For seven decades of the 20th century, research on the premorbid personality of psychotic patients were based on the concept of manic-depressive and schizophrenic psychosis forming two nosologically distinct entities (Kraepelin 1913). Hence, the aim was to search for a homogeneous premorbid personality structure for each of these two disorders." Kretschmer (1921) described the personality of patients with MDI as being as cyclothymic, and Bleuler (1922) described them as syntonic.

Von Zerssen concluded that Kretschmer's view of cyclothymia as the characteristic personality of MDI was wrong. It would seem that the main source of error was that Kretschmer stopped short of questioning Kraepelin's Unitarian concept and was thus prevented from linking his descriptive findings on temperament with subtypes of affective disorder.

REBIRTH OF BIPOLAR DISORDER

The breaking of Kraepelin's hold and the return to Falret's *folie circulaire* (bipolar disorder) took place gradually over decades. Among those who contributed to this process was the important school of Wernicke, Kleist and Leonhard. Wernicke (1906) convincingly contradicted the Unitarian view of MDI. His pupil Kleist (1926) described subtypes of *cycloid psychosis* and in 1953 created the concept of *unipolar psychoses* (recurrent mania, recurrent depression), maintaining that *bipolar psychoses* stemmed from an affinity between the two unipolar psychoses, which explained their frequent co-occurrence.

In 1930 Kleist had already posited a relationship between three polar groups of temperaments and three corresponding polar psychoses: (1) the

Table 2 Temperament and subtypes of mood disorders in relatives (adapted from Leonhard *et al.* 1962, and Leonhard 1963[1])

	Probands			
	Manic-depressive	*Melancholic*	*Depressive*	*Manic euphoric*[1]
Relatives	*(%)*	*(%)*	*(%)*	*(n)*
Hypomanic temperament/ psychosis	S 17 P 15	S 8.8 P 11.6	S 9.2 P 15.8	24
Depressive	S 5.3 P 7.5	S 15.5 P 23.3	S 12.2 P 11.1	6
Cyclothymic	S 14.9 P 15.0	S 6.6 P 18.6	S 8.2 P 6.5	2
Total	S 37.2 P 48.8	S 31.0 P 53.5	S 29.6 P 44.2	

S = siblings; P = parents.

hypomanic (sanguine) and depressive (melancholic) temperament, which corresponded to mania and depression (*Gemütskrankheiten*); (2) the motility temperaments, the lively (choleric) and sluggish, correlating with the hyperkinetic and akinetic motility psychoses; and (3) the mentally alert and mentally lazy thought temperaments, correlating with the two polar confusional psychoses (agitated confusion and stupor) (Kleist 1926).

Kleist's pupil Leonhard and co-workers (1962) applied this nosological model fruitfully to research on temperaments (Leonhard 1963a,b, Neele 1949) to family research. These authors hypothesized that if manic-depressive disorder could also take a monopolar course (the term used by Leonhard *et al.*), then the corresponding temperament should prevail in families: i.e. sub-depressive temperaments should be found in the families of monopolar depressive probands, a hypomanic temperament in the families of monopolar, manic and euphoric probands and a cyclothymic temperament in the families of manic-depressive probands. Among the siblings and parents of bipolars they found a preponderance of hypomanic and cyclothymic temperaments and psychopathies, and in the relatives of melancholies and depressives sub-depressive temperaments and psychopathies were found to predominate (Table 2). They interpreted their findings as confirmation of the monopolar-bipolar dichotomy, and believed somewhat questionably that these affective temperaments would *unspecifically* promote the manifestation of the disorder. They concluded that, among relatives, cyclothymia could manifest instead of manic-depressive disorder and a depressive temperament instead of depression and melancholia.

Leonhard *et al.* (1962) and Leonhard (1963b) rejected the possibility that the affective temperaments could be an expression of the endogenous disorder; however, Leonhard admitted that they could partially represent its latent forms. He wrote: "in the vast majority of affective temperaments there appears confirmation of the notion, expressed in earlier work, that a phasic psychosis breaks out only if it coincides with one of these temperaments" (Leonhard 1965, p. 115).

Despite these findings Leonhard *et al.* (1962) did not move mania and euphoria into the present-day group of bipolar disorder but kept them separate, like depression, as unipolar (Kleist 1953) or monopolar disorders.

RECENT DEVELOPMENTS

Modern developments in the field of personality and affective disorders have been authoritatively reviewed by von Zerssen (1982, 1999b), who distinguished research on depression, bipolar disorder and unipolar mania; only the last two groups will be of concern to us here.

It should be emphasized as a preliminary that a major methodological problem in modern studies of the premorbid personality of bipolar patients is the scarcity of prospective data. As stressed by Maier *et al.* (1995), most studies have been retrospective and have dealt with treated patients in university services (Matussek and Feil 1983, Akiskal *et al.* 1983, Hirschfeld *et al.* 1986, Cassano *et al.* 1992, von Zerssen *et al.* 1994). Nevertheless, von Zerssen's review maintains that valid premorbid measures may be obtained if patients are instructed to describe their state *before* the onset of their illness. This procedure cannot, however, completely rule out the effects of the illness: onset is frequently difficult to date, retrospective data on onset have been shown to be unreliable, and, as the study by Hirschfeld *et al.* (1983) showed, clinical states had a marked influence on personality scales, even though patients had been instructed to respond to items according to their 'usual self'.

PERSONALITY TRAITS OF PATIENTS WITH BIPOLAR DISORDER

Research into the personality of *bipolar patients* has somewhat surprisingly yielded almost completely negative results (review by Perris 1992); in both retrospective and prospective studies bipolars usually did not deviate from controls. This was true for different personality features assessed by the MMPI (Murray and Blackburn 1974), for psychogenic needs according to the concept of Murray (1938) (Bech *et al.* 1980, Bech and Rafaelsen 1980, Strandman 1978), for extroversion and for cyclothymia.

The only prospective study using true premorbid measures of personality traits (based on the Eysenck (1951) model) carried out on a community

cohort of young males showed no significant differences between subjects who later developed a bipolar disorder ($n = 26$) and controls ($n = 2842$) in terms of extroversion, neuroticism or aggression (Angst and Clayton 1986, Clayton *et al.* 1994).

PERSONALITY TYPES AND SUBGROUPS OF BIPOLAR DISORDER

Von Zerssen (1977a,b, 1980, 1988, 1992) proposed the spectrum hypothesis of affective disorders embracing all mood disorders (depression, bipolar disorder and mania) and postulated *two personality types*: a *"melancholic"* type (Tellenbach 1961) correlating with the depressive component, and a *"manic"* type correlating with the manic component of all subtypes of mood disorders.

A somewhat similar typology (melancholic type, circular type and mania type) had been proposed by Moriyama (1965, 1968) in Japan on the basis of the work of Shimoda (1941) on immodithymia (later called immobilithymia), corresponding to the melancholic type of personality of Tellenbach (1961).

According to von Zerssen's spectrum hypothesis of affective disorder the subtypes depression, bipolar II, bipolar I and mania would correlate with the proportional contributions of the two personality types: depressive patients would be characterized by the melancholic and manic patients by the manic type of personality. Von Zerssen explains the "normal personalities" found in bipolar patients by the hypothesis that they result from the mixture of personality features characteristic of manic and depressive subjects. Von Zerssen and Pössl (1990) developed an instrument to assess the two personality types on the basis of case history data; the measures demonstrated good stability over 4 years (Lauer *et al.* 1998) and recently Von Zerssen (1999a) developed an interesting circumplex model for the relationship between the two affective personality types and personality disorders.

The current distinction between bipolar I and bipolar II disorder is insufficient in order to test von Zerssen's spectrum hypothesis, because bipolar I embraces three separate groups: mania (M), mania with mild depression (Md) and the nuclear group of bipolars (MD). The concept proposed by Angst (1978) of a spectrum comprising several subtypes of bipolar disorder, rather than the traditional two, may provide a more fruitful basis for research on the premorbid personality of bipolars: the predominantly manic subtype (Md), the nuclear subtype (MD) and bipolar II (Dm), with the full spectrum of mood disorders also including major depression (D), milder forms of depression (d), pure mania (M), milder forms of mania (m), and cyclothymia (md). The subtype Md is frequently referred to in an abbreviated form as "manic", as pure mania with no symptoms of depression is virtually non-existent.

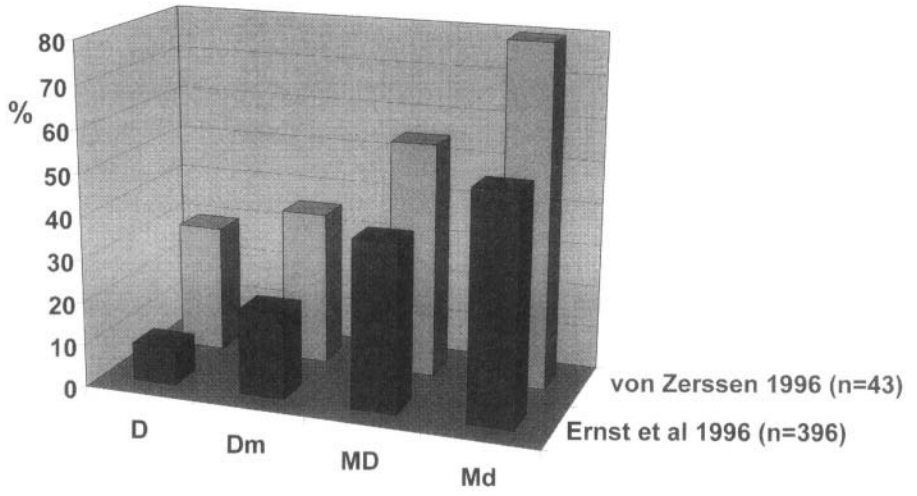

Figure 2 Subtypes of mood disorders and "manic" type of personality assessed "blindly" by biographical data.

In contrast to the generally negative findings in regard to bipolar disorder, the personality traits of preponderantly manic (Md) and unipolar manic (M) patients have been shown to deviate from those of controls (see review by von Zerssen 1982) in terms of their low neuroticism (Eiband 1979), high extroversion (von Zerssen 1982), hysterical traits (Eiband 1979, von Zerssen 1988), cyclothymia (Eiband 1979, Weigel 1981, von Zerssen 1979, 1980) and hypomanic tendencies (Arieti 1974). Angst and Ernst (1996), applying von Zerssen's VASSF to a community sample, found that on an analogue scale Md patients assessed themselves as more extroverted, less neurotic and more aggressive than MD patients and controls, whereas they did not differ from them in conscientiousness. These findings are compatible with von Zerssen's spectrum hypothesis.

The results of several retrospective studies are also in line with von Zerssen's hypothesis: patients with M or Md were frequently characterized by the predominance of a manic and the relative absence of a melancholic type of premorbid personality, differing significantly from both MD patients and controls. The findings for patients with Dm (bipolar II) lay between controls and major depressives (D), who were mainly characterized as melancholic types (Möller and von Zerssen 1987, von Zerssen 1982, Frey 1977, Dörr Alamos and Viani Barbagelata 1991, Sato 1995, von Zerssen 1996, Ernst *et al.* 1996, Hecht *at al.* 1998, 1998) (Figure 2).

Interesting prospective studies on the temperamental traits of adolescents have recently been conducted in the United States and Italy. Klein *et al.* (1996) assessed hypomanic personality traits in a community sample over 14 months; they found a normal distribution of the trait, a test–retest

stability of 0.54 and associations with behaviour problems; no predictive power for hypomania, mania or bipolar illness could be found over this short follow-up period, but neither can it be excluded.

Another prospective study on the temperaments of 14–18-year-old high school students in Italy carried out over 2 years showed considerable fluctuation and instability in depressive and hyperthymic temperaments, with changes longitudinally, mainly to cyclothymic temperaments (Placidi *et al.* 1998).

How to interpret the positive findings regarding the melancholic and manic subtypes of personality is an unresolved question. I would assume these subtypes to represent mild forms of the disorder itself (Akiskal *et al.* 1977, 1979, Akiskal 1981, Waters 1979, Wetzel *et al.* 1980) which cannot be differentiated from personality traits. This is the situation today for cyclothymia, which has become a subgroup of the bipolar spectrum (Klerman 1981, Akiskal *et al.* 1983, Pritz and Mitterauer 1984, Klein *et al.* 1985). Cyclothymia is predictive for the development of the bipolar disorder (Akiskal *et al.* 1977) and occurs in the families of bipolar probands (Hoffmann 1921, Klein *et al.* 1985), but so do depressive and hyperthymic/hypomanic temperaments (Hoffmann 1921, Maier 1993). Hypomanic personality disorder (Akhtar 1988) and depressive personality disorder (Hirschfeld 1994) could therefore be elements of the spectrum of mood disorders (axis I).

COMORBIDITY OF PERSONALITY DISORDERS WITH BIPOLAR DISORDER

In general, comorbidity is best determined by means of community studies in order to obtain valid odds ratios. Patient samples are not representative, and the findings based upon them can only have the status of hypotheses. So far speculation is more common than sound data. A recent Turkish study compared 90 cases of DSM-IIIR bipolar disorder with 58 controls, recruited from orthopaedic surgery (Ücok *et al.* 1998) and found all three clusters of personality disorders, (A, B and C) to be at least three times more frequent in bipolar patients; the differences were significant for paranoid, histrionic and obsessive–compulsive personality disorders and slightly less so for borderline personality disorder. These findings were considered consistent with the reports of O'Connell *et al.* (1991) and Peselow *et al.* (1995). The reviews of Gunderson *et al.* (1996), and Gunderson (1998) could find no convincing evidence of an association between borderline personality disorder and bipolar disorder, as has for instance been suggested by Akiskal *et al.* (1985) and Gunderson and Elliott (1985). Certain positive findings may be explained by definitional artifacts (Gunderson and Phillips 1991). In a review of the literature and an empirical investigation on "subaffective personality disorders", Sass *et al.* (1993) distinguished depres-

sive, asthenic and hyperthymic personality disorder on the basis of Schneider (1950) and DSM-III cyclothymic personality disorder, and concluded that a possible continuum of affective disorders is still far from being clarified. An exception was cyclothymic disorder, which was considered to contain an implicit conceptional overlap with affective disorders.

CONCLUSIONS

This brief historical review outlines the evolution of the concepts of temperament/personality in their relationship to mild and severe mood disorders over 2000 years, but it also shows how important conceptual shifts were masked by the persistence of terms such as melancholia, mania and temperament.

In the nineteenth century, significant progress was made in France and Germany both in psychiatric classification and the recognition that there was a continuum from normal to very mild and severe mood disorders; even so, the basic question of the relationship between personality/temperament and mood disorders is still unanswered.

Today we are inclined to accept the nineteenth-century *dimensional concept* of a continuum from normal typical characteristics of the personality (depressive, hyperthymic, cyclothymic "temperaments") to mild and severe mood disorders, a concept which was in the mind of many researchers since J.-P. Falret (1851), Baillarger (1854), J. Falret (1878), Kahlbaum (1863), Hecker (1898), Jung (1905), Wilmanns (1906), Stransky (1911), Kraepelin (1913), Reiss (1910) and Hoffmann (1921). But as Kraepelin found, it is difficult to distinguish between dispositional characteristics and the disorder itself, and even more so to differentiate residual states between episodes from personality or temperament. Today we still lack conclusive prospective data, collected with instruments measuring the specific concepts of premorbid personality types or temperaments.

The basic question of the nature of the causal relationship between typical personality characteristics and subtypes of mood disorders remains open; while there is little doubt about a shared genetic disposition, it remains to be established whether a typical premorbid personality is merely a specific vulnerability factor or whether it is an incomplete or early subclinical manifestation of the disorder itself.

An undoubted progress of the twentieth century lies in the *spectrum concept of mood disorder,* which is based on multiple descriptive clinical subgroups ranging from pure depression, through bipolar subgroups to pure mania, and which permits testing of sophisticated hypotheses, such as that of von Zerssen (1977a,b). The retrospective data on the distribution and preponderance of the melancholic and manic type of personality across these subgroups looks promising, but requires more evidence from pros-

pective studies. Prospective data from developmental psychopathological and family studies in representative cohorts from the community and embracing childhood, adolescence and adulthood would certainly give better answers to these questions.

Acknowledgement

The author thanks Professor Detlev von Zerssen for his valuable comments and suggestions.

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Chapter ten

Interactional styles in bipolar disorder

Christoph Mundt, Klaus T. Kronmüller
and Matthias Backenstraß

INTRODUCTORY REMARKS

Interest in the interactional styles of patients with affective disorders has been greatly stimulated by the great success of the expressed emotion research paradigm in schizophrenia. The very consistent finding that schizophrenic patients in HEE families show a higher relapse rate compared to those in LEE families (Kavanagh 1992) was connected with the vulnerability stress model of schizophrenia. Tarrier's group (Tarrier *et al.* 1979) could demonstrate that psychophysiology and neuropsychology change when patients start communicating with HEE key relatives, i.e. increased affective load raises autonomic arousal beyond the vulnerability threshold and the chain basic symptoms/transitional states/manifest psychosis can be set off.

Compared to this field the expressed emotion findings in affective disorders are much more inconsistent and inconclusive. Furthermore the very elusive theoretical vulnerability-stress model cannot be transferred straightforwardly to the affective disorders. The situation is more complicated here. We are confronted with a variety of competing pathogenetic models, focusing on temperament and affect regulation, autonomic instability, cognitions, self-image and self-esteem, and deficits in social competence and social network (Mundt 1998).

Hence, apart from the expressed emotion paradigm, other methodological approaches may have contributed more to our knowledge concerning about the impact of interactional styles on the development and course of affective disorder.

A. Marneros and J. Angst (eds). Bipolar Disorders: 100 years after manic-depressive insanity, 201–213.

THE MULTIMETHOD PERSPECTIVE OF INTERACTION RESEARCH

We briefly go through these methodological fields and report on the main results before presenting those of our own study.

Expressed emotion studies

There are seven studies which included bipolar patients when using the expressed emotion paradigm. All of them used the full Camberwell Family Interview (CFI); one in addition used the abbreviated form, the Five Minute Speech Sample (FMSS). The cut-off for critical comments as the principal criterion for the determination of high expressed emotion varied between seven in the Okasha *et al.* (1994) study and two in the Priebe *et al.* (1989) and Goring *et al.* (1992) studies. Hence it is difficult to compare the prevalence of HEE families among affective disorders across the studies, since the cut-off was obviously used to gain reasonable variance between HEE and LEE families. The follow-up period covered usually 9–12 months; only the study of Greil *et al.* (1992) followed up their patients for 5 years. This study was also the largest one, including more than 100 bipolar and schizoaffective patients, whereas the others worked with small samples which restricted their statistical power considerably. Four of the six follow-up studies – one was a cross-sectional-one only – found the EE index predictive for the 9-month course, one more found the patient's but not the partner's HEE status predictive, one found no prediction at all. The finding of Göring *et al.* (1992), that the actual partner EE was not predictive but the patient EE was, is an argument against the so-called "victimization" hypothesis of expressed emotion. The only study which found EE not predictive at all is the one with the longest follow-up. This supports a notion of many groups that the predictive power of the EE status depends on the stage of the illness when it was taken. It seems to be more influential if taken and applied at the beginning of the patient's carreer than in residual stages of the illness. This at least has been clearly demonstrated for schizophrenia by Schulze-Mönking (1993).

To sum up the results of EE studies one may assume that, for the very short-term course, there is a trend of the EE index to be predictive for the short-term course of bipolar disorder. The inconsistencies of the results compared to those of families with schizophrenic patients are discussed in literature with regard to the following factors. The assessment instrument may play a role. The application of a full CFI gains a higher rate of high EE families than the abbreviated form of the FMSS. However, the Heidelberg group developed a more sensitive FMSS form which used the criterion of "covert criticism" which made this instrument more sensitive for high EE families (Leeb *et al.* 1993). The cut-off score for critical comments may also influence the predictive value, as well as the reliability of the

Table 1 EE studies including bipolar patients

Study	*Diagnosis*	*Assessment*	*EE status*		*Follow-up*
Miklowitz *et al.* (1988)	Bipolar ($n = 11$) Schizomania ($n = 12$)	CFI, cut-off 6		HEE 43%	9 months predictive
Müller *et al.* (1988)	Schizophrenia ($n = 42$) Affective disorders ($n = 43$)	CFI	Schizophrenia Depression Bipolar Neuroses	HEE 64% HEE 53% HEE 57% HEE 63%	Cross-sectional only
Priebe *et al.* (1989)	Bipolar and schizoaffective disorders ($n = 21$)	CFI, cut-off 2		HEE 52%	9 months predictive
Göring *et al.* (1992)	Major depression and bipolar disorder ($n = 47$)	CFI, cut-off 2 FMSS, cut-off 2	Patient Partner Patient Partner	HEE 80% HEE 57% HEE 31% HEE 23%	6 months Partner-EE Not predictive Patient-EE predictive
Greil *et al.* (1992)	Bipolar disorder schizoaffective ($n = 101$)	CFI			5 years not predictive;
Okasha *et al.* (1994)	Unipolar depression ($n = 42$) Bipolar disorder ($n = 10$)	CFI, cut-off 7; PC		HEE 38%	9 months EE predictive; PC not predictive
Miklowitz *et al.* (1996)	Bipolar disorder ($n = 41$)	CFI, cut-off 6		HEE 32%	12 months predictive

CFI: Camberwell Family Interview; FMSS: Five-Minute Speech Sample; PC: Perceived Criticism; HEE: High Expressed Emotion; LEE: Low Expressed Emotion; cut-off refers to critical comments.

EE classification which is not always standardized with the Maudsley procedures.

The timing of the assessment, as well as the span of the follow-up period to which the prediction is applied, influence the rate of correct prediction. It is known that critical comments decrease during remission of the patient's symptomatology. The type of key relative also influences the EE status. Studies with families with a bipolar patient revealed that parents produce more critical comments than spouses (cf. Miklowitz *et al.* 1988: a study with parents, vs. Miklowitz *et al.* 1996: a study with partners and siblings).

The diagnostic subclassification of the sample can play a role, since this can influence the spontaneous course of the illness and, last but not least, the psychopathological status of the patient may influence the EE status, as shown by studies of Goldstein *et al.* (1996) with young patients at high risk for schizophrenia. The fact that, in families with bipolar patients, the patients themselves more often show high EE behaviour than relatives also highlights the problem of the interaction of the EE status and the psychopathological symptomatology of the patient at the time of its assessment.

Another important aspect of differences between EE studies on families with a schizophrenic and a bipolar patient was reported by Miklowitz *et al.* (1996). According to their observations the sensitivity–specificity relationship of the high EE versus low EE prediction is opposite in schizophrenics and bipolars. Among families of bipolar patients the specificity of EE predicting relapsing versus non-relapsing outcomes exceeded its sensitivity. Hence the authors conclude that EE is a stronger predictor of who does not relapse than of who does, for patients with bipolar disorder. In contrast, in schizophrenia, false-positive errors usually exceed false-negative errors, which means that, for them, HEE predicts relapse (Miklowitz *et al.* 1996).

This finding also supports the hypothesis that the vulnerability-stress model used for interpretation of the EE findings in families with a schizophrenic patient cannot plainly be applied to bipolars and their key relatives. LEE seems to indicate favourable circumstances in any case for them, but HEE seems to be the cause or sequelae of more diversive factors than in schizophrenia.

In their psychoeducative family intervention programme Goldstein and Miklowitz often found an initial resistance of the families to take up information about the illness in patients rather than in relatives. This finding again draws attention to the patient's contribution to creating a HEE family atmosphere. Goldstein *et al.* (1996) observed that schizophrenic patients usually reacted by self-criticism to critical comments of key relatives, whereas bipolar patients used to refuse relatives' criticisms routinely. Also Göring's *et al.* (1992) findings that their three bipolar patients' EE index predicted the course in this little subgroup, but not the partners' EE index, adds to questioning the victimization hypothesis of EE research, i.e. the

assumption that the key relative's attitude to the patient precipitates the manifestation of recurrences.

This in turn is an argument which emphasizes the importance of the confoundation between the EE index and the patients' psychopathological state, in particular lack of insight.

One of the studies used self-report assessments, namely that of Okasha *et al.* (1994) who did not find perceived criticism predictive, as we and others have found concerning unipolar depressives.

Experimental studies

These usually used standardized forms of conflict dialogues which were recorded by videotape and then analysed sociometrically. In our study on unipolar depressives (Mundt *et al.* 1996) we had one case with bipolar II disorder, i.e. a short hypomanic period after remission of the depression. This state was recorded while the patient performed the standardized conflict dialogue with her spouse. She showed some irritability and dominance in the conflict dialogue and symmetrical rather than complementary role behaviour – different compared to the unipolar patients. There are, however, no systematic studies on larger samples with this paradigm comparing bipolar patients to other groups.

Information concerning the transgenerational interactions is also sparse concerning bipolars. From the excellent studies on the impact of a unipolar depressive parent on the developmental psychopathology of adolescent depression (Hammen 1996) we know that rearing styles and types of attachment, losses, identification processes, status in peer groups, relational peculiarities and the family's social and economic status are relevant factors for the development of disturbed self-esteem in the adolescent who later becomes a unipolar depressive. There are, however, no systematic studies on bipolars' interactional behaviour as a parent. Furthermore this paradigm does hard in teasing apart the risk of genetic transmission from the risk of transmission by family interactions.

Personality

The last paradigm to be mentioned is the personality, which indirectly may coin the interactional styles of a patient. Akiskal (1996) emphasizes emotional disregulations as having a two-fold impact on the risk for depressive episodes mediated by temperament: first by the future patient being exposed to emotionally highly charged interactions of relatives bearing a similar genetic load, and secondly by disfunctional behaviour of the future patient, which in turn causes distressing resonance from the social environment. Von Zerssen (1996) has described features of the typus manicus personality which he has conceived as a counterpart to Tellenbach's typus

melancholicus personality (Tellenbach 1961) as the hypothesized premorbid personality of unipolar depressives. He found evidence that the typus manicus personalities are more unsteady, independent, imaginative, unconventional, and venturesome than premorbid personalities of unipolar depressives. Kraus (1996) has added aspects of the social role performance of these personalities. He found bipolars to strive for autonomy, to be self-determined rather than externally determined, to follow their self-interest, to be norm-givers rather than norm-recipients, and to behave autonomously rather than being externally guided. These are descriptions which can easily be tested in experimental situations. As an interactional consequence of this type of personality Kraus, in a crosscultural study of samples in German and Japanese psychiatric hospitals, found that fathers and brothers of bipolar patients showed a more autonomous standard of professions than relatives of unipolars, and that bipolars were more often divorced before the onset of their illness than were unipolars. He concluded that these were features of the non-morbid or not yet morbid personality (A. Kraus, personal communication).

THE HEIDELBERG STUDY

The study by our group uses the paradigm of patients′ self-report. The study was part of a larger investigation which compared psychosomatic patients with cardiovascular diseases and psychiatric patients with regard to type A and type B personality.

For our purpose we focus on the results gained with the self-rating scale ″Inventory of Interpersonal Problems″ (IIP), developed and validated by Horowitz *et al.* (1994). The study is restricted to a cross-sectional comparison. The IIP was submitted to the patients after the acute phase of their illness but still during their inpatient status. The sample consists of 36 patients, 22 with unipolar major depression and 14 with bipolar disorder. The gender relationship shows a 2:1 female to male ratio among the depressives and 1:1 among bipolars; the depressive patients are somewhat older than the bipolars; depression as measured by BDI is about the same in the two subsamples. This indicates a residual symptom level of about 17 total score on average (Table 2).

The IIP uses the circumplex model of interactions, which also underlies the objective rating system of the Structural Analysis of Social Behaviour (SASB) (Benjamin 1994) and some other similar research assessment instruments. Ratings on the vertical axis indicate the status ″domineering″ versus ″non–assertive″, the horizontal axis indicates the quality of ″cold″ versus ″overly nurturant″ affiliation.

For the statistical results we first used the raw values of the IIP subscales and secondly ipsative values which eliminate differences of the overall

Table 2 Sample characteristics: total sample $n = 36$; unipolar major depression 22 (61%); bipolar disorder 14 (39%)

	Major depression	*Bipolar disorder*
Gender	15 (68%) female; 7 (32%) male	7 (50%) female; 7 (50%) male
Age	46.8 years (SD = 12.7)	39.2 years (SD = 10.3)
Depression (BDI)	17.7 total score (SD = 7.7)	17.6 total score (SD = 11.5)

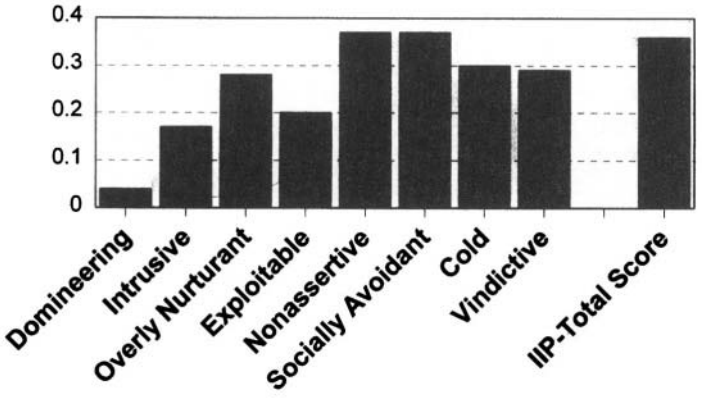

Figure 1 BDI total score and IIP subscores (Pearson correlation coefficient).

expressivity of the subgroups so that unipolars and bipolars, as well as normals, become comparable with regard to the qualitative differences in their interactional styles. Ipsative values equate raw values minus IIP total values. A resulting positive value indicates interpersonal problems above the average; negative values indicate interpersonal problems below average as measured by the overall level of interpersonal problems in the total sample.

The correlation of the IIP subscales with BDI depression (Figure 1) demonstrates that the highest correlations are found for the IIP total score and for the subscales non-assertive and socially avoidant. The lowest are found for the subscales domineering, intrusive and exploitable. This poses the question whether low depressivity enables a patient to recognize exploitability, whereas high depressivity makes the patient consider it acceptable to be exploitable.

The correlations of the IIP subscales to age (Figure 2) show that behaving overly nurturant and non-assertive are inversely correlated with age. The IIP total score (Figure 3) is higher in the bipolar subgroup than in the unipolar group. The comparison of these values with those of other diagnostic groups in literature shows that addiction and psychosomatoses indicate

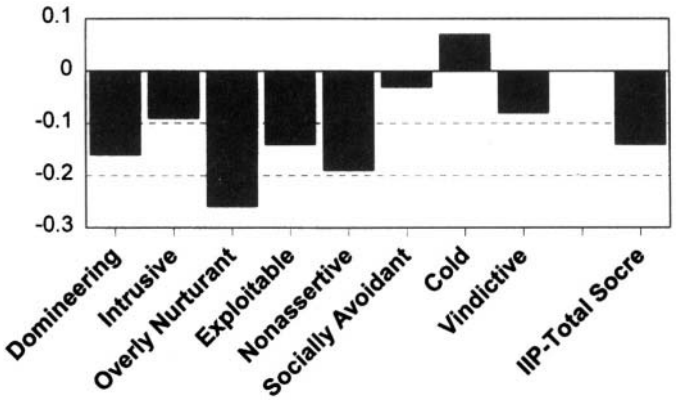

Figure 2 Age and IIP subscales (Pearson correlation coefficient).

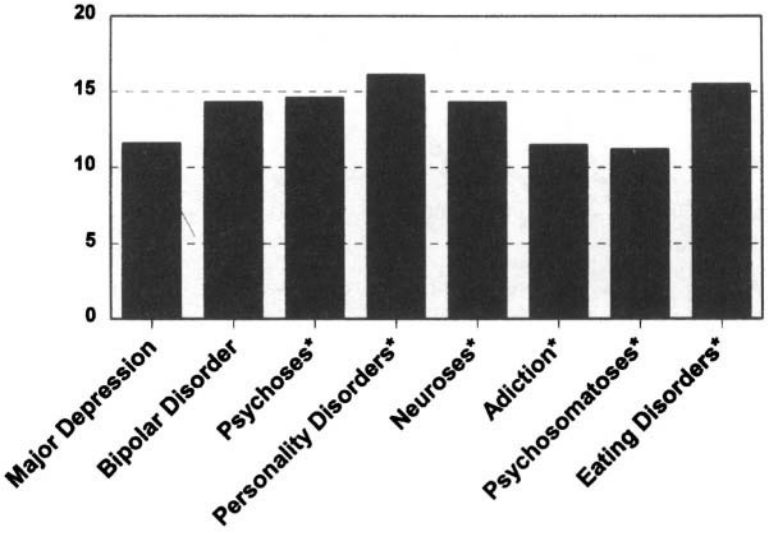

Figure 3 Diagnostic subgroups and IIP total score (*Values according to Wuchner *et al.* (1993)).

an IIP total score roughly the same as the one in our unipolar group, whereas personality disorders and eating disorders, as well as psychoses and neuroses, show higher values at the same level or above that of bipolar disorders.

The comparison of the IIP subscales for patients with unipolar depression and bipolar disorder (Table 3) shows a higher IIP total score for bipolar

Table 3 IIP subscales: unipolar major depression versus bipolar disorder

	Major depression (n = 22)		*Bipolar disorder* (n = 14)			
IIP subscales	m	*SD*	m	*SD*	*t/chi²*	p
PA: domineering	8.27	4.61	11.15	4.62	−1.79	0.04*
BC: vindictive	9.68	4.08	13.23	6.08	−2.07	0.02*
DE: cold	10.59	6.20	14.92	7.52	−1.85	0.04*
FG: socially avoidant	11.45	6.58	14.69	8.65	−1.25	0.11
HI: nonassertive	15.00	6.31	15.31	9.72	−0.11	0.45
JK: exploitable	13.86	4.28	15.31	6.37	−0.80	0,43
LM: overly nurturant	13.95	4.38	15.92	6.24	−1.10	0.14
NO: intrusive	9.68	5.07	13.62	5.55	−2.14	0.02*
IIP overall score	11.56	3.71	14.27	5.09	−1.82	0.04*

All IIP subscales indicate an overemphasis of the respective behaviour. $*p < 0.05$.

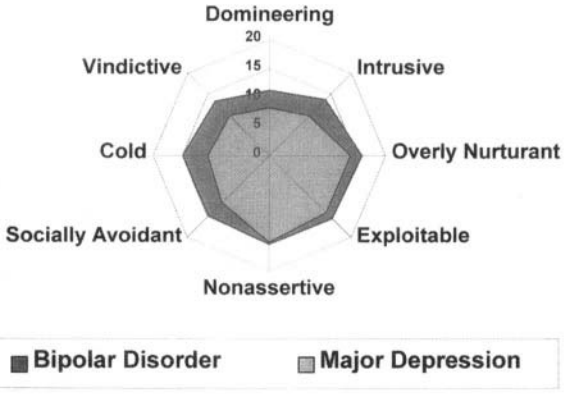

Figure 4 IIP interactional problems: unipolar depression versus bipolar disorder (raw values).

patients. The statistical differences between subscores indicate that bipolar patients perceive themselves as more domineering, vindictive, cold, and intrusive as compared to unipolar patients.

The visualization of the interactional space where unipolars and bipolars act within the circumplex model according to their self-rating (Figure 4) demonstrates that both subgroups tend to be non-assertive rather than domineering, but bipolars show an excess of range compared to unipolars except on the very status pole of non-assertive. The illustration suggests that unipolars indicate a restricted range of interactional variance, which we also have found in previous investigations with objective methods

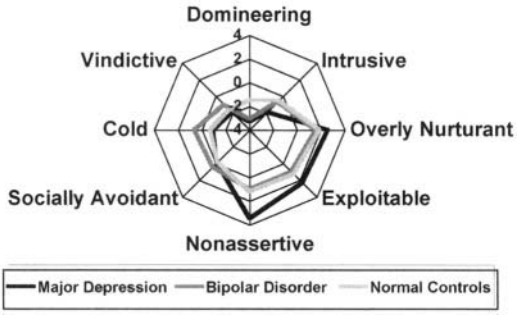

Figure 5 IIP interactional problems: unipolar depression, bipolar disorder and normal controls (ipsative values).

(Schröder *et al.* 1996). We therefore looked at the interactional space again on the basis of ipsative values (Figure 5) which relate the patients' individual values to the average values of the total sample and thus eliminate differences of overall expressivity of the groups. We also took a norm group from literature as further comparison. This revealed that bipolar patients come very close to the norm group with the exception that they feel less domineering than the norm group – the same as the unipolars – and more cold than the norm group. The unipolar subgroup in turn exhibits a more pronounced difference comapred with both the norm group and the bipolars with regard to the subscores non-assertive, exploitable and-overly nurturant which exceed the norm group's values. Furthermore the subscores domineering and intrusive are less pronounced in unipolar depressives than in the norm group.

The hierarchical discriminant analysis of single IIP items for the unipolar and bipolar subgroup (Table 4) lists nine out of 64 items which significantly discriminate between unipolars and bipolars. Bipolars perceive themselves as less trustful, more confronting, more expressive with anger and hostility, and more socially active than unipolar depressives. The correct reclassification was over 90%.

The IIP second-order factors domineering versus non-assertive and overly nurturant versus cold reveal that unipolar depressive patients show a higher degree of both submission and friendly affiliation than bipolar patients, who in turn are still more non-assertive than domineering and more overly nurturant than cold.

DISCUSSION

There are three conclusions we can make on the basis of these results. First, bipolar patients report having more self-perceived interpersonal problems than do unipolar patients; secondly bipolar patients consider themselves as

Table 4 IIP item hierarchy according to discriminant analysis; unipolar major depression versus bipolar disorder

IIP item			*Wilk's*	p
49	I am too distrustful	Up < Bp	0.75	0.005
8	I am too confronting with problems	Up > Bp	0.54	0.002
10	I show too openly that I am angry	Up > Bp	0.44	0.001
13	I become too aggressive, if necessary	Up > Bp	0.35	0.001
7	I try too much to please others	Up > Bp	0.23	0.001
34	I become too easily angry	Up > Bp	0.18	0.001
33	I ask others too often to be with me	Up < Bp	0.15	0.001
18	I talk about my feelings to freely	Up < Bp	0.13	0.001
28	I allow myself too much hostility even against beloved persons	Up > Bp	0.11	0.001

$F = 18.55$, $p = 0.001$; correct reclassification: 92%

more vindictive, cold and intrusive than unipolar patients; and thirdly the bipolar subgroup profile of the interactional space resembles the norm group whereas the unipolar one sticks out. Unipolar patients consider themselves as too exploitable and non-assertive, whereas bipolar patients consider themselves as too cold and vindictive.

A limiting factor for these conclusions can be seen in the fact that the data of our study were gained by self-reports which are not able to clearly disentangle morbid interactional styles as state factors from intermorbid interactional styles as trait factors. The comparability, however, between unipolar depressives and bipolars should be valid, since both subgroups showed the same mean BDI total score. We assume that the self-assessment encompasses features of intermorbid as well as morbid interactional styles in both subgroups. In literature the IPP is considered as an assessment instrument which resembles a personality inventory rather than a state-dependent self-rating scale (Horowitz *et al.* 1994).

Comparing the expressed emotion research as well as the self-report indications of interpersonal problems with the literature in the field of unipolar depression and schizophrenia, we can state that the results in the field of bipolar disorder are much more sparse, less conclusive than those for unipolar depression, and those for unipolar depression in turn are less conclusive than those for schizophrenia. Looking at the overall results of expressed emotion studies we assume that there may be some impact of the HEE status on relapse of bipolar disorder patients, probably restricted to the assessment in the early stage of the illness and to the prediction of the short-term course; but probably not for the long-term course and if the EE status is taken at the late stages of the illness. Both literature on premorbid personality as well as our self-report study on the interactional styles

of bipolar disorder patients show that bipolars come much closer to normal control groups than unipolars. It is unlikely that this is an artifact due to patients′ wishful thinking, but rather is a realistic self-observance.

It is too early to go into a more intricate exploration of mutual influences of interactional behaviour of bipolars and the attitudes and behavioural styles of their key relatives, their extrafamilial social environment, their self-conception and self-perception, their attributional style, their psychopathological symptoms, and their planning rehabilitation. The last point seems particularly important, since many bipolars either overstretch planning future tasks, which again puts too much stress on them, or they have to cope with the repair of a damaged social network after recovery. However, data available so far do not yet allow sound statements or conclusions concerning these questions.

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Chapter eleven

Comorbidity in bipolar affective disorder

Peter Brieger

COMORBIDITY – SOME GENERAL CONSIDERATIONS

Comorbidity can be defined as "joint occurrence of two or more mental disorders occurring with each other and/or with medical conditions" (Klerman 1990). While many "classical" psychiatrists, for example Karl Jaspers (1973), have postulated that all signs of an illness should be subsumed under a single diagnosis, nowadays much speaks for the view that in operational diagnostic systems such as DSM-IV (APA 1994) and ICD-10 (WHO 1993) comorbidity is the rule not the exception (Merikangas 1990). Although to our knowledge Feinstein (1970) was the first to use the term "comorbidity", the concept has been known for much longer. Already in Kraepelin's textbook (Kraepelin 1909) one finds a paragraph on "combined psychoses". Kraepelin referred to Erwin Stransky's excellent theoretical discussion of the problem of "combined psychoses" (Stransky 1906). Both Kraepelin and Stransky came to the conclusion that the occurrence of two illnesses at one time in one patient is "anything but rare" and makes the diagnostic process more difficult. Nowadays the literature on psychiatric comorbidity has grown enormously (Brieger and Marneros 2000a). Van Praag (1993) even spoke of comorbidity as a "parasite" of modern diagnostic systems.

There are various reasons why nowadays comorbidity has become such a focus of attention. Most of them have to do with the development of operational diagnostic systems.

- The claim that modern diagnostic systems are "atheoretical" and that they lead to a "complete suspension of hierarchies" (Klerman 1990)

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 215–229.

makes comorbidity more likely, as this claim makes it difficult to justify any exclusionary principles. Nowadays one has become so much accustomed to the fact that someone with a bipolar I disorder may also fulfil the criteria for a panic disorder that it is easily forgotten that such a double diagnosis would have broken Jaspers' hierarchical principles of psychopathology (*Schichtenregel*).

- Most psychiatric symptoms are unspecific. DSM-IV (and ICD-10) criteria of different disorders often overlap. This certainly results in comorbidity. The overlap between the symptoms of "cyclothymic disorder" and "borderline personality disorder" is one example (Akiskal 1994, Brieger and Marneros 1997a).
- DSM-III listed 229, DSM-III-R 311 and DSM-IV 395 psychiatric disorders (Saß *et al.* 1998). DSM-IV has become a "splitter's dream" and "lumper's nightmare" (Frances *et al.* 1990). The constantly growing number of disorders is quite likely to result in an increase in the figures for prevalence of psychiatric disorders in the general population, especially as "subthreshold" and "spectrum disorders" – with sometimes unclear clinical significance – now play a larger role in the newer diagnostic systems (Klerman 1990). Such an increase in the general prevalence of psychiatric disorders automatically leads to an increase in comorbidity. For example, from our clinical experience we are quite convinced that - at least in Europe – nicotine dependency has a very high prevalence amongst persons suffering from a bipolar disorder. Nevertheless, the clinical significance of such comorbidity seems debatable.
- Modern therapies do not treat illnesses. Rather, cognitive-behavioural, social and pharmaceutical therapies have become syndrome- and symptom-oriented. Such syndromes are no entities and therefore may occur multiply in one person.

COMORBIDITY LEADS TO METHODOLOGICAL PROBLEMS

- The validity of the diagnostic process decreases with the number of comorbid diagnoses. If, for example, a certain diagnostic process (for example a clinical interview) arrives correctly at one diagnosis in 80% of all cases, it will be able to identify four comorbid diagnoses correctly in only 41% of all cases. Therefore, in the majority of such cases it will fail to give all four correct diagnoses.
- The temporal relation between two diagnoses is often difficult to establish. Normally a primary/secondary distinction of two diagnoses will depend on retrospective recollection on the part of the patient, a procedure with known poor reliability (Andreasen *et al.* 1981).
- Quite often lifetime comorbidity rates between two diagnoses are reported. This requires some caution, as the reliability and validity of

lifetime diagnoses may be lower than often assumed (Bromet *et al.* 1986). Furthermore, using lifetime diagnoses leads to the problem of the relevance of "longitudinal comorbidity". Comorbidity between two lifetime diagnoses will often not mean that the two disorders have ever occurred at the same time. Such a definition of comorbidity certainly increases its frequency, although it is not fully in line with the definition given at the beginning of this chapter. In general, not all studies on comorbidity distinguish sufficiently between "intra-episodical" and "longitudinal" comorbidity (Angst 1994, Zarate and Tohen 1999a).

- Bipolar disorders are probably not as rare as they were still thought to be 10–20 years ago. They are nowadays more often diagnosed (Zarate *et al.* 1997), and a birth cohort effect is being discussed (Lasch *et al.* 1990). Also, the concept of bipolar disorder has become "broader" (Angst 1998). Nevertheless, bipolar disorders are undoubtedly much rarer than unipolar affective disorders. Therefore, in many studies which have assessed both unipolar and bipolar subjects the bipolar group is often very small. Even in the National Comorbidity Survey (NCS), with 8098 respondents, the narrowly defined bipolar I group consisted of 29 subjects (Kessler *et al.* 1997b). Such small groups may, in the comparison with large groups, e.g. subjects with a lifetime history of a major depressive episode (17.1% in the NCS (Kessler 1999)), lead to statistical problems, such as large 95% confidence intervals. The NCS (Kessler 1999), for example, reports an odds ratio of 14 between bipolar disorder and panic disorder. At the same time the 95% confidence interval for this number ranges from 2 to 102! To our knowledge the NCS is the second-largest psychiatric epidemiological study ever published. If even such a large study encounters problems of this nature, one should not overvalue results of single smaller studies or studies with less stringent methodology.

COMORBIDITY WITH SUBSTANCE ABUSE

In most societies substance abuse is common amongst subjects suffering from bipolar disorders. Nevertheless, substance abuse is – more than most other psychiatric disorders – transculturally heterogeneous. The accessibility of illegal drugs varies fundamentally from country to country. Even alcohol is not available to the same extent in all countries and cultures. For example, the common North American finding that bipolar patients misuse cocaine frequently (Sonne and Brady 1999) is not true to the same extent in Europe, as cocaine abuse in general has a much lower frequency there.

Large epidemiological studies have found that a high proportion (more than 50%) of bipolar subjects in North America have a lifetime history of alcohol abuse/dependency [Epidemiological Catchment Area Study, ECA: 46% (Regier *et al.* 1990); Edmonton Study: 45% (Fogarty *et al.* 1994); NCS:

64% (Kessler *et al.* 1997a)]. In clinical samples numbers differ more considerably [lifetime comorbidity: 66% (Mueser *et al.* 1992); 30% (Winokur *et al.* 1998); 67% for males and 31% for females (Rabinowitz *et al.* 1998)]. Such numbers may be significantly lower in societies where alcohol is less well accepted. For example, a Taiwanese group (Tsai *et al.* 1999) found a lifetime prevalence of less than 10% for alcohol abuse disorders in a cohort of bipolar patients. Nevertheless, all studies that have come to our knowledge speak for the fact that bipolar disorders are associated with a higher frequency of alcohol abuse/dependency. Also bipolar spectrum disorders such as hypomania or brief recurrent mania go along with a significantly raised frequency of alcohol abuse/dependency. In the Zurich study, Angst (1998) found a more than 20% frequency of alcohol abuse in the "bipolar spectrum group", compared to 8% amongst controls. Comorbid alcohol abuse may be a predictor of a more unfavourable course of a bipolar disorder, although this has not been fully proven (Sonne and Brady 1999). Nevertheless, several studies that have compared bipolar patients with and without alcohol abuse have presented results which support such a view: bipolar patients with alcohol abuse commit more suicide attempts, suffer more often from dysphoric ("mixed") mania, have an earlier age of onset and their outcome after 15 years can be worse than that of patients without alcohol abuse (Coryell *et al.* 1998, Feinman and Dunner 1996, Sonne *et al.* 1994, Winokur *et al.* 1995). A large study of 2713 subjects found a frequency of bipolar disorders of 2.3% amongst "alcoholics" compared to 1.0% amongst controls (Schuckit *et al.* 1997). In another large sample (n = 12 607) (Hoff and Rosenheck 1999) the reported frequency of "bipolar disorder or schizophrenia" was 5.9%.

The prevalence of drug abuse is difficult to estimate, as drug users often have an interest – for example for legal reasons – in not confirming their problem. Therefore the quality of diagnostic information gathered from persons with a drug problem is often low, resulting in unclear reliability of such "dual diagnoses" (Bryant *et al.* 1992). The availability of illegal drugs varies amongst different societies and groups. In epidemiological studies the lifetime prevalence of drug abuse in the general population ranges from 0.1% (Taiwan) to 11.9% (USA) (Kessler *et al.* 1994, Merikangas *et al.* 1996, Weissman *et al.* 1996). Also, the substance classes used differ considerably. ECA (Regier *et al.* 1990) (41%), NCS (Kessler *et al.* 1997a) (46%) and the Edmonton Study (Spaner *et al.* 1994) (34%) found rather high lifetime prevalence rates for drug abuse in subjects with a lifetime diagnosis of bipolar disorder in the general population. Comparable rates have been reported from clinical populations [e.g. 34% stimulant abuse (Mueser *et al.* 1992)]. Amongst subjects with a history of drug abuse the Edmonton Study found a more than 7 times higher risk of fulfilling diagnostic criteria for a bipolar disorder (Russel *et al.* 1994) (prevalence 3.3%), although in a large

cohort of opioid abusers the prevalence of bipolar disorders was not raised (Brooner *et al.* 1997).

Since the early 1980s there has been discussion of whether there is a specific connection between cocaine abuse and bipolar disorder. Some clinical observations supported the view that cocaine abusers are more prone to cyclothymic mood swings. However, such observations were not fully supported by later studies. One possible explanation was that, due to the fact that cocaine had become very popular in the 1980s, the "special" personality of cocaine consumers had changed and the original "bipolar" consumer subtype had lost some of its significance (Gawin and Kleber 1984, Nunes *et al.* 1989, Weiss and Mirin 1986, Weiss *et al.* 1988). Nevertheless, this relation between "bipolarity" and cocaine abuse led to treatment trials with lithium, which showed some efficacy (Gawin and Kleber 1984, Nunes *et al.* 1990) in cocaine abusers. Altogether much speaks for the view that bipolar patients tend to abuse cocaine and other stimulant drugs more often than controls and more often than subjects with other psychiatric disorders, especially those suffering from unipolar depression (Sonne and Brady 1999, Winokur *et al.* 1998).

There is some dispute as to the effect of substance abuse on the course of bipolar disorder. Overall, bipolar patients with and without substance abuse do not seem to differ from each other as much as one might expect. Amongst consecutive admissions to a psychiatric hospital, Rabinowitz *et al.* (1998) found that severe substance abuse (versus no substance abuse) led to a raised frequency of suicide attempts in the previous 6 months and to more antisocial behaviour, but concerning psychopathology and course no dramatic differences were found. Several studies, e.g. the Collaborative Study of Depression (CDS) (Winokur *et al.* 1998) and others (Feinman and Dunner 1996), have reported that bipolar patients with substance abuse have an earlier onset of the bipolar disorder. Alcohol abuse at baseline characterized poor outcome at 15 years, although this finding was not robust through all statistical analysis (Coryell *et al.* 1998). For cocaine abusers a recent study (Rosenblum *et al.* 1999) showed that a primary bipolar disorder was a positive predictor of treatment outcome compared with secondary bipolar disorders.

COMORBIDITY WITH ANXIETY DISORDERS

Lifetime diagnoses of anxiety disorders are very common in bipolar patients. The NCS (Kessler 1999) reported a 93% frequency of lifetime anxiety disorders in bipolar I disorders, including 39% post-traumatic stress disorder. The odds ratio was calculated at 35, a very high value. Comparable results were found in the Edmonton Study (Fogarty *et al.* 1994). In the NCS the comorbidity rate and the odds ratio were even higher when only those

subjects were assessed who had had a bipolar disorder in the past 12 months: then, 95% had a lifetime diagnosis of an anxiety disorder, which leads to an extremely high odds ratio of 82.

Panic disorders are particularly frequent amongst subjects with bipolar disorders. Epidemiological studies found an 18–33% frequency of a lifetime panic disorder in subjects with a lifetime bipolar disorder (Chen and Dilsaver 1995b, Fogarty *et al.* 1994, Kessler *et al.* 1997a), with odds ratio up to 14. Also in clinical populations comparable numbers [15–37% (Cosoff and Hafner 1998, Keck *et al.* 1995, Pini *et al.* 1997)] have been reported. An interesting finding is that patients with "pure" or "pseudo-unipolar" mania may have far lower rates of panic disorder than "truly manic-depressive" bipolar patients (Dilsaver *et al.* 1997). Compared with subjects with a unipolar depressive disorder, subjects with bipolar disorders seem to have twice the risk of suffering from a panic disorder (Chen and Dilsaver 1995b). This led to theoretical considerations that panic disorders may have a relation to a "soft bipolar spectrum" (Perugi *et al.* 1999). Conversely, in subjects with panic disorders epidemiological studies found a frequency of bipolar disorders of 8%, also a markedly raised number (Dick *et al.* 1994a). In a clinical population this number reached 14%, when a broad concept of bipolarity was administered (Savino *et al.* 1993). Genetic studies also yield evidence (MacKinnon *et al.* 1997, 1998) that bipolar disorder and panic disorder have some kind of connection. These studies come to the hypothesis that the comorbidity of the two disorders may delineate a genetic subtype, in which chromosome 18 (18q) loci may play a major role.

Comorbidity between phobias and bipolar disorders has received less attention than that between panic disorder and bipolar disorder. For narrowly defined bipolar I disorder the NCS (Kessler 1999) reported comorbidity rates even higher than those with panic disorder. Lifetime comorbidity rates were 62% for agoraphobia (odds ratio 24), 67% for simple phobia (odds ratio 16) and 47% for social phobia (odds ratio 6). As these rates were far higher than corresponding ones for major depressive disorder (Kessler *et al.* 1999), again this supports the idea of a bipolar/phobic disorder connection. Comparable results were reported in the Edmonton Study (Dick *et al.* 1994b), where 3.4% of the subjects with a lifetime diagnosis of a phobic disorder also had a bipolar affective disorder. In a comparison of the relative risk of having a comorbid bipolar disorder additionally to the phobic disorder (both lifetime), agoraphobia had the highest rating (16-fold) and simple phobia the lowest (6-fold), with social phobia ranging between the two (8-fold).

Both epidemiological (Kessler 1999) and clinical studies (Pini *et al.* 1997) have reported rather high lifetime rates of generalized anxiety disorder (GAD) in bipolar subjects (43% compared to 32%). Nevertheless, much speaks for the hypothesis that GAD has a strong connection to unipolar affective disorder, advocated, amongst others, by a specific analysis of NCS

data (Judd *et al.* 1998), genetic studies (Roy *et al.* 1995) and a comorbidity study in a primary health-care setting (Olfson *et al.* 1997).

Some results support the idea that bipolar disorders with anxiety disorders have a more unfavourable course than those without anxiety disorder. One study (Young *et al.* 1993) showed that such comorbid patients had more suicide attempts, more substance abuse and a trend towards more non-response to lithium.

A connection has also been postulated between bipolar disorder and obsessive–compulsive disorder (OCD) (McElroy *et al.* 1996). The ECA reported a lifetime frequency of OCD in subjects with bipolar affective disorder of 21%, versus 12% in unipolar disorder (Chen and Dilsaver 1995a). In the Edmonton Study the corresponding figures were 15% (bipolar) and 10% (unipolar) (Fogarty *et al.* 1994, Spaner *et al.* 1994). One clinical study found no significant difference between unipolar and bipolar patients concerning comorbidity with OCD (Krüger *et al.* 1995), while another study (Pini *et al.* 1997) supported the idea of a higher frequency of OCD in bipolar than in unipolar disorder. Some authors (Perugi *et al.* 1998, Strakowski *et al.* 1998) have formulated a theory of an episodic (sub)type of OCD which is strongly related to bipolar disorder. There is strong evidence that Tourette's syndrome goes along with a markedly elevated risk for bipolar disorder (Berthier *et al.* 1998, Kerbeshian *et al.* 1995).

COMORBIDITY WITH PERSONALITY DISORDERS

In the prospective Zurich study, adolescents who later developed a bipolar disorder did not differ from controls concerning any personality dimension of the Freiburg Personality Inventory at baseline (Clayton *et al.* 1994). This is a finding that challenges theories of a premorbid bipolar personality (Brieger and Marneros 1999, von Zerssen *et al.* 1994). Much of the personality pathology that is observed in bipolar illness, and is often attributed to a "premorbid personality", may be the consequence of (rather than a predisposition for) the disorder. Therefore, the state–trait controversy is unresolved and has a severe impact on all studies on personality disorders in bipolar illness. Besides, the question of the validity of DSM-IV axis II diagnoses in subjects with a severe axis I diagnosis (e.g. bipolar disorder) is rarely addressed in comorbidity studies. Thus it cannot be ruled out that a certain proportion of studies on the personality of bipolar patients reports "epi-phenomena" of bipolar disorders, as the problem of incomplete remission or persisting alterations (Marneros and Rohde 1997) is rarely observed.

More than for other disorders, the frequency of personality disorders depends on the applied methodology and varies considerably from study to study. There are no general population epidemiological studies for personality disorders of the same quality as for axis I disorders (e.g. ECA or NCS). The design of studies on the comorbidity of axis II disorders in

bipolar illness is generally such that a cohort of bipolar patients is assessed with a standardized personality disorder instrument (interview or questionnaire). Unfortunately the effect of axis I psychopathology or subthreshold or spectrum diagnoses on axis II diagnoses is rarely assessed in these bipolar patients. Therefore, we do not know much about the relation of axis I psychopathology to such measured personality features.

It is not unexpected that in all studies bipolar patients exhibit more personality disorders than controls (Zarate and Tohen 1999b). Nevertheless, numbers vary considerably from study to study. Reported frequencies of personality disorders in bipolar patients range from 3% (Mezzich *et al.* 1990) to more than 80% (Turley *et al.* 1992). Many results, though, roughly cluster around a 50% frequency of personality disorders in bipolar patients [35% (Carpenter *et al.* 1995), 45% (Barbato and Hafner 1998), 48% (Dunayevich *et al.* 1996, Ucok *et al.* 1998), 55–60% (Peselow *et al.* 1995), 58% (O'Conell *et al.* 1991)]. Compared with controls, bipolar patients have a 3–3.5-fold risk of fulfilling criteria of a personality disorder (Samuels *et al.* 1994, Ucok *et al.* 1998) in such studies.

There is some evidence that the co-occurrence of personality disorders and bipolar disorders has an unfavourable effect on social adjustment, treatment success and course (Barbato and Hafner 1998, Carpenter *et al.* 1995, Dunayevich *et al.* 1996). Bipolar patients with multiple hospital admissions exhibit personality disorders more frequently than first-admission patients. This may mean either that the course of bipolar disorder is complicated by a primary personality disorder, or that in these patients personality disorders are secondary consequences of chronic bipolar disorders, which lead to "persisting alterations" or "residual states" (Marneros and Rohde 1997).

Most studies agree that in bipolar patients cluster B personality disorders (antisocial, borderline, narcissistic, histrionic) are more common than cluster A or cluster C personality disorder (Zarete and Tohen 1999b). This is not very surprising, as there is a certain overlap between diagnostic criteria for cluster B personality disorders and bipolar disorders. Several behaviours, which can occur in a manic episode may, when they are exhibited repeatedly in the longer course of a bipolar disorder, seem "histrionic", "borderline", "narcissistic" or even "antisocial". Akiskal (1994) has advocated such a standpoint repeatedly and therefore criticized the concept of borderline personality disorder, while others (e.g. Gunderson 1998) have opposed the view that a large proportion of "borderline patients" are truly "bipolar". Nevertheless, there is little doubt that borderline personality disorder patients have a raised frequency of bipolar disorders (Zimmerman and Mattia 1999).

COMORBIDITY WITH OTHER PSYCHIATRIC DISORDERS AND MIGRAINE

There are several other disorders in which affected subjects have been reported to exhibit bipolar affective disorder symptomatology more fre-

quently than expected. These include body dysmorphic disorder (Perugi *et al.* 1997), somatization disorder (Brown *et al.* 1990) and bulimia (Braun *et al.* 1994, Brewerton *et al.* 1995). Nevertheless, for these disorders the available data do not permit any more than hypothetical conclusions.

Migraine is significantly more frequent in bipolar patients than in controls. This is known from large studies in Zurich (Merikangas *et al.* 1990) and Detroit (Breslau *et al.* 1994). In these studies the odds ratio for subjects with bipolar disorder to suffer from migraine was 5–6. Earlier studies have also reported such a strong connection (see Stevens *et al.* 1995).

COMORBIDITY WITH MEDICAL ILLNESS

Secondary mania (Krauthammer and Klerman 1978) is not as rare as it was long thought to be. Obviously, drugs ranging from cortisol to ifosfamide (Brieger *et al.* 2000b) can cause secondary manias. However, secondary manias can probably occur in almost any general medical condition that affects the central nervous system (Sax and Strakowski 1999). There has to be some doubt whether such secondary manias actually constitute the same kind of "comorbidity" discussed above, or whether one should rather speak of co-occurrence, or maintain the term "secondary mania". Nevertheless, reports of secondary manias may be valuable to develop aetiological hypotheses of bipolar disorder. For example, concerning brain localization, studies of mania in post-stroke patients have led to the hypothesis that a right anterior lesion predisposes for a manic syndrome (Starkstein *et al.* 1988). In genetic research the cosegregation of bipolar disorders with other syndromes offers opportunities for hypotheses concerning chromosome loci of bipolar disorders. Research in bipolar disorder and velo-cardio-facial syndrome (Papolos *et al.* 1996) and Darier's disease (Dawson *et al.* 1995) are examples.

CONCLUSION

What are the consequences of comorbidity in bipolar disorders? Two aspects deserve further consideration. First, comorbidity may delineate subtypes. Bipolar disorder and OCD together might be another type of disorder than each alone. Secondly, several studies have indicated that, when a patient suffers from more than one psychiatric disorder, treatment becomes more difficult and the course is more unfavourable (Sharma *et al.* 1995, Shwartz *et al.* 1996, Vogel and Huguelet 1997). However, is this also true for bipolar disorders? Recent studies, for example the NCS (Kessler 1999), have found that during their lifetime virtually all bipolar patients suffer from an additional psychiatric disorder. This casts some doubt on the relevance of such "lifetime comorbidity". Can it actually worsen course and treatment

response, when suffering from such a comorbid disorder seems to be the rule for patients with bipolar disorders? Furthermore, hardly any prospective studies have compared the course of comorbid and non-comorbid bipolar patients. Therefore, and due to the chronicity of bipolar disorders, comorbidity in bipolar disorder has to be assessed in a more complex way. In addition to the mere – categorical – diagnosis of a second disorder, its course, duration, severity and consequences must be assessed dimensionally. Truly multidimensional or multiaxial diagnostic strategies have to be developed further.

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Chapter twelve

The genetic epidemiology of bipolar disorder

Ming T. Tsuang and Stephen V. Faraone

INTRODUCTION

For the psychiatric geneticist the pattern of illness within families provides clues about the effects of genes and environment. Thus, genetic epidemiological studies use different family structures to answer specific questions. Studies of nuclear and extended families indicate if a disorder is familial, i.e. that it "runs in families". However, such studies cannot disentangle the relative contributions of genes and environmental factors. To do so we must examine twin and adoption studies. After establishing that genetic factors play a role, the next task is to determine the mode of transmission and, eventually, the genetic and environmental mechanisms of the disease. We provide a detailed discussion of these methodologies elsewhere (Faraone *et al.* 1999). A complete examination of relevant work is beyond the scope of this overview; those who wish to learn more should consult comprehensive reviews (Faraone *et al.* 1990, Tsuang and Faraone 1990, 1996), along with the original studies.

FAMILY STUDIES OF BIPOLAR DISORDER

If genes cause bipolar disorder, then the relatives of bipolar patients should have a greater prevalence of the illness than the relatives of non-patients. Before examining family studies of bipolar disorder it is useful to examine population-based epidemiological data (Tsuang and Faraone 1990). Such studies are useful in this regard because they provide a context in which family study data can be interpreted. Early epidemiological studies of

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 231–241.

"manic-depressive psychosis", performed from 1938 to 1952, found the prevalence of the illness in the general population to range from 0.4% to 1.7%. The mean risk was 0.7%. Relatively recent reports of lifetime rates of bipolar disorder range from 0.1% to 1.6%. Thus, the population risks for bipolar disorder are similar to the risks reported for manic-depressive psychosis from earlier studies.

Early family studies of bipolar disorder were conducted from 1929 to 1954. They did not make the distinction between major depression and bipolar disorder, and only reported the prevalence of manic-depression among relatives of manic-depressive patients (Tsuang and Faraone 1990). The prevalence among parents ranged from 3.2% to 23.4%, with a mean of 14.6%. The prevalence among siblings ranged from 2.7% to 23.0% with a mean of 10.9%. Each of the studies found relatives of mood-disordered patients to have a greater prevalence of manic-depressive psychosis than the 0.7% general population prevalence reported by the early epidemiological studies.

Family studies performed during the past three decades benefited from increased methodological rigour. The double-blind, controlled study of Gershon *el al.* (1982) examined first-degree relatives of bipolar, depressed and control subjects. They found a 1.5% prevalence of bipolar disorder among relatives of depressed patients, a 0.0% prevalence among relatives of controls and a 4.5% prevalence among relatives of bipolar patients. The 16.6% prevalence of depression among relatives of depressed patients was not much greater than the 14.0% prevalence of depression among relatives of bipolar patients, but both were nearly three times the risk observed in the control group. These results are similar to those of other studies (Gershon *et al.* 1975, Tsuang *et al.* 1980, Weissman *et al.* 1984, Endicott *et al.* 1985, Andreasen *et al.* 1987, Sadovnick *et al.* 1994); each of these studies found strong evidence for a familial component to bipolar disorder and depression. Moreover, most of these studies suggest that there is a familial link between bipolar disorder and some cases of depression.

TWIN STUDIES OF BIPOLAR DISORDER

After the family study method has been used to establish that a disorder is familial, the next question is: "What are the relative contributions of genetic and environmental factors to disease aetiology?" To answer this question it is necessary to use twin and adoption studies.

Twinning provides a valuable opportunity to look at the factors involved in human genetics. Monozygotic (MZ) twins have 100% of their genes in common and dizygotic (DZ) twins have only 50% of their genes in common. Although the two types of twins are significantly different in terms of their genetic make-up, both MZ and DZ twins share a relatively common environ-

ment. The genetic similarity between DZ twins is the same as any pair of siblings, but MZ twins are genetic copies of one another. Since DZ twins are not genetic copies of each other, differences within a DZ twin pair can be due to either environmental or genetic factors. In contrast, environmental influences must be responsible for differences between MZ pairs. Thus, twins can be used to disentangle the relative contributions of genetic and environmental factors in the aetiology of psychiatric disorders.

Concordance rates are often used to summarize twin studies of psychiatric disorders. A twin pair is concordant for illness if both twins are ill; if one is ill and the other well, the pair is discordant. If genetic factors are important and the effects of a common environment are the same for both types of twins, we expect a higher concordance rate for a disorder in MZ twins compared with DZ twins. In addition to concordance rates, we can estimate the heritability of a disorder from twin data. Heritability is a measure of the degree to which genetic factors influence the phenotypic variability of a disorder.

A Danish twin study (Bertelsen *et al.* 1977) identified twins through the Danish Psychiatric Twin Register. The investigators found a concordance rate of 0.67 for bipolar disorder in MZ twins, which was more than three times greater than the rate of 0.20 in DZ twins. From these data they calculated the heritability of bipolar disorder to be 0.59.

Tsuang and Faraone (1990) reviewed six twin studies of "manic-depressive disorder", that did not distinguish between major depression and bipolar disorder. Overall, these studies attributed 60% of the variance in bipolar disorder to genetic factors; 30–40% of the variance was assigned to common environmental factors. Unique environmental effects accounted for less than 10% of the variance.

Overall, twin studies are consistent with family studies in suggesting that genetic factors play a substantial role in the aetiology of bipolar disorder. However, the finding of MZ concordance rates lower than 100% documents the importance of environmental factors. These factors include sources of experimental error (e.g. psychiatric diagnostic, and zygosity misclassification). Twin studies are less consistent in their attribution of environmental sources of variance to unique versus common environmental factors.

ADOPTION STUDIES OF BIPOLAR DISORDER

Like twin studies, adoption studies can disentangle genetic and environmental contributions to the familial transmission of a disorder. The adoption study capitalizes on two types of relationships: adoptive and biological. In doing so it seeks to show whether genetic or adoptive (i.e. environmental) relationships account for the transmission of disorders. Clearly, children adopted at an early age have a primarily genetic relationship with their

biological parents and an environmental relationship with their adoptive parents.

An adoption study from Belgium (Mendlewicz and Rainer 1977) found the prevalence of psychiatric illness to be greater among the biological parents compared with the adoptive parents of bipolar adoptees. Compared with a control group the biological parents of bipolar non-adoptees had an increased prevalence of bipolar disorder but the adoptive parents of bipolar adoptees did not. These results showed that genetic – not adoptive – relationships mediated the familial prevalence of bipolar disorder.

Wender *et al.* (1986) identified a mixed sample of bipolar and depressed adult adoptees and control adoptees with no record of psychiatric illness. They matched the ill and control adoptees on demographic features of the adopting parents. Among relatives of ill adoptees the risk to biological relatives was greater than the risk to adoptive relatives. Notably, the biological relatives of ill adoptees were six times more likely than the adoptive relatives to have completed suicide. The biological relatives had three times the rate of major depression and alcoholism compared with the adoptive relatives of ill adoptees. Thus, the Danish study of Wender *et al.* confirmed the study from Belgium by implicating genetic but not environmental relationships in the transmission of bipolar disorder.

MECHANISM OF INHERITANCE OF BIPOLAR DISORDER

Segregation analysis examines the pattern of disorders in families and determines if it is consistent with a specific mode of genetic transmission. In theory, such analyses can provide strong evidence for one mode of transmission over others. These analyses can examine several modes of transmission (e.g. single major gene, environmental transmission, polygenic inheritance).

Unfortunately, mathematical analyses of mood disorder pedigrees have not been able to consistently support a mode of genetic transmission for bipolar disorder. Reviews of segregation analysis studies find no strong support for either single-gene or polygenic transmission, even when such factors as gender and polarity are taken into account in the analyses (Faraone *et al.* 1990, Tsuang and Faraone 1990, Moldin *et al.* 1991).

LINKAGE AND ASSOCIATION STUDIES OF BIPOLAR DISORDER

Despite the failure of segregation analyses to confirm a specific mode of transmission, psychiatric geneticists turned to genetic linkage analyses to determine if genes influencing bipolar disorder could be discovered. To date several regions of the genome have been implicated but, because these

findings have not been consistently replicated, they remain suggestive, not definitive.

Prior to the discovery of DNA markers, several studies examined bipolar pedigrees informative for protan (red deficiency) or deutan (green deficiency) colour blindness, recessive X-linked traits with known chromosomal locations. Using these genetic markers, linkage between bipolar disorder and colour blindness was suggested over two decades ago, but these early results were not easily replicated.

Gershon and colleagues (1979) reported results from an international collaborative study of X-linkage under the auspices of the World Health Organization, This collaboration examined 16 pedigrees that had been ascertained through bipolar patients in the United States, Belgium, Switzerland and Denmark. The overall evidence for linkage was equivocal, but separate analyses of subsamples strongly suggested the presence of significant heterogeneity.

Additional positive studies of X-linkage have examined linkage to glucose-6-phosphate-dehydrogenase (G6PD) deficiency and various DNA markers. All of these provide X-chromosome markers close to the locus for colour blindness. Of the three studies examining linkage with G6PD, two suggested X-chromosome involvement in affective disorders. Additional studies of the locus for blood clotting factor IX (FIX) suggest that the X-linked locus is located on Xq27.

In 1987 Egeland *et al.* (1987) reported significant evidence in favour of linkage for the HRAS1 locus on the short arm of chromosome 11. The original report was very compelling and, although some limited support for the finding was reported, most subsequent reports were not consistent with linkage to this region. Moreover, a follow-up study of Egeland *et al.'s* pedigree cast doubt on the original finding (Kelsoe *et al.* 1989).

On the other hand, there is some additional evidence suggesting that a gene in the HRAS1 region may be involved in bipolar disorder. Joffe *et al.* (1986) reported a family in which bipolar-related disorders and thalassaemia minor appeared to cosegregate. Thalassaemia minor is caused by a mutation of a gene on the short arm of chromosome 11 close to the HRAS1 locus. This region is close to the gene for tyrosine hydroxylase (TH). DNA markers at the TH locus were associated with bipolar disorder in some samples but not others, so the relevance of this gene remains uncertain.

A gene near the ABO region on chromosome 9 may play a role in bipolar disorder. Several studies have compared ABO blood groups between patients with bipolar disorder and healthy individuals. Nine of 16 studies found a significant increase in blood type O; one reported a significant decrease of blood type O among mood-disordered patients. Two studies found a significant increase in blood type B and one study found a significant increase in blood type A (Tsuang and Faraone 1990). Three studies found a significant decrease in blood type A. The primary inference from

these studies is the fairly strong suggestion that blood type O is found with greater frequency among patients with bipolar disorder in comparison to individuals from the general population (Lavori *et al.* 1984).

Unfortunately, the reported ABO associations are inconsistent with six of eight studies rejecting linkage to ABO (Tsuang and Faraone 1990). It is nevertheless interesting to note that the gene for dopamine-beta-hydroxylase (DBH) is closely linked to the ABO locus on chromosome 9q34. Since DBH is critical to the synthesis of catecholamines, it is a reasonable candidate as an aetiological gene for bipolar disorders.

Using the affected sibling-pair method, Berrettini *et al.* (1994) reported a potential linkage between bipolar disorder and marker loci near the centromere of chromosome 18. LOD scores were positive but not significant. In contrast, based on results of a non-parametric affected sib-pair analysis, Berrettini *et al.* concluded that chromosome 18 may harbour a gene of small effect that plays a role in the complex inheritance of bipolar disorder. Subsequent studies (reviewed by Van Broeckhoven and Verheyen 1999) provide additional evidence for linkage but implicate a broad region including 18p11-23, which is essentially all of the long arm of chromosome 18.

Evidence for a 21q21–22 locus for bipolar disorder was reported by Straub *et al.* (1994). A review of subsequent studies shows that, despite some negative reports, there is now mounting evidence for a bipolar disorder susceptibility locus in this region (Curtis 1999).

DO SCHIZOPHRENIA AND BIPOLAR DISORDER SHARE SUSCEPTIBILITY GENES?

The possibility that schizophrenia and bipolar disorder may share one or more susceptibility genes has intrigued researchers for many years. For example, Crow suggested that schizophrenia, schizoaffective disorder and affective illness exist along a continuum of psychosis that crosses diagnostic boundaries (Crow 1987). Although he accepted the view of prototypical entities corresponding to schizophrenia and affective illness, he rejected the idea that they had distinct aetiologies. Rather, he suggested that individual disease entities did not actually exist; instead, natural variation along one or more dimensions produced the prototypical disorders. He postulated that a common genetic deficit, located in the pseudoautosomal region of the sex chromosomes, was shared by psychotic disorders, and he hypothesized that genes related to psychosis were responsible for cerebral dominance and the localization of language (Crow 1990, 1991).

Although support for the pseudoautosomal hypothesis is weak, and a psychosis gene shared by all psychotic disorders has yet to be discovered (Asherson *et al.* 1992, Freije *et al.* 1992, Yoneda *et al.* 1992, Wang *et al.* 1993, 1994, Crow *et al.* 1994, d'Amato *et al.* 1994, Kalsi *et al.* 1995), there are some

hints from molecular genetic studies that implicate shared susceptibility genes for schizophrenic and mood disorders.

In a linkage study of schizophrenia, Maziade *et al.* (1997) failed to detect linkage at 6p24–22 in 18 large, multigenerational pedigrees from Eastern Quebec, using either broad or narrow definitions of the disorder. But they did find suggestive evidence in one large pedigree that this region was linked to both schizophrenia and bipolar disorder. This result derived from an analysis which used a broad phenotypic definition that included schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder (I and II) and major depression (recurrent). Wildenauer *et al.* (1996) reported a similar result.

Wildenauer *et al.* (1996) also reported suggestive evidence of linkage to a region on chromosome 18p, using a sib-pair analysis. Their strongest evidence for linkage derived from an analysis using a broad phenotypic definition that included schizophrenia, bipolar disorder, schizoaffective disorder and major depression. This chromosomal region has also been implicated in studies of bipolar disorder (Berrettini *et al.* 1994, Stine *et al.* 1995).

Although these studies suggest that schizophrenia and bipolar disorder may share susceptibility genes, that conclusion must remain tentative until the apparent connection between the two disorders is confirmed and replicated in large samples.

SUMMARY AND FUTURE DIRECTIONS

Family, twin and adoption studies provide firm evidence that bipolar disorder has a substantial genetic component. The concordance rate for mood disorder among monozygotic twins is approximately three times the rate observed among dizygotic twins. This strongly suggests that genes play a crucial role in the familial transmission of these disorders. The monozygotic twin concordance rate is approximately 0.70 for bipolar disorder. Since concordance is not perfect, non-familial environmental factors must play a role in the aetiology of bipolar disorder. Nevertheless, both twin and adoption studies suggest that the familial transmission of these disorders has a primarily genetic source. The environmental factors that cause illness are likely to be non-familial. However, since the adoption study literature contains some conflicting reports, we need more adoption studies to provide convergent support for these assertions.

The genetic relationship between major depression and bipolar disorder is poorly understood. Further research into this area must distinguish recurrent depressed cases that are not likely to have a subsequent manic episode from non-recurrent cases that may be bipolar. It is probably true that cases of major depression within families that manifest bipolar disorder are genetic variants of bipolar disorder. The clearest and most consistent

difference between the two forms of mood disorder is that relatives of bipolar patients have a greater prevalence of both depression and bipolar disorders than relatives of depressed patients. Evidence from both family and twin studies supports this conclusion. Thus, it is likely that bipolar disorder has a greater familial component than does major depression, which appears to be more affected by non-familial, environmental factors.

Although molecular genetic studies have identified several regions of interest, they have not yet found the genes that underlie the inheritance of bipolar disorder. There have been many attempts to explain this situation as due to the clinical and epidemiological features of psychiatric disorders that point to complex inheritance – as opposed to single-gene inheritance (Gershon and Cloninger 1994).

Clearly, if bipolar disorder is due to the additive and/or epistatic (i.e. interactive) effects of several genes, then linkage to any single gene would be difficult to detect and, in some cases, extremely difficult to replicate (Suarez *et al.* 1994). Furthermore, assortative mating, genetic heterogeneity, sporadic cases, misclassification, and low penetrance may further complicate the picture. Although these problems can be overcome (Faraone *et al.* 1999), to do so may require very large samples of well-characterized pedigrees. Tsuang *et al.* (1993) noted that, given the variable phenotypic expression of psychiatric genotypes, future genetic epidemiological work should attempt to define more heritable phenotypes.

Moreover, future work needs to examine the spectrum of subclinical conditions that may share genetic causes with bipolar disorder. These could be milder mood disorders such as dysthymia and cyclothymia or aberrations in brain structure or function as measured by neuropsychological tests, psychophysiological paradigms, neurochemical assays or neuroimaging assessments. These subclinical syndromes and neurobiological markers may have an underlying genetic architecture that is simpler than that for bipolar disorder. If so, then molecular genetic studies of such phenotypes might facilitate the detection of genes relevant to bipolar disorder.

Acknowledgements

Preparation of this article was supported in part by National Institute of Mental Health Grants 1 R01MH41879-01, 5 UO1 MH46318-02 and R37MH43518-01.

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Chapter thirteen

Genetics of bipolar affective disorder

Henrik Ewald

INTRODUCTION

The identification of genes involved in susceptibility to bipolar affective disorder (BPAD) will make further research into the aetiology and pathophysiology possible. Despite considerable efforts no DNA sequence variation of relevance for BPAD has yet been found.

Due to contradictory findings criticism of molecular genetic studies of BPAD has been harsh (e.g. Risch and Merikangas 1996). However, this seems only partly justified because a number of factors make the identification of disease genes particularly difficult for severe psychiatric disorders. BPAD is among the complex diseases as it has no clearly recognizable mode of Mendelian inheritance, i.e. dominant, recessive or sex-linked, and the phenotype relevant for finding disease genes is uncertain. Oligo- or polygenic inheritance with interaction between loci and other genetic mechanisms, such as imprinting or repeat expansion at some of the loci, are possibly involved. The possibility of aetiological and genetic heterogeneity and non-genetic cases, phenocopies, makes BPAD even more difficult to study. Among complex disorders BPAD and schizophrenia have been termed "complex complex" disorders (Kennedy 1996) as there is no universally recognized biological abnormality to separate affecteds from unaffecteds, to identify homogeneous subgroups or to identify carriers of the disease susceptibility genes, each of which would greatly facilitate the identification of the relevant genes. To this could be added the reluctance of some patients and relatives to participate in research investigations, and the possible denial of psychiatric symptoms at interviews.

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 243–280.

The first association and linkage studies of BPAD were performed around four and three decades ago respectively (Parker *et al.* 1961, Winokur and Tanna 1969, Reich *et al.* 1969). Though progress has been slow, developments in diagnostic instruments and criteria, molecular genetics, computer programs and statistics have helped to identify more than 10 candidate chromosome regions potentially containing genes which increase susceptibility to BPAD. Presently the attempts to identify genes involved in BPAD susceptibility seem promising compared to most other psychiatric disorders.

THE PHENOTYPE

The phenotype relevant for genetic studies of BPAD is uncertain though it is probably one of psychiatry's most robust diagnostic entities (Tsuang *et al.* 1993, Blacker and Tsuang 1992). This may make the search for psychiatric disease genes more difficult.

At the present time family studies and twin studies give the best support for the validity of BPAD as a disease entity. Bipolar and unipolar depressive disorder aggregate in the families of bipolar probands, and unipolar depressive disorder is increased in the monozygous co-twins of BPAD probands. These results indicate that BPAD patients and some unipolar depressive patients share some genetic liability.

In molecular genetic studies of BPAD families a phenotype is often applied that includes broader categories in addition to BPAD with overt manic syndrome. Patients with hypomania only, who have also experienced at least one major depressive episode, are often included as affected, even though some studies have suggested that BPAD with hypomania only is a separate disease entity which may breed true (Endicott *et al.* 1985). Variants of schizoaffective disorder may also be included. In most populations unipolar depression is the most common affective diagnosis among relatives of BPAD probands but unipolar depression is also common in the population and it is likely that the proportion of sporadic cases is larger in this diagnostic category (Gershon *et al.* 1982). Blacker and Tsuang (1993) estimated that at least 65% of unipolar relatives of bipolar probands are bipolars from a genetic point of view. Thus, including persons with unipolar disorder will decrease the number of false-negative cases and increase power, but may also introduce false-positive cases. In order to identify unipolar depressive patients which may share risk genes with BPAD, most research groups have focused on severity of symptoms and rates of recurrence as suggested by Gershon *et al.* (1982). Most investigators will not include less severe and less reliable diagnoses such as minor depressive episodes or cyclothymia.

The use of diagnostic categories to divide persons into affected, unknown or unaffected have been applied in most genetic studies of BPAD, though the use of quantitative dimensions are also possible. A few other methods

have been used in order to diminish the possibility and effects of misclassification of unipolar individuals. Family members may be given different probabilities of being affected based on subjective clinical judgements of psychopathology, stability of diagnoses or other kinds of information as suggested by Ott (Ott 1990a, Baron *et al.* 1990, Curtis and Gurling 1991, De Bruyn *et al.* 1994a).

CLINICAL DIAGNOSIS

Classification of diseases according to aetiology usually leads to better prediction, treatment and prevention (Kendell 1989). Though the classification of affective disorders is still based on symptoms and course, and not on aetiology, the reliability and comparability of psychiatric diagnoses has been improved.

The reliability of psychiatric diagnoses has been increased by the development and use of diagnostic instruments and criteria for specific disorders, assessment of intra- and inter-rater reliability and the use of lifetime best estimate diagnoses based on interview data, medical records and information from relatives (Bertelsen 1990, Wing *et al.* 1990, Nurnberger *et al.* 1994, Leckman *et al.* 1982). Follow-up of cases may increase the reliability of diagnoses as the reliability of a lifetime diagnosis of major depression increases when focusing on individuals with recurrent episodes (Kendler *et al.* 1993a). Approaches which allow diagnoses to be made according to different classification systems make comparison between and pooling of different clinical samples possible (McGuffin *et al.* 1991).

Improvement of the validity of the various classification systems of psychiatric disorders will have to await more specific knowledge concerning their aetiology.

ENDOPHENOTYPES

A continuous measure of the liability to affective disorder based on a biologically meaningful parameter might improve the delineation of the relevant phenotype, help to identify more homogeneous subgroups and help to distinguish between generic and non-genetic cases. Such endophenotypes can be defined as state independent biological or perhaps psychological measures which reflect an intermediate step between causal factors and symptomatology (Moldin and Erlenmeyer-Kimling 1994). Direct measures of brain dysfunction may better reflect the genetic component of the disease, and perhaps be more easily and reliably assessed and be more penetrant (Lander 1988). No endophenotype for BPAD has been widely recognized (Gershon 1990) and only a few attempts have been made to include such in molecular genetic studies of BPAD (Blackwood *et al.* 1993, 1996a).

HOMOGENEOUS SUBGROUPS

The identification of genes might be facilitated if a genetically more homogeneous subgroup could be collected (Greenberg 1992). Such a subgroup could be defined on the basis of characteristics including type of or severity of symptoms, comorbidity, age of onset, personality dimensions, treatment response or even environmental risk factors involved. An endophenotype could be applied. Sampling of BPAD patients from geographically or culturally isolated populations such as the Amish (e.g. Egeland *et al.* 1987), the Icelandic (e.g. Curtis *et al.* 1993), the Costa Rican (Freimer *et al.* 1996), the Bulgarian Gypsies (Kaneva *et al.* 1998), French Canadian (Barden *et al.* 1995) and the Faroese (Ewald *et al.* 1999) seem to be the best method available at present to increase genetic homogeneity.

FAMILY, TWIN AND ADOPTION STUDIES

Among the common psychiatric disorders a genetic predisposition is most apparent for BPAD, and genetic factors are the most solid clues to the aetiology of this disorder as evidenced by family and twin studies (Bertelsen *et al.* 1977, Tsuang and Faraone 1990).

The use of different methods and diagnoses makes direct comparison of studies difficult.

If genes are involved in BPAD, first-degree relatives of BPAD probands, who share on the average 50% of their gene variants with the proband, will more often have affective disorder than second-degree relatives, who on average share only 25% of their gene variants with the proband. Parents, children and siblings are first-degree relatives of the proband, while uncles, aunts, nephews and nieces are second-degree relatives. More than 30 family studies have been performed in the 20th century. The more recent studies, after 1960, have included the distinction between BPAD and unipolar depression, and around 10 000 relatives of BPAD probands have been examined. Many of these studies have used age correction, blinding of interviewers and control groups.

The family studies have consistently shown an increase of both BPAD and unipolar depression among the relatives of BPAD probands compared to relatives of normal controls. The exact percentages vary between studies but around 15–20% of the first-degree relatives of bipolar probands have BPAD or unipolar depression, with a preponderance of unipolar depression. The age-corrected lifetime risk for BPAD in the general population ranges between 0.3% and 1.5% (Weissman *et al.* 1996) while the risk for unipolar depression in the population varies widely between studies. The increase in relative risk for first-degree relatives of a bipolar proband is highest for BPAD.

As familial resemblance also may be due to shared cultural or environmental factors the suggestion of a genetic component based on family studies is only tentative. Twin and adoption studies can help to separate the genetic and environmental effects and allow estimates of their relative contribution to be calculated. Such studies are more difficult to perform.

All 12 twin studies of BPAD have found a higher concordance rate for monozygous (MZ) than for dizygous (DZ) twins, supporting a genetic component (Tsuang and Faraone 1990, Kendler *et al.* 1993b). MZ twins have 100% of their gene variants in common, while DZ twins, like siblings, on average share 50%. It is assumed that the effects of a common environment are similar for MZ and DZ twin pairs. Results from twin studies are usually expressed as concordance rates which may either be calculated as pairwise concordance, which is the proportion of twin pairs in which both twins are ill, or preferably as the probandwise concordance rate, which is the number of concordant co-twins divided by the number of probands. A concordance rate among MZ twins less than 100% means that environmental factors are of importance. In this context environmental factors include everything, apart from the DNA-sequence of the 46 original chromosomes inherited from the parents, which affects the individual from the stage of the zygote and onward. This includes random cellular changes during neural development (McGuffin *et al.* 1994). The concordance rates in DZ twins will depend on the number and penetrance of the involved genes.

The two most recent and largest twin studies of BPAD, which included a total of 209 monozygotic and 378 dizygotic twin pairs (Bertelsen *et al.* 1977, Kendler *et al.* 1993b), found MZ and DZ probandwise concordance rates for "narrow" affective disorder of 0.48–0.67 and 0.20–0.23 respectively, and 0.70–0.87 and 0.35–0.37 for a more "broad" definition of affective disorder. Furthermore, concordance rates, and thus the influence of genes, increase with the severity of affective disorder. Bertelsen *et al.* (1977) found around 80% proband-wise concordance for affective disorder in identical twins if the proband had bipolar disorder, around 33% for unipolar probands with fewer than three episodes and around 60% for probands with three or more depressive episodes. This study also suggested that the genetic background is different between BPAD and unipolar depression because fewer than expected MZ pairs were found in which one twin was bipolar and the other unipolar.

Family and twin studies point to a higher, or at least comparable, genetic influence in bipolar disorder compared to several common medical disorders for which monogenic subgroups have been identified (Plomin *et al.* 1994).

Adoption studies are potentially very useful for disentangling genetic and environmental components of a disease. A number of different methods exists. Disadvantages of adoption studies include the facts that they are difficult to perform, that adoptees overall may have increased psychopathol-

ogy and that the environment may differ between biological and adoptive parents. Two of the five adoption studies of affective disorder have specifically investigated BPAD and both supported the involvement of genes in BPAD (Mendlewicz and Rainer 1977, Wender *el al.* 1986).

MODE OF INHERITANCE

Genes may be located on one of the 22 autosomal chromosomes, the sex chromosomes or on the mitochondrial DNA. A single, a few or many disease genes may be involved, i.e. inheritance may be monogenic, oligogenic or polygenic. If polygenes and non-genetic factors are involved the disease is termed multifactorial. The mode of inheritance at a single locus may be Mendelian, i.e. dominant, intermediate or recessive. However, non-Mendelian inheritance involving mitochondrial DNA or mechanisms such as genomic imprinting or nucleotide repeat expansion is also a possibility for some loci. Each of these modes of inheritance has been suggested in at least a few studies of BPAD but not finally confirmed (Flint 1992, McInnis *et al.* 1993, Stine *et al.* 1993, Petronis and Kennedy 1995, McMahon *et al.* 1995, O'Donovan *et al.* 1995, Mendlewicz *et al.* 1997, Lindblad *et al.* 1998).

It has been known for many years that simple monogenic inheritance cannot account for all, or probably even the majority of, cases of BPAD. Statistical analysis of information from pedigrees, segregation analysis and prevalence analyses in different classes of relatives and comparisons between concordance rates in monozygotic and dizygotic twins have been used but no consistent results have emerged (Faraone *et al.* 1990, Risch 1990). A study by Craddock *et al.* (1995), considering only autosomal loci, suggested a model including three or more multiplicative loci. Others have suggested that BPAD may result from the additive or subtractive effects of multiple genes (Philibert *et al.* 1997).

Linkage analyses of Danish families have found evidence in favour of susceptibility loci on chromosome regions 12q24, 16p13.3, 4p16 and 10q, suggesting that, even in single large families with many affected individuals, several genes are involved simultaneously (Ewald *et al.* 1998a,b). Without knowing the exact genes and DNA sequence variations involved it is not possible to estimate the relative risk imposed by individual genes and the environment. However, it seems very likely that in the individual patient different combinations of genes of relatively minor effects, each contributing a relative risk of 2–3, influence disease susceptibility.

GENES OF RELEVANCE FOR BIPOLAR DISORDER

Genes are of importance for a number of characteristics of BPAD patients. Individual genes which influence disease susceptibility are probably neither

Table 1 Strategies for finding disease genes

Positional cloning
A chromosome region which is inherited from a common ancestor is identified by genetic mapping methods
Then the relevant DNA sequence variation is found
Direct investigation of genes
Based on pathophysiological knowledge
Located in a region identified by positional cloning
Identified by cytogenetic studies
Which are known neurogenes

necessary nor sufficient for development of the disease as for monogenic disorders. Rather they should be viewed as risk factors. Protective genes which decrease the risk of BPAD are also a possibility and have recently been proposed on chromosome 4 (Ginns *et al.* 1998). Other genes may only modify certain aspects of BPAD analogous to the recent finding of a locus which modifies the risk of meconium ileus in patients with cystic fibrosis (Zielenski *et al.* 1999).

Nearly all studies till now have focused on genes which increase the disease risk for BPAD. In BPAD patients genes may also be relevant for a number of other characteristics such as biological treatment response and side-effects, the risk of alcohol and substance abuse and related medical complications, comorbidity, personality factors influencing compliance, and suicide risk. For some of these characteristics evidence favouring the involvement of genes has been found.

STRATEGIES FOR FINDING DISEASE GENES

The main strategies used in the search for psychiatric disease genes are shown in Table 1. If knowledge exists on the biological background of the disease the corresponding genes may be directly investigated. However, there is no really good candidate susceptibility gene for BPAD among the potentially perhaps more than 30 000 neurogenes (Crowe 1993) of which only relatively few are presently known. Direct investigation of neurogenes makes most sense if they are located in a specific chromosome region which has been implicated by genetic mapping, by cytogenetic studies or co-occurrence with a monogenic disorder. However, this has been the exception rather than the rule in studies made so far.

The main strategy for finding genes of importance for psychiatric disorders and other complex disorders such as several forms of cancer and Alzheimer's disease has been by genetic mapping, also termed positional cloning, in which the first step is to identify a chromosome region which

Table 2 Methods for genetic mapping of disease genes

Lod score method
Affected sib-pair and other affected relative pair methods
Consensus segment search
Homozygosity mapping
Association studies with family controls
Association studies using cases and controls

is inherited together with the disease from a common ancestor (Collins 1992). By this strategy the genes may be found even if there is a complete lack of knowledge about the pathophysiology of the disease.

GENETIC MAPPING OF DISEASE GENES

The most useful of the currently available methods for mapping disease genes is shown in Table 2. The biological principle behind these methods is that neighbouring pieces of DNA from the same chromosome tend to be inherited together in families and in the population. Such pieces of DNA contain disease genes and marker polymorphisms which, if located close to each other, tend to be coinherited more often than expected by chance.

The required clinical material consists of families of different size and structure for studies of linkage or unrelated, in reality very distantly related, cases and controls for studies of association.

Most markers used today consist of DNA sequence variation, most often of no known functional significance. Up to 1993 most linkage studies used restriction fragment length polymorphism (RFLP) as DNA markers. RFLP usually have only two alleles and are thus less informative than microsatellite markers because a smaller percentage of the parents will be heterozygous at the marker locus. Today most studies use microsatellites, also termed simple sequence tandem repeats. Microsatellites are tandem repeats of two to five nucleotides distributed throughout most of the genome. They may be amplified by the polymerase chain reaction (Weber and May 1989). At a given location the number of tandem repeats often varies between individuals and this variation in length is useful as a genetic marker. Each microsatellite marker represents a specific chromosomal region.

There has been considerable debate concerning the choice of the most appropriate and powerful method for mapping genes for BPAD and other complex diseases (Risch and Merikangas 1996, 1997, Greenberg 1993). Presently there are strong proponents of "brute force" genome-wide association studies using a very large number of markers on a large sample of patients. However, other strategies should also be tried and supported (Goldman 1999, Baron 1999) because there is no way to determine *a priori*

the optimal strategy for genetic mapping, and no guarantee that the same approach will work for different complex diseases or even different loci involved in the same disease. For diseases such as BPAD, in which the number, strength and mode of inheritance of the risk genes are unknown, it still seems reasonable to apply a range of the available methods. Until now the lod score method and case–control studies have been the most commonly used methods and will be very briefly described.

Linkage approaches to human disorders have made substantial progress since the finding of X chromosome linkage of colour blindness and haemophilia in the 1930s. In the 1950s the lod score method was developed by Morton (1955) to overcome the problems of small numbers of progeny. In the 1970s statistical algorithms and computer-based analysis were introduced by Elston and colleagues and by Ott. In the 1980s DNA-based polymorphisms were introduced as markers and in the 1990s dense genetic maps of these markers have been developed. These advances have made it possible to use linkage analysis to search for disease genes at every chromosomal region in the human genome. Among several available methods, the lod-score method is the most commonly used statistical method for linkage analysis. This method makes possible the mapping of disease genes, the estimation of the genetic distance and detection of interlocus heterogeneity. The lod score is the logarithm of an odds ratio of the likelihood of linkage at a specific recombination fraction, θ versus no linkage ($\theta = 0.5$). The use of the lod score method with random markers for finding genes in complex disorders has been criticized for several reasons. The lod score method is a so-called "parametric method" that requires specification of the mode of inheritance, the penetrances at the disease locus and the disease allele frequency. Since all of these are unknown it has been feared that this may result in false-negative studies. However, if both dominant and recessive models (Clerget-Darpoux *et al.* 1986) and reasonable penetrance ratios are applied (Ott 1994) which allow for some degree of misclassification (Risch and Giuffra 1992) the lod score method may detect both monogenic subgroups of complex diseases and oligogenes. Affecteds-only analysis should also be included (Ott 1990b, Edwards 1982). In affecteds-only analyses all unaffected individuals are considered to have unknown phenotype, and there is no possibility of including false-negative cases.

In two-point analyses only one marker is tested at a time, while multipoint analyses use information from two or more markers simultaneously.

The lod score method has proven successful for detecting disease genes for subgroups of several complex diseases and even diseases previously thought of as non-genetic (Passarge 1993). The majority of the most interesting genetic mapping results of BPAD until now have also been found using the lod score method. An advantage of the lod score method is that computer programs exist which enable power calculations (Ott 1989, Weeks *et al.* 1990) and calculations of empirical *p*-values (Ott and Terwilliger 1992),

Table 3 Lod scores

For monogenic disorders the traditional criterion for acceptance of linkage to an autosomal locus has been a lod score at or above 3, and for exclusion of linkage a lod score below −2
Currently a lod score threshold of 3.3 in extended families has been recommended
Positive lod scores are designated suggestive of linkage if between 2 and 3
The size of the lod score in itself is of limited value
The interpretation of a lod score depends upon many factors including: the diagnostic model number and size of families tested number of chromosome regions tested genetic parameters chosen and may be aided by empirical *p*-values.

based on simulations of non-linkage given the specific pedigrees, phenotypic model, genetic parameters and marker allele frequencies.

Proof of a linkage finding may be obtained from independent replication using similar diagnostic criteria, phenotypic and genetic model and markers as in the original study (Leboyer *et al.* 1990), and ultimately by finding the relevant DNA sequence variation.

As the interpretation of a lod score is rather difficult, and depends on a number of factors, the use of specific thresholds has been suggested by Lander and Kruglyak (1995). The thresholds most often used are shown in Table 3. Evidence against linkage using the lod score method also has to be evaluated carefully and is valid only for the families tested, the phenotypic model chosen, the mode of inheritance assumed, the genetic parameters chosen and the markers with specific location and heterozygosity. Weaker genes than specified in the genetic model may be missed or excluded. Some characteristics of the lod score method are shown in Table 3. The lod score method has been thoroughly described by Ott (1991) and Terwilliger and Ott (1994).

Sib-pair analysis is based on the fact that, under independent assortment, two siblings will share two, one or zero alleles at a given locus 25%, 50% and 25% of the time. Increased marker allele sharing will be present among two affected siblings for a marker locus linked to the disease, and several methods for analysing this exist (Sham 1998).

A number of different affected relative methods such as the affected pedigree member method (Weeks and Lange 1988, 1992), extended relative pair analysis (Curtis and Sham 1994), the SimIBD method (Ott 1989, Weeks *et al.* 1990, Davis *et al.* 1996, Cottingham *et al.* 1993) and as implemented in the GENEHUNTER program (Kruglyak *et al.* 1996) exists. The last three meth-

ods measure the sharing of alleles which have been inherited from a common ancestor, in pairs of affected relatives. Increased sharing suggests linkage at that locus. Sib-pair and other affected relative pair methods are often termed non-parametric as opposed to the lod score method. As discussed by Sham (1998) these methods may not be as advantageous as often claimed, and may have unknown advantages and limitations in relation to different genetic backgrounds. However, they seem reasonable to use together with the lod score method to reduce the risk of obtaining false-negative and perhaps also false-positive lod score findings.

Recently a method has been developed for finding shared chromosomal segments among affected individuals assumed to be descended from a common ancestor in an isolated population related a few centuries back. This method, which has been termed consensus segment search (Table 2), has been used to map a gene for benign recurrent intrahepatic cholestasis (Houwen *et al.* 1994). The principle in the method is that identical chromosomal segments shared by affected individuals related through a common ancestor not too many generations ago will only occur rarely by chance, and such a region may thus harbour a disease locus.

Homozygosity mapping is a powerful method in which children with a rare recessive disease whose parents are consanguineous are genotyped. The principle is to search for a chromosomal segment at which the patients are homozygous having received two copies of the same segment flanking the disease allele. The method has been used to locate a number of rare recessive diseases (Lander and Botstein 1986, Farrall 1993). In principle it could be used to map some recessive risk genes for complex diseases but it has not yet been applied in BPAD.

A systematic search for disease genes on all chromosomes is termed a genome-wide scan. This involves genotyping of around 500 DNA markers evenly spaced about every 10 cM for the lod score method, affected sib-pair method, consensus segment search method and for homozygosity mapping. The power of, and sample size needed for, a given method depends on a number of factors such as aetiological heterogeneity, number and strength of disease genes involved and mode of inheritance. However, methods such as the lod score and affected sib pairs methods requires testing of at least a few hundred persons, while fewer persons may be sufficient when using consensus segment search or homozygosity mapping.

Association studies comparing cases and controls have been increasingly used in recent years because simulation studies have suggested that weaker risk genes can be localized more readily by association than by linkage analysis (Greenberg 1993, Nothen *et al.* 1992).

Apart from pure coincidence, an association between a disease and DNA marker alleles may have several causes (Cooper and Clayton 1988):

1. The association may reflect a direct causal relationship if the marker polymorphism itself contributes to the pathogenesis of the disease.

2. The association may be due to linkage disequilibrium, also termed allelic association, between alleles at a marker locus and a closely linked disease locus. This means that an excess of one specific marker allele on the chromosome bearing the disease allele is present among the descendants of a common ancestor.
3. Association may occur due to population stratification.

Allelic association may be due to a number of other factors including selection and genetic drift in smaller populations (Spiess 1989).

Population or sample stratification of marker alleles can occur if in reality the study population consists of two or more groups, which have different frequencies of both the disease allele and a specific marker allele not involved in the aetiology of the disease. An association which is not causal between the disease and a marker allele may then be present in the pooled sample, even if no association is present in any of the subpopulations. A true association may also be hidden by population stratification.

Non-related, and ideally randomly chosen cases and controls from the same random mating population are used. In fact either a common DNA sequence variation occurs in a single-risk gene or a proportion of the affected individuals have to be very distantly related if an association which is due to inheritance of a marker allele very close to a disease allele is to be demonstrated. Usually controls have been chosen from convenient available samples thought to be representative of the population from which the cases were selected. As one can really never be sure of this, even after matching controls for ethnicity and geography, other approaches including the use of family controls have been proposed. One method uses data from one affected child and both parents. The control sample are the non-transmitted alleles from the parents (e.g. Terwilliger and Ott 1992, Schaid and Sommer 1994, Spielman and Ewens 1996). The use of such methods has been strongly recommended for genetic mapping of susceptibility genes (Risch and Merikangas 1996, 1997). Such a design has also been advocated for testing genotype–environment interaction (Khoury 1994). There has been a tendency to regard results from such studies as more valid than results from case–control studies. However, a serious drawback of the method is that it is not possible to collect parents for many of the patients with BPAD. Furthermore, patients with available and participating parents may represent a selected and atypical sample of patients also concerning psychiatrically relevant risk genes (Bruun and Ewald 1999). Finally, population stratification will still be a possibility if the parents′ ethnicity is different.

In large outbred populations there will be linkage disequilibrium in only a small chromosomal area of less than one million base pairs around the marker. At least a few thousand markers are required to make a systematic search in such populations. Currently association studies therefore usually are performed with markers in or near candidate genes.

Critical evaluation of association studies in psychiatric genetics is far from simple, due to small sample size in relation to a possibly low relative risk contributed by the disease allele and aetiological heterogeneity, absence of linkage disequilibrium near a true disease gene, pitfalls in the selection of cases and controls, the varying plausibility of the candidate gene tested, the possibility that the relevant gene involved is another closely linked gene, the possible insignificance of an associated DNA sequence variation, and uncertainty of the choice of an appropriate significance level (Crowe 1993, Kidd 1993).

Association studies are also used for fine-mapping of the risk genes. Once there is evidence of close linkage, and no more recombinants can be detected, the demonstration of linkage disequilibrium in a population association study may be helpful in the final identification of the relevant gene in the chromosome region (Bodmer 1986).

It has been estimated that in 1999 around 5% of the human genome has been sequenced and that at least parts of the sequence of half of the 70 000 genes or so are known. It will be increasingly possible to use this information to find risk genes. Two of the familial forms of Alzheimer's disease are caused by mutations in a gene termed presenilin 1 on chromosome 14 or presenilin 2 on chromosome 1. Following the discovery of presenilin 1 a second candidate gene, presenilin 2, was found on chromosome 1 by searching databases for sequence homology with presenilin 1. Subsequently the mutation was detected in families with Alzheimer's diseases linked to that region (Rogaev *et al.* 1995). This method has been termed "in silico mapping".

A number of textbooks and papers describe methods for genetic mapping and their interpretation in detail (Lander and Kruglyak 1995, Ott 1991, Terwilliger and Ott 1994, Sham 1998, Houwen *et al.* 1994, Lander and Botstein 1986, Lander and Schork 1994).

The interpretation of the results from molecular genetic studies is difficult. Apart from statistical evidence such as the presence of linkage, association or a haplotype, and a DNA sequence variation of possible functional significance, it has to be demonstrated that the DNA sequence variation is of relevance for aspects of the phenotype investigated.

In the following the main results from genetic mapping studies in BPAD will be presented. The main linkage findings are shown in Table 4.

GENOME-WIDE SCANS

Relatively few research groups have finished and published results based on testing very large numbers of DNA markers from many or most chromosome regions on families with BPAD. What constitutes a sufficient amount of markers to be tested in order to have covered all chromosome regions

Table 4 Chromosome regions with suggested linkage to bipolar affective disorder

Location	*Lod score*	*References*
Xq28	–	Reich *et al.* 1969
11p15	4.9	Egeland *et al.* 1987
Xq27	3.1	Mendlewicz *et al.* 1987
Xq28	2.1	Baron *et al.* 1993
*5q35	1.4	Coon *et al.* 1993
*21q22	3.4	Straub *et al.* 1994
12q23	2.1	Craddock *et al.* 1994
*18p	–	Berrettini *et al.* 1994
18q	1.7–3.1	Stine *et al.* 1995
Xq24–26	3.5	Pekkarinen *et al.* 1995
*16p13	2.7	Ewald *et al.* 1995
11p15, 21q22	–	Gurling *et al.* 1995
*18q23	–	Freimer *et al.* 1996
*4p16	4.8	Blackwood *et al.* 1996
*6p25, 13q13, 15q21	2.5, 1.4, 1.1	Ginns *et al.* 1996
5p15.3	2.4	Kelsoe *et al.* 1996
18q22–q23	2.2	Coon *et al.* 1996
22q	2.5	Lachman *et al.* 1997
*4q35	3.2	Adams *et al.* 1998
*12q24, 4p16	3.4, 2.0	Ewald *et al.* 1998
*4p16, 4q28	protective loci	Ginns *et al.* 1998
*13q32, 1q31–q32	3.5, 2.7	Detera-Wadleigh *et al.* 1999

* Genome-wide scans.

depends on family structure, especially the number of key persons in whom genotypes have to be estimated, how informative the DNA markers are and the crossover rate in specific chromosome regions.

Longitudinal studies of BPAD among members of the Old Order Amish, Lancaster County, Pennsylvania, USA, have been carried out for more than 20 years. A report of positive linkage using the lod score method between BPAD and markers closely linked to the tyrosine hydroxylase locus within the 11p15 region in a single large pedigree (OOA 110) from the Amish population was published in 1987 (Egeland *et al.* 1987). This created great interest in psychiatric genetic linkage studies. The highest two-point lod score found was around 4.32 for marker HRAS1. Simultaneously negative studies were published by Hodgkinson *et al.* (1987) and Detera-Wadleigh *et al.* (1987). Later the positive report of linkage in the Amish population was followed by decreased evidence (Kelsoe *et al.* 1989), when two family members developed an affective disorder and several new family members were added. However, the Amish study group has consistently reported low positive lod scores, around 0.5, using markers at the tyrosine hydroxy-

lase locus (Pakstis *et al.* 1991, Sidenberg *et al.* 1994), while more negative results have been found in other extensions of the OOA 110 (Pauls *et al.* 1991).

Ginns *et al.* (1996) reported an investigation of 551 RFLP and microsatellites in the combined pedigrees from the Old Order Amish. The pedigrees were analysed as such and as nuclear families. No lod scores above 2.5 were found. Positive lod scores and some evidence of increased allele sharing for a few markers on each of chromosomes 6p25, 13q13 and 15q21 were presented. Though the Amish population is supposedly relatively homogeneous and founded by relatively few ancestors, no common haplotype among BPAD patients was reported. Results from other candidate regions were not reported in any detail. LaBuda *et al.* (1996) investigated 367 loci on 14 of the chromosomes also on a smaller subset of the extended OOA pedigrees. They reported some evidence of increased haplotype sharing distal on chromosome 6p and on chromosome 9p.

A very large sample of pedigrees have been collected by Baron's research group (Baron *et al.* 1994). In 1994 Straub *et al.* reported a lod score of 3.41 at zero recombination fraction for the marker PFKL in one out of 47 of these families with affective disorder. Simulations with an unlinked marker yielded only one lod score above 3.4 in 5000 replicates in that family, corresponding to an empirical p-value of 0.0002. The finding received support from non-parametric testing of the other families. Testing additional markers and including additional families the highest homogeneity lod score is still found on chromosome 21q22 (Aita *et al.* 1999).

The research group headed by W. Byerley has tested many candidate genes and in 1993 reported an investigation of 328 markers in eight families (Coon *et al.* 1993). The highest lod score found was 1.27 at D5SS43 on chromosome 5q35-qter. This group has also reported a lod score of 2.22 for marker D18S43 on chromosome 18q22.3-q23 (Coon *et al.* 1996), and some evidence of increased allele sharing distal on chromosome 21q (Byerley *et al.* 1995).

Investigating two Costa Rican pedigrees with BPAD from a genetically isolated population a common haplotype including markers on 18q23 was possibly shared by most affected family members (Freimer *et al.* 1996). A haplotype may be defined as a group of closely linked alleles on a single chromosome which very often are inherited as a unit. A 3 cM haplotype was potentially shared among 23 out of all 26 BPAD patients. Formal lod scores were not reported but were below the level of significant linkage (Escamilla *et al.* 1999). Using "linkage / association", lod scores of 3.70 and 4.06 at zero recombination fraction were obtained for two of the most distal markers on 18q23, D18S554 and D18S70. Allele frequencies for four markers were different comparing the affected family members with a population control sample (Freimer *et al.* 1996). Lod scores above 2 were also found in

one of the pedigrees for markers D3S1285 and D7S510 on chromosome 3p14.2–p14.1 and 7p15 (McInnes *et al.* 1996).

Blackwood *et al.* (1996b) found a lod score of 4.09 at marker D4S394 on chromosome 4p16 investigating 193 DNA markers in a single, very large Scottish family with BPAD. Analyses including nearby markers yielded a lod score of 4.8. Affecteds-only analysis with D4S394 yielded a lod score of 3.9. Inspection of the most likely haplotype revealed that only two out of 16 patients with recurrent depression had not inherited the relevant haplotype.

A number of studies have been performed on a collection of more than 20 North American pedigrees of European descent. Berrettini *et al.* (1991) investigated 107 markers, Gejman *et al.* (1993) investigated additional 57 markers and Detera-Wadleigh *et al.* (1994) 142 markers in these pedigrees. A single pedigree yielded a lod score of 2.39 for a marker at D1S103 on chromosome 1q32–q44 (Gejman *et al.* 1993) and in 21 pedigrees a total lod score of 3.03 at D7S78 on chromosome 7q21–q22 was found (Detera-Wadleigh *et al.* 1994). More informative markers on chromosome 7 implied that this was a spurious positive finding. Other studies including these pedigrees have provided possible evidence for linkage to chromosome 18p near the centromere (Berrettini *et al.* 1994) which was still suggested after investigating 310 markers (Berrettini *et al.* 1997). Some evidence of increased allele sharing was also found on chromosome 21q (Detera-Wadleigh *et al.* 1996). Testing 607 DNA markers in these pedigrees using different methods of linkage analyses Detera-Wadleigh *et al.* (1999) found a maximum lod score of 3.5 at 13q32. Parametric or other lod scores above 2 were also found at 1q31–q32, 7q31, 14q11-q13, 18p11.2 and 22q11-q13.

The NIMH Genetics Initiative Pedigrees examined 319 DNA markers in 97 pedigrees (Nurnberger *et al.* 1997, Detera-Wadleigh *et al.* 1997, Edenberg *et al.* 1997, Rice *et al.* 1997, Stine *et al.* 1997). No evidence of significant linkage was found. The most interesting findings were on chromosome 1p31, 6q, 7q22–q31, 10p12 and 16p12 where affected sib-pair analyses yielded *p*-values below 0.01 and below 0.05 at a nearby marker.

A genome-wide scan with more than 600 DNA markers in two Danish families with BPAD has found significant evidence for linkage on chromosome 12q24 with a lod score of 3.37 (Ewald *et al.* 1998a), and lod scores at or above 2 on chromosome 16p13.3 (Ewald *et al.* 1995), chromosome 4p16 (Ewald *et al.* 1998b) and chromosomes 1p, 6 and 10q (unpublished). This suggests the simultaneous involvement of specific oligogenes.

A number of studies have been performed on a collection of Australian pedigrees of European descent (Mitchell *et al.* 1991, Adams *et al.* 1998). Testing 214 DNA markers in a large pedigree Adams *et al.* (1998) found a two-point lod score of 2.20 and a multi-point lod score of 3.19 on chromosome 4q35.

For all chromosome regions negative reports have been published, further stressing the complexity of the genetic background of BPAD. Lander and Kruglyak (1995) have suggested specific criteria for suggestive and significant linkage using extended families as lod scores above 1.9 and 3.3 respectively, and nominal *p*-values of 0.01 for confirmation of a significant linkage. Empirical *p*-values are seldom reported.

It is worth remembering that even false-positive findings may receive support from independent studies, that some risk genes may be too weak to be found by linkage strategies and that it perhaps may be quite difficult to replicate a true finding (Suarez *et al.* 1994).

Concerning replications of significant and suggestive findings on chromosomes 4p, 12q, 18, 21q and the X chromosome a brief survey follows below.

CHROMOSOME 4

The locus on chromosome 4p16 suggested by Blackwood *et al.* (1996b) has received additional support. Including both BPAD patients and patients with recurrent depressive episodes, Ewald *et al.* (1998b) found a lod score of 2.00 at 0.03 recombination fraction from D4S394 with an empirical *p*-value of 0.0006, i.e. the marker which was also most significant in the original Scottish study. Though this formally replicates the Scottish findings according to the criteria suggested by Lander and Kruglyak (1995) some caution is warranted, as the modes of inheritance which yielded the highest lod score in the two studies were different. Polymeropoulos and Schaffer (1996) have reported lod scores of up to 1.68 for markers near D4S394 assuming a dominant mode of inheritance including BPAD patients as affected in a single sub-branch of Old Order Amish pedigree 110. Searching for protective loci in Old Order Amish pedigree 110 and other Amish pedigrees, Ginns *et al.* (1998) found evidence of a protective locus in the vicinity of D4S394 with the most significant finding around 9 cM proximal to D4S394, i.e. within the region of interest.

The dopamine D5 receptor (DRD5) is an interesting candidate gene in this region on chromosome 4p. However, no sequence variation was found in the coding region of DRD5 in a person with bipolar disorder from the large, linked Scottish family (Blackwood *et al.* 1996b). Wolfram syndrome (WS) is a recessive disease which includes diabetes mellitus and bilateral optic atrophy and psychiatric symptoms. The gene for WS is located in the region of interest and has recently been cloned. WS may include psychiatric symptoms such as severe depression, and one study has suggested an increase of psychiatric illness among putative carriers of one copy of the WS mutation (Swift *et al.* 1998). Mutations in the Wolfram gene were not detected in the Scottish BPAD families showing linkage to chromosome 4p (Evans *et al.* 2000).

Ginns *et al.* (1998) also reported evidence for a protective locus for markers at chromosome 4q28, i.e. more than 55 cM proximal to the locus suggested at chromosome 4q35 by Adams *et al* (1998). Recently Alda *et al.* (1998) found a decrease in NN genotype at the MN blood group locus among lithium-responding BPAD patients. The MN blood group is located on chromosome 4q28.2–q31.1.

Weaker and / or preliminary support has been reported by other research groups on chromosome 4p and 4q (Kennedy *et al.* 1999).

CHROMOSOME 12

Significant evidence for linkage to BPAD has been found in two Danish families on chromosome 12q24 with a lod score of 3.37, empirical *p*-value 0.00002 also supported by non-parametric analyses with *p*-values being between 0.00003 and 0.005 (Ewald *et al.* 1998a).

This finding supports a previous report by Craddock *et al.* (1994a) of cosegregation between affective disorder and Darier's disease (keratosis follicularis) which yielded a lod score of 2.11 assuming a broad phenotype and using Darier's disease as a phenotypic marker. A gene causing Darier's disease has been mapped to chromosome 12q23–q24.1 (Craddock *et al.* 1993). Though the region implied by these studies may be around 20 cM wide these findings may represent the same locus (Ewald *et al.* 1998a). Preliminary findings of significant linkage to this region have also been reported in Canadian families (Barden *et al.* 1995, 1997), and studies on North American families (Detera-Wadleigh *et al.* 1999) and English families (Detera-Wadleigh 1999) further support this region.

CHROMOSOME 18

Chromosome 18 has been probably the most heavily investigated chromosome in the search for genes involved in BPAD, and several regions have been suggested (Ewald *et al.* 1997, van Broeckhoven and Verheyen 1998).

Berrettini *et al.* (1994) suggested that a susceptibility locus for affective disorder might be located in the pericentromeric region on chromosome 18. Analysing a large number of affected sib-pairs Berrettini *et al.* (1994, 1997) and Stine *et al.* (1995) found more alleles shared than not shared for marker D18S37 located at 18p11.22-p11.21. Nöthen *et al.* (1999) found a lod score of 1.08 at 0.10 recombination fraction from D18S37 assuming a recessive mode of inheritance, and a multi-point lod score of 2.54 in the same region when separately analysing pedigrees with apparent paternal transmission of affective disorder. Some support for this region has also been published by Pauls *et al.* (1995) and Maier *et al.* (1995). Investigations of candidate genes in the region such as Golf, a G protein alpha receptor

subunit, and a ACTH-MC receptor have not supported the involvement of these genes in BPAD (Turecki *et al.* 1996, Tsiouris *et al.* 1996, Detera-Wadleigh *et al.* 1995).

Chromosome 18p11.3 has been implicated in a few studies. Berrettini *et al.* (1994) found *p*-values <0.001 for D18S21 on chromosome 18p11.3 including all 22 families. In the genome scan of two large Costa Rican families the second-highest lod score found in one of the families was 1.43 at D18S59 at chromosome 18p11.3 (McInnes *et al.* 1996). This region has received further support from an association study of 48 other Costa Rican cases with BPAD (Escamilla *et al.* 1999). Cytogenetic abnormalities involving chromosome 18p11.3 have been reported in a bipolar and in a schizophrenic patient (Mors *et al.* 1997).

The long arm of chromosome 18 may also harbour risk genes for BPAD. When Stine *et al.* (1995) subdivided their sample they found evidence of excess sharing of paternally transmitted alleles for both phenotypic models for three neighbouring markers D18S41, D18S64 and D18S38 at chromosome 18q21.2–q22.3. The *p*-values were not very different from their *p*-values obtained at D18S37 mentioned above. In 11 pedigrees with probable paternal transmission the highest affecteds-only lod scores found were at D18S41 in the paternal pedigrees, 3.16 at 0.02 recombination fraction including patients with bipolar disorder as affected and 3.51 at zero recombination fraction (empirical *p*-value <0.002) for the broader phenotypic model. A reanalysis of D18S41 by Cleves *et al.* (1997) yielded less support for this locus. McMahon *et al.* (1997) tested 30 additional families and D18S541 more than 20 cM distal to D18S41 appeared most interesting, also when including the families tested by Stine *et al.* (1995). This marker is located in the 18q23 region mentioned below. The study by McMahon *et al.* (1997) found only limited evidence of either a paternal or maternal effect suggested by earlier investigations (McMahon *et al.* 1995, Gershon *et al.* 1996).

Lod scores of 1.18 and 2.22 for marker D18S43 located at 18q22.3–q23 have been found in a single Belgian and in a sample of six North American pedigrees by De Bruyn *et al.* (1996) and Coon *et al.* (1996) respectively. De Bruyn *et al.* had already (in 1993) drawn attention to chromosome 18q. The lod score found by Coon *et al.* (1996) was mainly derived from one family.

The earlier mentioned region of chromosome 18q23 identified by Freimer *et al.* (1996) has received further support in a sample of 48 other BPAD patients from Costa Rica (Escamilla *et al.* 1999). This study found linkage disequilibrium to D18S1121 which is part of the haplotype reported in 1996 by Freimer *et al.* (1996). This region has received some support from the study by McMahon *et al.* (1997) mentioned above. Suggestive evidence for increased haplotype sharing in the same region has also been reported among lithium-responding BPAD patients from the Faroe Islands (Ewald *et al.* 1999). A lod score of 2.1 assuming a dominant mode of inheritance

and excess allele sharing has also been reported by Nöthen *et al.* (1999) for markers in this region in 57 German families with BPAD. Chromosome 18q23 has also received some support from a cytogenetic study (Calzolari *et al.* 1996).

CHROMOSOME 21

Mania is perhaps less common in patients with trisomy 21, and this might imply that a dominant or recessive disease gene for manic-depressive illness is located on chromosome 21 (Craddock and Owen 1994). The critical region for developing Down's syndrome involves at least part of 21q22.3, the same region for which linkage has been reported in a single large family (Straub *et al.* 1994) as earlier mentioned. Testing additional markers and including additional families the highest homogeneity lod score is still found on chromosome 21q22 (Aita *et al.* 1999). This region has received some support from a number of other research groups (Byerley *et al.* 1995, Detera-Wadleigh *et al.* 1996, 1997, Gurling *et al.* 1995, Smyth *et al.* 1997, Kwok *et al.* 1999). Additional support has been presented at workshops (Gurling 1998, Curtis 1999).

In the above-mentioned chromosome regions a number of research groups are now searching for linkage disequilibrium and investigating candidate genes in BPAD patients and controls.

THE X CHROMOSOME

The possibility of a gene for BPAD on the X chromosome has attracted attention for several decades due to the observation that unipolar disorder is twice as common among female relatives of bipolar probands, and a possibly decreased frequency of male-to-male transmission. The first linkage studies of BPAD used colour blindness as a phenotypic marker (Winokur and Tanna 1969, Reich *et al.* 1969). Evidence for linkage has been reported with classical, less polymorphic markers such as colour blindness (Xq28) (Mendlewicz and Fleiss 1974) and glucose-6-phosphate dehydrogenase deficiency (Xq28, very close to the colour blindness loci) (Mendlewicz *et al.* 1980). Mendlewicz *et al.* (1987) found linkage to a DNA marker at the factor IX locus around 35 cM proximal to the above-mentioned loci.

The ongoing search for an X-linked gene for BPAD has yielded inconsistent results even when the same pedigrees have been re-examined with more informative markers (Gershon 1990, Hebebrand 1992, Baron *et al.* 1993). However, additional linkage support for a gene near the factor IX locus has been provided by Lucotte *et al.* (1992), Jeffries *et al.* (1993), De Bruyn *et al.* (1994b) and Pekkarinen *et al.* (1995), as well as Gill *et al.* (1992) reporting a family with three males with factor IX deficiency and

affective disorder. Pekkarinen *et al.* (1995) reported significant linkage to markers near the factor IX locus in a single large Finnish family. This finding was supported by a haplotype covering a 20 cM region. A reanalysis of previously published data (Pekkarinen *et al.* 1995), and further investigations of additional families (Stine *et al.* 1997), have also supported this region. However, further studies are needed. It should be considered that, even in pedigrees with male-to-male transmission of BPAD, a common X-linked allele may increase the risk or act as a protective or modifying allele.

Progress has been accomplished despite fears that limitations concerning phenotypic knowledge and genetic mapping methods would hinder this. As genetic mapping studies of BPAD differ to some extent concerning diagnosis of probands; number and size of families; affection status models; genetic parameters used in lod score analyses; use of other methods for disease gene mapping; number, chromosomal location and informativity of markers tested; and total number of tests performed it is encouraging that at least a handful of promising chromosome regions exists. These findings seem plausible as they have mainly been detected in large families considering patients with bipolar disorder as affected, and supported also by relatively large lod scores, low empirical *p*-values and a shared haplotype. The loci for BPAD suggested on chromosome 1q, 6p, l0q, 13q, 18p, 22q and Xq have also been implicated in mapping studies of schizophrenia.

CANDIDATE GENE STUDIES

The number of studies which investigate for association between anonymous DNA markers or DNA sequence variation of possible functional significance in or near putative candidate genes and BPAD has increased rapidly in recent years. Currently around 60 different genes have been investigated in such studies. More than 30 studies each have investigated the serotonin transporter gene, the tyrosine hydroxylase gene, and the five dopamine receptors combined, while around 10 studies have been reported of the monooxidase A (MAO A) gene, the tryptophan hydroxylase gene and the catechol-*O*-methyltransferase gene, respectively. More than 120 studies have been performed on these candidate genes which have been by far the most reported candidate genes for BPAD until now.

The serotonin transporter (SERT) gene has probably been the most heavily investigated candidate gene within the past 3 years. Sequencing of the exons has been done in patients with bipolar and unipolar affective disorder. No important DNA sequence variation has yet been found in this part of the gene, except in one out of 73 patients investigated, which may be of no importance (Lesch *et al.* 1995, Di Bella *et al.* 1996). Two variants, a common variation in the 5′-flanking regulatory promoter region consisting of the

presence or absence of 44 base pairs of probable functional significance (Heils *et al.* 1996, Collier *et al.* 1996) and a VNTR marker located in the second intron of SERT, have been investigated in a number of studies which have been mostly negative. Two linkage studies using markers at the SERT gene have also been negative (Kelsoe *et al.* 1996a, Ewald *et al.* 1998c). The possible phenotypic importance of the 44 base pair deletion and other variations at the SERT gene is still uncertain.

Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the catecholamine pathway. The gene encoding TH is located at chromosome 11p15.5. Almost all investigations have failed to show that tyrosine hydroxylase is a risk gene for BPAD. Many linkage, case–control and haplotype relative-risk association studies have been performed (Turecki *et al.* 1997, Furlong *et al.* 1999, Craddock and Lendon 1999). Apart from the studies on the Old Order Amish, mentioned earlier, a few linkage studies have found relatively low lod scores in the region (Byerley *et al.* 1992, Lim *et al.* 1993, Smyth *et al.* 1996). Reported mutations in the TH gene lead to neurological phenotypes.

Monoamine oxidase A (MAO A) is involved in the degradation of catecholamines and serotonin. In 1993 an abnormal MAO A gene was reported in a single Dutch family with aggressive and impulsive behaviour (Brunner *et al.* 1993). This finding has not yet been replicated, and most association studies reported between BPAD and markers at the MAO A gene have been negative.

Functional variants have been described in some of the dopamine receptor genes; however, none of these has been shown to be of importance in BPAD.

Similar to other kinds of neuropsychiatric studies candidate gene linkage and association studies of BPAD have mainly focused on enzymes and receptors involved in the synthesis of neurotransmitters and drug binding, and to a lesser degree on intracellular second- and third-messenger systems. It is one of the potential strengths of molecular genetic studies of BPAD that it may find risk genes though they may be presently completely unknown, and very probably different from the mainly synaptic neurogenes which for decades have been central to traditional neurobiological research.

CYTOGENETIC STUDIES

Cytogenetic studies may yield clues to candidate regions for BPAD or support regions suggested by linkage studies. Co-occurrence or cosegregation between BPAD and chromosomal abnormalities may identify candidate regions which could harbour risk genes. A number of such regions have been reported (Table 5), and some studies have investigated a large number of cases based on nationwide cytogenetic registers (Mors *et al.* 1997). Cytogenetic abnormalities among family members may perhaps be related to illness if they are present among all or almost all affected individuals or

Table 5 Cytogenetic abnormality reported in patients with affective disorder

	References
*1q32 fragile site	Turecki *et al.* 1995
**t(1; 11) (q43; 21)	St Clair *et al.* 1990
*t(8; 15) (p21; q24)	Kunugi *et al.* 1995
**t(9; 11) (p22q22.3)	Smith *et al.* 1989
*11q23.3–q25 duplication	Craddock *et al.* 1994
*del (15) (q11.1q12)	Ewald *et al.* 1994
**Partial trisomy 15pter-q13.3 and 18q23-qter	Calzolari *et al.* 1996
*INV (18)(p11.3; q21.1)	Mors *et al.* 1997

* Single cases; ** families.

Table 6 Bipolar disorder and monogenic disease

	References
Hailey-Hailey's disease (3q21-q24)	Körner *et al.* 1993
Beta-thalassaemia (11p15.5)	Joffe *et al.* 1986
Darier's disease (12q23)	Craddock *et al.* 1993
Factor IX deficiency (Xq27)	Gill *et al.* 1992
Red–green colour blindness (Xq28)	e.g. Reich *et al.* 1969
G6PD-deficiency Xq28)	Mendlewicz *et al.* 1980

arise *de novo* in a single affected case. For a complex disorder such as BPAD the absence of relevant environmental factors and other risk genes in family members may explain that psychiatric diagnoses vary, and that carriers of a specific cytogenetic abnormality may be unaffected.

Investigations of chromosomal breakpoints in patients with BPAD (Millar *et al.* 1998) may make the identification of the relevant gene possible in a single patient. This is at odds with current trends of large-scale high-throughput search for linkage disequilibrium with a very large number of polymorphisms (Risch and Merikangas 1996, Kruglyak 1999, Nothen *et al.* 1992). However, for complex diseases the identification of genes at chromosomal breakpoints, in regions implied by linkage or other genetic mapping studies, seems very promising compared to searching for linkage disequilibrium.

The cytogenetic abnormality reported at chromosome 1q32 (Turecki *et al.* 1995) supports the finding by Detera-Wadleigh *et al.* (1999).

Similar to cytogenetic abnormalities co-occurrence or co-segregation between BPAD and monogenic diseases for which genes have been localized may identify candidate regions for BPAD risk genes (Table 6).

ENVIRONMENTAL FACTORS

Non-genetic factors are involved in the aetiology of BPAD as the concordance rate among monozygous twins is less than 100%. Though concordance rates less than 100% might be due to non-genetic aetiology in some discordant monozygous twin pairs, studies of the offspring of discordant monozygous bipolar affective or schizophrenic twins have indicated that reduced penetrance is also a possibility (Bertelsen and Gottesman 1986, Gottesman and Bertelsen 1989). Reduced penetrance is traditionally ascribed to unknown external environmental factors, but may be due to random cellular events during neural development (McGuffin *et al.* 1994). So the environment as implied from classical genetic studies includes a range of non-inherited factors ranging from cellular changes to external environmental factors. Classical twin studies have also been used for estimation of variance components to heritability, shared and non-shared environment.

Though genetic factors are important for influencing who may develop BPAD the environment often seems to influence the timing and frequency of episodes as more life events occur before episodes (Johnson and Roberts 1995, Malkoff-Schwartz *et al.* 1998) and childbirth may precipitate episodes (Terp and Mortensen 1998). A few interesting studies of gene–environment interaction have been performed in patients with major depression. However, none of these has included molecular genetic data. Genetic factors seem to influence the probability of development of major depression after severe stressful events (Kendler *et al.* 1995) through the action of genes that may determine sensitivity to the environment. Furthermore, the environment may not be randomly distributed in relation to the genotype. Genes may influence the way people interact with and experience their environment, so that what is traditionally viewed as external to the individual may be partly under genetic influence. A study has suggested that genes involved in major depression may act through predisposing individuals to place themselves in stressful environments (Kendler and Karkowski-Shuman 1997) and that this perhaps explains one-third of the association between stressful life events and major depressive episodes (Kendler *et al.* 1999). Another study has suggested that genetic factors may influence how people experience life events (Thapar and McGuffin 1996).

Recently there has been renewed interest in the role of parental deprivation. A study by Agid *et al.* (1999) found a marginally significant increase of early parental separation or parental death among BPAD patients.

Currently only a few studies of BPAD have tried to include risk genes and putative environmental factors (Souery *et al.* 1998) and more such studies are needed. Knowledge of specific environmental risk factors may help the identification of specific risk genes and vice-versa, and perhaps guide specific interventions.

GENETIC COUNSELLING

Genetic counselling of families with BPAD is still based on empirical risk estimates (Tsuang and Faraone 1990). Most patients with BPAD and spouses choose to have children, and in general the risk of illness does not justify avoiding having children, although clinicians may choose to advise against a BPAD patient having children if the disease is severe and clinically untreatable, or if the other parent has a severe psychiatric illness (Bertelsen and Gottesman 1995).

Though combinations of risk genes and non-genetic factors may increase the risk of BPAD by a factor 10 or so, the relative risk imposed by specific genes involved in BPAD will most likely be small, e.g. around 2–3 or less. As in the case of Alzheimer's disease and the apolipoprotein E polymorphism (Scott 1998) the size of the effect of a specific risk gene for BPAD may vary to some extent, and will probably be influenced by variation at the same and other genes and non-genetic factors involved in the life history of each patient.

It seems questionable whether knowledge of all genes affecting the risk of BPAD and their interplay will be available in the near future, or if such knowledge will be of any practical value for predictive testing and counselling. However, counselling will still be sought, and some patients may be willing to buy commercially available genetic tests even if they only convey very little and imprecise information. More studies are needed to investigate how patients with BPAD, their families and others will respond to the possibilities of genetic testing (Smith *et al.* 1996) (Nuffield Council on Bioethics. Mental Disorders and genetics: the ethical context. London: Nuffield Council on Bioethics, 1998) (http:/ /nuffield.org.bioethics).

PSYCHOPHARMACOGENETICS

Treatment response, degradation and side-effects of drugs may be influenced by genetic variation. The initial molecular target is known for at least the antipsychotic drugs, cyclic antidepressants and selective serotonin reuptake inhibitors. The slow onset of therapeutic action of these drugs indicates that the therapeutic mechanism of action is different. It is likely that genes that influence treatment response for drugs currently used in the treatment of BPAD are different from the genes related to these initial targets. Such genes may also be different from the risk genes, though perhaps related to the same functional or a counterbalancing pathway.

Antidepressants block the reuptake of serotonin and / or noradrenaline from the synapse. A recent study has suggested that patients with BPAD or unipolar depression who carry two copies of the 44 base pair deletion at the SERT gene respond more poorly to fluvoxamine treatment, and that

this could be improved by the administration by pindolol (Smeraldi *et al.* 1998). More studies on antidepressant treatment response are necessary, including genes involved in intracellular pathways of possible significance for this response.

A few studies have investigated polymorphism in relation to neuroleptic treatment response.

Among schizophrenic patients clozapine response and side-effects seem to be independent of variations in the very polymorphic dopamine D4 receptor (Rao *et al.* 1994, Shaikh *et al.* 1995, Rietschel *et al.* 1996). Currently neuroleptic drug response variability is investigated in relation to polymorphism in the serotonin 5-HT2A gene (Arranz *et al.* 1998, Joober *et al.* 1999).

Putative candidate genes involved in the action of lithium such as tyrosine hydroxylase (Cavazzoni *et al.* 1996), genes involved in the phosphoinositide cycle (Steen *et al.* 1998, Turecki *et al.* 1998), MAO A (Turecki *et al.* 1999) and chromosome regions which could harbour presently unknown candidate genes (Ewald *et al.* 1999) are now being investigated in lithium-responsive BPAD patients.

Concerning drug metabolism many polymorphisms have been found in relation to a subset of the around 60 cytochrome P450 genes which catalyse the metabolism of many drugs including neuroleptics, antidepressants and monoamine oxidase inhibitors (Nebert 1997). It is hoped that future knowledge of gene polymorphism may guide the choice of drugs, and perhaps dosage, in order to reduce the possibility of side-effects and toxicity.

CLINICAL AND SCIENTIFIC PERSPECTIVES

In the future the consequences of knowing the specific disease risk genes will make it possible to understand the basic biological effects of these genes. Judged from experience of monogenic and other complex diseases this may take several years.

It is uncertain to which additional benefits these findings will contribute, and how fast these benefits will be available. New and powerful forms of treatment will undoubtedly be developed. It seems likely that the choice of biological treatment may be guided by DNA-based tests. Reasonable animal models may perhaps be available. Knowledge of which persons might be genetically susceptible to environmental factors may make it possible to detect these environmental factors. If carriers can be detected with a reasonable certainty, preventive measures may be directed at such persons. It may perhaps be possible to predict course and severity of patients who have had their first episode. Finally, knowledge of the genes involved in BPAD will also yield molecular insight into brain function and mood.

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Chapter fourteen

The biology of bipolar disorder

Mary J. Kujawa and Charles B. Nemeroff

Bipolar disorder is a complex, potentially lethal, often chronic psychiatric illness. As noted elsewhere in this volume, bipolar disorder is characterized by the presence of a wide range of affective states including mania or hypomania, depression or mixed states. At any given time these affective states may also have a psychotic component. Transitions between affective states are often abrupt, inconsistent and unpredictable. The rate of suicide in bipolar disorder is believed to be approximately 15%. The pathophysiology of bipolar disorder remains obscure, despite the fact that clinical symptoms can be effectively treated for many with currently available mood stabilizers.

Lithium was the first specific antimanic agent identified. It is still one of the first-line treatments for acute mania, and the only treatment approved in the United States for the long-term treatment of bipolar disorder. Lithium maintenance has also recently been reported to be associated with marked reduction of life-threatening suicidal acts. In this study the number of suicidal acts sharply increased after the discontinuation of lithium (Tondo *et al.* 1998).

The diversity of clinical manifestation of bipolar disorder presents a major therapeutic challenge. The challenge centres on arriving at the correct diagnosis, successfully managing an acute episode and deciding on a course for prophylaxis (Freeman and Stoll 1998). Symptoms fluctuate from one episode to the next. Recurrence of manias and depressions is common. One must differentiate between classic or euphoric manias (bipolar I), hypomanias with episodes of depression (bipolar II), mixed episodes (simultaneously presenting with symptoms of both mania and depression) and rapid cycling.

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 281–314.

Rapid cycling is defined as at least four episodes of mood disturbance in the previous 12 months that meet DSM-IV criteria for a major depressive, manic, mixed or hypomanic episode. These distinctions are important because the differential responsiveness to pharmacological interventions is probably due to differences in underlying pathophysiology of these bipolar subtypes.

Many symptoms characteristic of bipolar disorder, such as grandiose and persecutory delusions, impulsivity and irritability, are common to those observed in other psychiatric disorders (American Psychiatric Association 1994a). Misdiagnosis contributes to the underdetection and undertreatment of bipolar disorder. Reported prevalence rates of this illness vary: 0.46% in the Old Order Amish Study (Egeland 1983), 0.7–1.6% in a study of five community clinics (Weissman *et al.* 1988), and 0.9–2.1% in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (American Psychiatric Association 1994a).

At present a broad-spectrum medication that is effective in monotherapy to control mania, depression and mixed state disturbances is not available. Although lithium is viewed as the gold standard in treating bipolar disorder, only approximately 40–50% of patients with bipolar disorder actually exhibit adequate responsiveness to lithium monotherapy. In addition, patients with initial excellent response to lithium may develop breakthrough episodes of mood disturbance in extended follow-up (Maj *et al.* 1989, Post *et al.* 1992). Interestingly, lithium non-responsiveness was reported in patients who were initially excellent responders, but then discontinued treatment, either due to non-compliance or physician discontinuation; following relapse, failure to respond once lithium is reinstituted is unfortunately common (Koukopoulos *et al.* 1995, Post *et al.* 1993a, Post *et al.* 1992). This, however, has not been confirmed in larger studies. Some bipolar patient subtypes are particularly prone to lithium non-responsiveness; among these are patients with dysphoric mania, rapid cycling, a negative family history for bipolar illness in a first-degree relative, the episode sequence pattern of depression–mania–well interval (i.e. the D–M–I pattern as opposed to the M–D–I pattern), more than three episodes prior to the initiation of prophylaxis, a history of comorbid substance abuse, and those patients with a history of head trauma or other medical comorbidities such as multiple sclerosis (Denicoff *et al.* 1997, Gelenberg *et al.* 1989, O'Connell *et al.* 1991, Sarantidis and Waters 1981).

The underlying mechanisms leading to different states and subtypes of bipolar disorder are not well understood. The possibility of markers of underlying biological alterations specific to subtypes of bipolar disorder such as mixed mania and/or as predictors of treatment response to specific medications would represent an incremental advance in the field. Cortisol is one such candidate biological marker. Three studies provide concordant evidence that mixed mania is characterized by hypercortisolism, whereas

pure mania is not (Evans and Nemeroff 1983, Krishnan *et al.* 1983, Swann *et al.* 1986). Thus patients with mixed, but not pure mania, exhibit dexamethasone suppression test (DST) non-suppression at high rates, as well as increases in plasma and cerebrospinal fluid (CSF) cortisol concentrations, and an increase in 24-hour urinary free cortisol concentrations. This suggests that patients with mixed mania, like those with depression, hypersecrete corticotropin-releasing factor (CRF) and consequently exhibit hypothalamic–pituitary–adrenal axis (HPA) hyperactivity. Ultimately, understanding the pathophysiological underpinnings of bipolar disorder will probably lead to more accurate diagnosis, early detection, and more optimal treatments.

In this chapter the biology of bipolar disorder will be reviewed with brief discussions of areas covered elsewhere in this volume, e.g. genetics, with a major focus on psychopharmacology, molecular biology, neuroimaging and neurobiology.

GENETICS

Bipolar disorder, more so perhaps than any other psychiatric disorders, is strongly influenced by genetic factors (Cohn 1997). The genetic components in complex diseases such as bipolar disorder do not follow single-gene inheritance patterns. Although patients may show a common clinical phenotype, the cause of the syndrome probably results from a heterogeneous collection of genetic and/or environmental influences. One remarkably consistent finding has been the considerably higher concordance rate of bipolar disorder in monozygotic twins compared to dizygotic twins, a universally agreed-upon observation. Unfortunately, genetic linkage and association studies have failed to identify the specific gene(s) which carry this risk.

However, several groups have provided evidence suggesting that chromosome 18 carries the genetic risk for bipolar disorder (Berrettini *et al.* 1994, Stine *et al.* 1995, Freimer *et al.* 1996, Escamilla *et al.* 1999). Other promising candidate genes and genomic regions of interest include chromosome 21q (Detera-Wadleigh *et al.* 1996, Straub *et al.* 1994), chromosome Xq (Hattori *et al.* 1993, Kennedy *et al.* 1992, Pekkarinen *et al.* 1995), and chromosome 6pter-p24 (Ginns *et al.* 1996). In the 1980s, linkage was reported between bipolar disorder and markers on the X chromosome (Baron *et al.* 1987). Most studies pointed to the Xq28 region as the location of the putative X-linked gene, but reports of linkage to factor IX in Xq27 (Mendlewicz *et al.* 1987) suggested incompatibility in these sets of findings. When investigators attempted to replicate linkage using highly informative DNA markers, several recombinations between the disease and the markers were noted in these individuals, eliminating most of the support for linkage on the X chromosome (Baron *et al.* 1997).

Table 1 Volumetric brain imaging studies in mood disorders

Areas of atrophy or cell loss
Lateral or third ventricle enlargement
Reduced frontal lobe volumes or areas
Reduced temporal lobe volume or area
Reduced basal ganglia volumes
Reduced amygdala–hippocampus volume or area

ALTERATION IN BRAIN STRUCTURE

The idea that bipolar illness may be related to an alteration in brain structure arose from the astute clinical observation that certain brain lesions produced by brain tumours, stroke or head injury resulted in manic-like behaviour (Cummings 1986, 1993, Robinson and Starkstein 1990, Strakowski *et al.* 1994). In general, brain lesions are far more likely to cause depression than mania, but lesions that do induce mania occur more commonly in the orbito-frontal and baso-temporal cortices, the head of the caudate and the thalamus (Cummings 1986, 1993, Robinson and Starkstein 1990, Strakowski *et al.* 1994). It was initially felt that lesions in the left frontal lobe tend to result in depression, whereas right fronto-temporal lesions cause mania. These generalizations about laterality are believed by many investigators to be too simplistic, because there are many exceptions to this rule. To understand structural brain alterations in bipolar disorder, more detailed evaluation is required.

There have been few anatomical postmortem studies of patients with confirmed bipolar disorder. However, computed tomography (CT) results had suggested that patients with bipolar disorder tended to have larger ventricles than normal volunteers. Ventricular enlargement is typically characteristic of cell loss, but potentially confounding factors such as previous treatment, head injury, and substance use obscured the interpretation of these results.

Volumetric brain imaging studies using CT and magnetic resonance imaging (MRI) in patients with mood disorders have suggested atrophy or cell loss in several areas of the brain (Table 1). Lateral or third ventricle enlargement has been noted by several investigators (Schlegel and Kretzschmar 1987a,b, Andreasen *et al.* 1990, Dewan *et al.* 1988, Strakowski *et al.* 1993). Reduced frontal lobe volumes or areas have also been noted (Sax *et al.* 1999). Atrophy or cell loss has also been suggested in the temporal lobe (Hauser *et al.* 1989, Altshuler *et al.* 1991). Reduced basal ganglia volumes in the putamen complex (Husain *et al.* 1991), caudate (Krishnan *et al.* 1992), and in both caudate and putamen complex (Krishnan *et al.* 1993) have been reported. Additionally, reduction in amygdala–hippocampus volume or area has been observed (Swayze *et al.* 1992). It has been suggested that

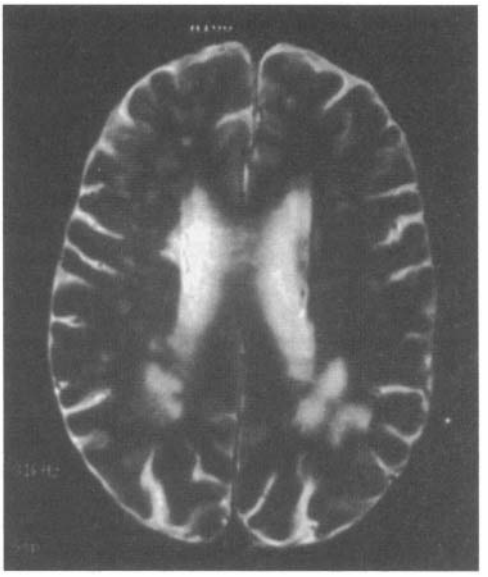

Figure 1 Unidentified bright objects (UBOs). Hyperintense regions visualized by magnetic resonance imaging (MRI) of a patient with bipolar disorder.

pathophysiological abnormalities in these neuroanatomical circuits underlie both the affective symptoms and associated attentional dysfunction in bipolar disorder.

MRI of patients with bipolar disorder reveals an inordinate number of hyperintense regions. These so-called unidentified bright objects (UBOs) are typically associated with vascular diseases such as hypertension, Binswanger's disease and carotid arteriosclerosis. The percentage of bipolar patients exhibiting these findings ranges from 5% to 50% compared to approximately 3% for controls.

These UBOs (Figure 1) tend to localize in deep white-matter structures that contain fibres that facilitate communication between frontal and temporal regions. The disruption of communicating fibres between fronto-temporal regions may play a major role in the pathophysiology of bipolar disorder. Follow-up postmortem studies of patients with UBOs have demonstrated a number of histological changes in these regions, including small vascular malformations, dilated perivascular spaces, brain cysts, infarcts and necrosis. It is possible that these lesions represent damage from a comorbid disease process unrelated to bipolar disorder; however, recent studies in children and adolescents with mania also reveal an abundance of these UBOs (Altshuler *et al.* 1998, Aylward *et al.* 1994, Botterton and Figiel 1997, Coffman *et al.* 1990, Dupont *et al.* 1995, Hauser *et al.* 1989, Pearlson *et al.*

Table 2 ^{31}P MRS findings in bipolar disorder

Abnormal high-energy phosphate metabolism (PCr, ATP)
Abnormal phospholipid metabolism (PME, PDE)
Low pH

Table 3 ^{1}H MRS findings in bipolar disorder

High "choline" or Co/Cr in basal ganglia
Frontal lobe decreased Na/Cr
Unchanged in temporal cortex

1997, Sax *et al.* 1999, Schlaepfer *et al.* 1994, Strakowski *et al.* 1999, Strakowski *et al.* 1993, Swayze *et al.* 1992).

Recent advances in functional neuroimaging allow measurement of subtle changes in receptor density, blood flow, and glucose metabolism. Functional neuroimaging takes advantage of the observation that when synaptic activity increases in a brain region, the blood flow to that region transiently increases and an excess of oxygenated blood temporarily bathes the region. Both functional MRI (fMRI) and positron emission tomography (PET) can be used to measure this blood flow increase. PET can also be used to directly measure local glucose metabolism which also increases with increased neuronal activity.

Early studies revealed that bipolar depressed patients had significantly lower cerebrocortical metabolism when compared to either controls or patients with unipolar depression. These changes were state-dependent, i.e. when patients recovered from their depression, these imaging abnormalities resolved.

In-vivo phosphorus-31 magnetic resonance spectroscopy (P-31 MRS) studies of patients with bipolar disorder have shown (Table 2) lower than normal frontal lobe phosphomonoester (PME) values and pH in the euthymic state, as well as increased PME and pH in depressed and manic states (Kato *et al.* 1991, 1992, 1993). Bipolar patients have also been noted to have significantly lower phosphomonoester (PME) values and significantly higher phosphodiester (PDE) values in both the right and left frontal lobes (Deicken *et al.* 1995a). In addition, the right-to-left ratio of frontal phosphocreatine (PCr) was higher in bipolar patients (Deicken *et al.* 1995a). Significantly lower PME levels have been noted in both the left and right temporal lobes of patients with bipolar disorder (Deicken *et al.* 1995b). Data such as these support altered temporal lobe phospholipid metabolism in bipolar disorder.

Localized proton (H-1) magnetic resonance spectroscopy of tissues *in vivo* has demonstrated several findings in brains of patients with bipolar disorder (Table 3), including high Co/Cr ("choline") in basal ganglia (Sharma *et al.*

1992, Stoll *et al.* 1996), decreased NA/Cr in the frontal lobe (Hamakawa *et al.* 1999), and no change detected in temporal cortex (Stoll *et al.* 1992, Silverstone *et al.* 1999).

Magnetic resonance spectroscopy has also been used to examine treatment effects of lithium. No changes in the temporal lobes of normal controls treated with lithium for 1 week were noted (Silverstone *et al.* 1998); however, significant changes in the temporal lobes were noted with amphetamine co-administration (Silverstone *et al.* 1999). Increased Cho/Cr in the basal ganglia with lithium treatment has been reported (Stoll *et al.* 1996). However, no effect on Cho/Cr in the basal ganglia with lithium treatment was noted in two other studies (Stoll *et al.* 1996, Kato *et al.* 1996). Bipolar disorder patients who are lithium responders have been noted to have high baseline basal ganglia Cho/Cr (Stoll *et al.* 1996).

Functional brain imaging studies using PET and SPECT have shown reduced general blood flow (Delvenne *et al.* 1990) in bipolar disorder patients. Reduced perfusion of the dorsolateral prefrontal cortex has also been reported in depressed individuals. Reduced perfusion (Goodwin *et al.* 1993, Starkstein *et al.* 1990) and reduced metabolism (Baxter *et al.* 1985, Buchsbaum *et al.* 1986) have been reported in the basal ganglia of patients with bipolar disorder. In the limbic system, increased perfusion of the left amygdala in manic patients (Goodwin 1996) and hypometabolism of the temporal lobe in bipolar patients (Post *et al.* 1989) have been noted. Frontal lobe metabolism is reduced in depressed patients with bipolar disorder (Buchsbaum *et al.* 1986, Baxter *et al.* 1989); this may be state-dependent because frontal lobe metabolism has been observed to be increased in mania (Goodwin *et al.* 1997).

NEUROCHEMICAL CHANGES

Biological studies in bipolar disorder have been hampered by several methodological confounds including diagnostic heterogeneity, trait versus state disturbances, effect of treatment and withdrawal of treatment, and dependence on peripheral models.

Despite these limitations, numerous biochemical abnormalities in bipolar disorder have been detected by measuring neurotransmitters and/or their metabolites or hormones in plasma, cerebrospinal fluid and postmortem tissue. The neurochemicals receiving most attention in the biology of bipolar disorder are 3-methoxy-4-hydroxy-phenylglycol (MHPG), norepinephrine (NE), serotonin (5-HT), and dopamine (DA).

Variable results of plasma MHPG levels do not generally support the concept of a unipolar/bipolar distinction. However, plasma MHPG in unipolar depressed patients tends to be similar to that of controls with greater alteration in plasma MHPG seen in bipolar depressed individuals.

Depressed dexamethasone suppression test (DST) non-suppressors have higher levels of plasma MHPG, similar to findings with plasma NE. In general, plasma MHPG levels tend to be lower in bipolar than unipolar depressed patients and, interestingly, are higher in bipolar patients when manic than when depressed. In a recent study of manic patients, plasma MHPG correlated with their manic symptoms but not with anxiety, depression, motor behaviour, acute psychosis, or severity of illness.

Although depression has often been hypothesized to be at least partially due to a relative deficiency of certain monoamines, including serotonin and norepinephrine, the role of these neurotransmitters in the pathophysiology of bipolar disorder is less clear. Whether unipolar depression and bipolar depression represent distinct biological entities remains unresolved.

Levels of NE, or its major metabolite, are consistently altered in the CSF of patients with bipolar disorder. Schildkraut (1965) proposed NE as the main culprit in both depression and mania; the catecholamine hypothesis, simply stated, was that depression resulted from low relative NE levels and mania resulted from high relative NE levels. This has been a difficult hypothesis to evaluate, because of a lack of availability of the necessary tools, but most evidence supports this hypothesis. Interestingly, NE elevations apparently precede the switch into mania.

In dysphoric mania, NE in CSF correlates modestly but significantly ($r \sim 0.5$) with ratings of dysphoria and anxiety but not with ratings of mania, suggesting CSF NE may be positively correlated with the degree of anxiety across a variety of psychopathological syndromes (Post *et al.* 1989).

Numerous alterations in the serotonergic and dopaminergic systems have been detected in depression, but little evidence is currently available in bipolar disorders. Alterations in the serotonergic system in depression include decreased CSF 5-hydroxyindolacetic acid (5-HIAA), questionably increased 5-HIAA in psychotic depression, increased postsynaptic 5-HT2 receptors, questionably decreased [^{3}H]-imipramine binding and decreased [^{3}H]-paroxetine binding (markers of the 5-HT transporters), blunted prolactin response to fenfluramine, L-tryptophan and clomipramine, and depressive relapse upon tryptophan depletion. Dopamine agonists have been observed to precipitate manic symptoms in susceptible patients. Alterations in the dopaminergic system in depression are supported by the following: (1) reduced homovanillic acid (HVA), the major DA metabolite, in CSF of depressed patients; (2) electroconvulsive therapy (ECT) enhances DA turnover and CSF HVA levels; (3) chronic antidepressant therapy possibly enhances DA function; (4) depression occurs in up to 40% of Parkinson's disease cases, and (5) the requirement for intact relationships of dopamine, serotonin, and norepinephrine for antidepressant response.

Table 4 PKC abnormalities in bipolar disorder

Elevated platelet membrane/cytosol PKC activity in mania
Enhanced serotonin-stimulated platelet PKC translocation in mania
Lithium "normalizes" changes
Increased PKC activity and translocation in brain cortices in bipolar disorder
Significantly decreased ^{3}H-PDBU binding sites in membranal and cytosolic postmortem brain samples in teenage suicide victims

Table 5 PKC in kindling and behavioural sensitization

Enhanced PKC activity as mediators of long-term alterations in neuronal excitability in CNS following kindling procedures
Acute and chronic amphetamine produce an alteration in PKC activity, PKC cytosol to membrane distribution, and phosphorylation of GAP-43
PKC inhibitor, H7, blocks both acute response to cocaine and cocaine-induced sensitization

MOLECULAR AND CELLULAR ALTERATIONS IN BIPOLAR DISORDER

Protein kinase C

Protein kinase C (PKC) is a family of phosphorylating enzymes which plays a seminal role in modulating transmembrane signalling and in regulating many cellular functions.

Friedman and associates (1993) found elevated platelet membrane/cytosol PKC activity, and enhanced serotonin stimulated platelet PKC translocation in mania (Table 4); 2 weeks of lithium treatment "normalized" both measures. The same laboratory has also reported increased PKC activity and translocation in brain cortices of patients with bipolar disorder compared to controls, effects which were accompanied by elevated levels of cytosolic α and membrane-associated γ and ξ PKC isozymes. Augmented PKC activation and phorbolester-induced enzyme redistribution have been reported in postmortem frontal cortex of bipolar disorder patients (Wang and Friedman 1996). The above results may be specific to bipolar disorder, because significantly decreased [^{3}H]-PDBU binding sites in both membranal and cytosolic postmortem brain samples (Brodmann's areas 8 and 9) have recently been found in teenage suicide victims compared to control subjects (Pandey *et al.* 1997).

Several studies have implicated persisting enhanced PKC activity as mediators of long-term alterations in neuronal excitability in the CNS following kindling (Table 5). Several laboratories have demonstrated that both acute and chronic amphetamine treatment produce an alteration in PKC activity, PKC cytosol to membrane distribution, as well as the phos-

Table 6 Effects of lithium and valproic acid on PKC isozymes and substrates

	Lithium	*Valproic acid*
PKC activity	↓	↓
PKC α	↓	↓
PKC ε	↓	↓
MARCKS levels	↓	↓
Inositol responsive	+	−

Table 7 Effects of a PKC inhibitor (Tamoxifen) on Mania

Significant decrease in manic symptomotology with a drop of 12.00 in the YMRS
Significant decline in CARS-M by 13.00

phorylation of a major PKC substrate, GAP-43, which has been implicated in long-term alterations of neurotransmitter release (Giambalvo 1992a,b, Gnegy *et al.* 1993). Injection of a PKC inhibitor, H7, has been shown to block both the acute responses to cocaine (as assessed by both behavioural and *in-vivo* microdialysis studies), as well as cocaine-induced sensitization (Pierce *et al.* 1998).

Heightened PKC-mediated signal transduction has been recently associated with acute mania (Wang *et al.* 1999). This is in contrast to decreased PKC-signal transduction reported in patients with unipolar depression or schizophrenia. Using blood platelets, these investigators demonstrated higher membrane PKC activity in manic patients compared to unipolar depressed or control subjects. The ratio of membrane to cytosolic PKC activity was significantly higher in mania, when compared to control, depressed or schizophrenic patients. Following stimulation of platelets with serotonin (5-HT) *in vitro,* greater membrane to cytosol ratio was noted in manic patients compared to the other three groups. The responsiveness of platelets to PMA (a PKC activator) and thrombin was greater in manic patients than in depressed or schizophrenic subjects, but not greater than controls. In this study both the schizophrenic and depressive patient groups were less active than controls.

Both lithium and valproic acid have been shown to reduce PKC activity, PKC α, PKC ε, and MARCKS levels (Table 6). The distinction between lithium and valproic acid is that lithium is inositol-responsive, but valproic acid is not. Treatment of bipolar mania with a PKC inhibitor, tamoxifen, resulted in a significant decrease in manic symptomotology (Table 7) rated by the Young Mania-Rating Scale (YMRS) (Young *et al.* 1978) with a drop of 12.00 in the YMRS. In this study the Clinician-Administered Rating Scale for Mania (CARS-M) (Altman *et al.* 1994) also showed a decline of 13.00,

which approached statistical significance ($p = 0.76$); the YMRS and CARS-M scores were highly correlated ($r \geq 0.9$). These preliminary results suggest that tamoxifen has antimanic efficacy, and that PKC inhibitors may be useful agents in the treatment of bipolar disorder, and in further understanding of the biology of this disorder. Larger, double-blind, placebo-controlled studies of tamoxifen and other novel selective PKC inhibitors in the treatment of mania are clearly warranted. Interestingly, both male and female patients responded in this preliminary study; the role of oestrogen receptor blockade remains to be elucidated.

Lithium's effects on PKC isozymes and substrates and G proteins may represent the mechanism of action by which chronic lithium blocks the development of supersensitive dopaminergic, adrenergic and cholinergic receptors. The modulation of PKC isozymes and substrates and G proteins may also explain lithium's protection against spontaneous, stress-induced and drug-induced (e.g. antidepressant or psychostimulant) cyclic affective episodes.

Cyclic adenosine monophosphate (cAMP) in bipolar disorder

In recent years numerous studies have reported abnormalities in components of the cyclic adenosine monophosphate (cAMP) signal transduction system, including G proteins, in postmortem brain and peripheral cells of patients with bipolar disorder (Avissar *et al.* 1996, 1997a,b, Friedman and Wang 1996, Manji *et al.* 1995a, Mitchell *et al.* 1997, Schreiber *et al.* 1991, Warsh 1996, Young *et al.* 1991, 1993, 1994).

The cAMP-dependent protein kinase (protein kinase A [PKA]) is a central component of the cAMP signalling cascade because in most situations the intracellular events mediated by cAMP occur through its activation. The PKA holoenzyme is organized as an inactive tetrameric complex composed of a regulatory subunit dimer and two monomeric catalytic subunits. The binding of cAMP to a regulatory subunit dimer results in the release and concomitant activation of the catalytic moieties, which in turn are able to phosphorylate specific substrate proteins, thereby regulating numerous cellular functions (Scott 1991, Spaulding 1993, Taylor 1989, Walas and Greengard 1991).

The binding of cAMP to PKA regulatory subunits and the activity of PKA are altered by the administration of antidepressants and lithium (Duman *et al.* 1997, Mori *et al.* 1998a,b, Nestler *et al.* 1989, Perez *et al.* 1989, 1991). Also, alterations in the levels of PKA have been reported after lithium treatment (Mori *et al.* 1998a). Moreover, changes in either the phosphorylation state or the levels of other cAMP-dependent phosphoproteins have been reported following treatment with antidepressants and lithium (Casebolt and Jope 1991, Duman *et al.* 1997, Guitart and Nestler 1992, Jensen

and Mork 1997, Miyamoto *et al.* 1997, Nibuya *et al.* 1996, Perez *et al.* 1995a, Rocha and Rodnight 1994).

The cAMP-stimulated phosphorylation of a low-molecular weight platelet protein has been shown to be significantly higher in untreated euthymic patients with bipolar disorder than in controls (Perez *et al.* 1995b, Zanardi *et al.* 1997, Perez 2000). This phosphoprotein has been identified as Rap1, a small guanosine triphosphate (GTP)-binding protein. The levels of PKA and Rap1 in platelets from untreated euthymic, depressed, or manic patients with bipolar disorder and healthy controls have been studied (Dubovsky *et al.* 1989). Levels of Rap1 and the catalytic subunit of cAMP-dependent protein kinase were significantly higher in untreated depressed and manic patients with bipolar disorder.

Evidence suggests that Rap1 may be involved in several cellular events such as calcium mobilization, cytoskeletal organization, and phosphoinositide metabolism; most of these measures have also been found to be altered in patients with bipolar disorder (Bokoch 1993, Corvazier *et al.* 1992, Dubovsky *et al.* 1989, 1991, Emamghoreishi *et al.* 1997, Farrell *et al.* 1992, Friedman *et al.* 1993, Jope *et al.* 1996, Lazarowski *et al.* 1990, Magnier *et al.* 1995, Shimon *et al.* 1997, Soares and Mallinger 1997, Torti and Lapetina 1992, Wang and Friedman 1996). Recently, Rap1 was found to be involved in the regulation of signal cascade coupled to neurotrophic factors (Vossler *et al.* 1997, York *et al.* 1998). This is intriguing, especially in light of recent data suggesting an involvement of neurotrophic factors in mood disorders (Duman *et al.* 1997, Nibuya *et al.* 1996, Smith *et al.* 1995). It is difficult to envision the molecular mechanisms underlying the alterations in Rap1, PKA and other signalling mechanisms, but findings such as these suggest alterations in the transcriptional, post-transcriptional, translational, or post-translational processes that are known to regulate proteins that may be involved in the pathobiology of bipolar disorder.

Phosphoinositide abnormalities

Several studies have supported abnormalities in the phosphatidyl inositol second-messenger system in bipolar disorder (Table 8). The relative percentage of platelet membrane PIP2 was found to be significantly higher in manic patients than in comparison subjects (Brown *et al.* 1993). Increased sensitivity to agonist stimulation of the Ca^{2+} response in neutrophils of bipolar disorder patients has been observed; these effects were "normalized" by lithium treatment (Van Calker *et al.* 1993). Also, numerous studies have reported elevated basal and post-receptor stimulated Ca^{2+} responses in peripheral cells from bipolar disorder patients.

Mathews and associates (1997) found increased G alpha q/11 immunoreactivity in postmortem occipital cortex from patients with bipolar disorder.

Table 8 Phosphoinositide abnormalities in bipolar disorder

Percentage of platelet membrane PIP2 significantly higher in manic patients
Increased sensitivity to agonist stimulation of Ca^{2+} response in neutrophils of bipolar patients
Effects "normalized" by lithium treatment
Elevated basal and post-receptor-stimulated Ca^{2+} responses in peripheral cells from bipolar disorder patients
Increased G alpha q/11 immunoreactivity in postmortem occipital cortex from patients with bipolar disorder
Reduced agonist-induced PI turnover in bipolar disorder

These elevated levels of G alpha q/11 in bipolar patient brains were accompanied by reduced agonist-induced PI turnover (Jope *et al.* 1996).

Kindling mechanism

Many, if not most, patients with bipolar disorder show a pattern of increasing frequency of cycling over time. This pattern, observed in other disorders such as epilepsy, has suggested that a model of kindling and sensitization might apply to bipolar disorder. Kindling refers to increased responsivity to repeated low-level electrical stimulation. This is seen commonly in seizure disorders, where a seizure focus becomes increasingly sensitive to other electrical events; i.e. the more seizures one has, the more likely the occurrence of additional seizures. The kindling hypothesis also explains the observation that early manic episodes tend to be triggered by external events whereas, after several episodes, manias tend to occur without any precipitants.

Certain anticonvulsants such as carbamazepine and valproate and, perhaps, lamotrigine, topiramate and gabapentin, are effective treatments for certain patients with bipolar disorder, lending further support for the kindling hypothesis. However, not all anticonvulsants are effective in the treatment of bipolar disorder (e.g. phenytoin and phenobarbital).

LITHIUM

The antimanic properties of lithium were discovered by John Cade, who stated "that lithium, a single inorganic ion, can reverse a major psychotic reaction which must have, quite apart from its substantial therapeutic value, profound theoretical significance in unraveling the mystery of the so-called functional psychoses. It must be regarded as a major research tool". Numerous controlled studies have established the efficacy of lithium for both acute and maintenance treatment of bipolar disorder (Hopkin and Gelenberg 1994). Lithium remains the only drug shown to be efficacious

for maintenance treatment of bipolar disorder, and appears to be more effective as monotherapy than any other. However, lithium is effective in only 40–50% of patients with bipolar disorder (Vestergaard 1992). Also, many patients are unable to tolerate it because of numerous side-effects including nausea, vomiting, dyspepsia, diarrhoea, hair loss, acne, tremor, sedation, decreased cognition and impaired coordination (Gaulin 1996). Additionally, lithium may be associated with long-term adverse effects on the thyroid. Although lithium's adverse effects on the kidney were of concern for many years, at therapeutic doses such effects are quite rare even after long-term treatment. Lithium has a narrow therapeutic window; some patients may experience toxicity near the upper limits of therapeutic blood level window. Laboratory monitoring is necessary. Inadvertent dosage changes by even a few tablets a day, or losing fluid through perspiration, can convert a therapeutic level to a toxic level. Lithium overdose constitutes a medical emergency.

Lithium has moderate to marked antimanic properties. It is less effective in patients with rapid cycling and the mixed state.

Mechanism of action

Understanding the mechanism of action of the mood stabilizer medications, such as lithium, may provide a clue to search for the biological alterations that underlie bipolar disorder at the cellular level, though the risk of tautology is considerable.

Lithium is an ion and consequently does not have a receptor to which it binds in the brain. Rather, lithium is believed to enter the neuron via sodium channels. When a neuron depolarizes, the voltage-sensitive sodium channels open and both sodium and lithium rush into the cell. The sodium is actively pumped out of the cell by the sodium–potassium ATPase pump, but lithium stays inside. Once inside the cell, lithium appears to modulate several second-messenger systems, including cyclic AMP and phosphoinositol pathways. Lithium blunts receptor-activated adenylate cyclase activity; this is a major intracellular pathway through which NE acts. Rather than causing large changes in baseline cellular activity, lithium appears to attenuate responsivity to other neurotransmitters. Other neurotransmitter systems affected by lithium include those that utilize serotonin, dopamine, and gamma-aminobutyric acid (GABA) as neurotransmitters. Lithium may act therapeutically by diverse neurobiological effects, rather than an effect on a single system.

Recent reports have suggested that lithium may achieve its therapeutic effectiveness by interfering with signal transduction mechanisms related to the phosphoinositide second-messenger system and the activation of protein kinase C (Bitran *et al.* 1990, Song and Jope 1992, Wang and Friedman 1989). (For reviews, see Manji and Lenox 1994, Manji *et al.* 1995b).

One of the intriguing properties of lithium treatment of acute mania is that a lag time is required before lithium produces its clinical efficacy. Moreover, lithium's beneficial effects on mood stabilization do not disappear suddenly after lithium treatment is discontinued (Birch 1991, Goodwin and Jamison 1990, Post *et al.* 1992). An explanation for these delayed and lasting effects of lithium could be given by postulating that lithium resets the ionic homeostasis in neurons and/or the activity and interaction of second-messenger systems of various receptors.

Recent work from Chen and Chuang (1999) has revealed actions of lithium that may well explain why a lag time is noted before therapeutic effects occur. In this work, cultured neurons derived from the rat cerebellum, cortex and hippocampus were studied. These cells are vulnerable to glutamate-induced excitotoxicity which is mediated via the *N*-methyl-D-aspartate (NMDA) receptor. The excitatory amino acid neurotransmitter glutamate, which is a ligand at the NMDA receptor, can be toxic to neurons expressing NMDA receptors under experimental conditions. Perhaps even more relevant to psychiatrists, glutamate has been implicated in neuronal cell death in several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's chorea (Blandini *et al.* 1996, Bowen 1990, Meldrum and Garthwaite 1990).

Glutamate is toxic to cultured hippocampal cells, cerebellar granule cells and cerebrocortical cells. However, preincubation with therapeutically relevant concentrations of lithium for approximately 1 week protects these cells from glutamate toxicity. Remarkably, preincubation with lithium for 24 hours provided no protection to the cells from glutamate exposure (Nonaka *et al.* 1998a).

Interestingly, lithium also protects cells from other chemical insults (Nonaka *et al.* 1998b) and protects neurons to a significant extent from ischaemic damage. It appears that the neuroprotective properties of lithium may be explained by lithium-induced inhibition of NMDA receptor-mediated calcium influx (Nonaka *et al.* 1998a). Recently Manji (personal communication) has reported that lithium increases hippocampal neurogenesis in adult rats.

Lithium also inhibits stimulus-induced redistribution of PKC activity from the cytosol to the particulate fraction of rat brain homogenates (Brennan *et al.* 1984). Data such as these suggest that inhibition of PKC activation by lithium may be relevant to its effectiveness in the treatment of bipolar disorder.

During acute mania, patients have been found to have enhanced platelet membrane PKC activity and serotonin-induced platelet PKC translocation (Friedman *et al.* 1993). The activation of PKC in these subjects was reduced after lithium treatment. Lithium has also been demonstrated to decrease PKC-mediated phosphorylation of membrane proteins (Casebolt and Jope 1991, Lenox *et al.* 1992, Manji *et al.* 1993).

Table 9 Neuroprotective effects of lithium

Protects cultured neurons against glutamate and NMDA-induced cell death
Protects cerebellar granule cells from KCl deprivation and anticonvulsant- or age-induced apoptosis
Induced survival of PC12 cells after serum/NGF deprivation
Protects PC12 and SY5Y cells from ouabain toxicity
Delays radiation-induced apoptosis in external granule cells of mouse cerebellum
Protects SY5Y cells from Ca^{2+} and MPP toxicity
Attenuates behavioural deficits and ChAT activity reduction by cholinergic system lesions
Reduces middle cerebral artery occlusion-induced infarct size and neurological deficits

Recent studies by Manji's group have demonstrated that lithium has robust effects on AP-1 mediated gene expression that is cation-specific. They have also demonstrated that both lithium and valproate have significant AP-1 DNA binding activity in frontal cortex and human neuroblastoma cells.

Are neurotrophic and neuroprotective effects of lithium relevant for mood disorders? Several lines of data suggest that they are (Table 9). Psychological and physical stress is associated with hippocampal atrophy and impairment of CNS neuronal regeneration. As discussed previously, mood disorders are associated with volumetric changes in frontal and temporal cortices. Prefrontal cortex volume reductions have been reported to be smaller in lithium-treated patients. Postmortem studies using three-dimensional cell counting methods have shown reductions in the number of neurons and glia in frontal cortices in mood-disorder patients. To explore this further at a molecular level, Manji and co-workers have demonstrated that both lithium and valproate have significant effects on levels of Bcl-2 in rat frontal cortex; this effect is evident even with low doses of lithium. There are several experimental paradigms in which lithium has been demonstrated to exert neuroprotective effects. Lithium protects cultured neurons against glutamate and NMDA-induced cell death (Nonaka *et al.* 1998a). Lithium also protects cerebellar granule cells from KC1 deprivation and anticonvulsant- or age-induced apoptosis (Nonaka *et al.* 1998a,b). Moreover, lithium induces survival of PC12 cells after serum/NGF deprivation (Volonte and Racker 1988), protects PC12 and SY5Y cells from ouabain toxicity (Li *et al.* 1993), and delays radiation-induced apoptosis in external granule cells of mouse cerebellum (Inouye *et al.* 1995). Lithium also protects SY5Y cells from Ca^{2+} and MPP^{+} toxicity (Manji *et al.* 1999), attenuates behavioural deficits and ChAT activity reduction by forebrain cholinergic system lesions (Pascual and Gonzales 1995), and reduces middle cerebral

artery occlusion-induced infarct size and neurological deficits (Nonaka and Chuang 1998).

ANTICONVULSANT MOOD STABILIZERS

The positive clinical response of bipolar disorder, particularly mania, to certain anticonvulsants has prompted discussion of possible links between seizure disorders and psychiatric illnesses.

The mechanisms by which these agents ameliorate certain psychiatric symptom severity remain obscure. Review of their pharmacological properties reveals some potential mechanisms of action. Many anticonvulsants facilitate GABA-mediated inhibition in the CNS (Olsen and Leeb-Lundberg 1981). This may have implications for mechanism of action in bipolar disorder and has sparked interest in theories relating defects in GABAergic transmission to the underlying pathophysiology of affective disorders (Van Kammen 1977). Depolarization-induced release of GABA from nerve endings is subject to feedback inhibition through autoreceptors on GABAergic terminals (Brennan *et al.* 1979, 1981). This has led to interest in a possible role for alterations of GABA systems in the pathophysiology of mania, and provides a putative mechanism for anticonvulsant mood stabilizers such as valproate (Brennan *et al.* 1984).

Comparing and contrasting clinical efficacy and mechanism of action of the different mood stabilizers may shed further light on our understanding of the cellular mechanisms of this illness. Thus, the spectrum of efficacy of valproate appears somewhat broader than that of lithium. Both appear effective in treatment of classic acute mania, but valproate appears to have greater additional efficacy in certain subtypes of the illness such as rapid cycling and mixed states. The evidence of comparable clinical benefits for lithium and valproate has stimulated studies that indicate overlapping effects on specific G protein-linked signal transduction for lithium and valproate, but not for carbamazepine (Bowden 1998).

Both lithium and valproate significantly reduce PKC and G protein activity with specificity for alpha and epsilon moieties. Both also reduce myristolated analine-rich C kinase substrate (MARCKS) protein, which is linked to G protein signal transduction and conveys some cytoskeletal integrity to neuronal membranes (Lenox *et al.* 1992). Both selectively enhance DNA binding activity of the transcription factor activator binding protein. The onset of these actions occurs earlier with valproate than with lithium, which may be relevant to the clinical impression of an earlier onset of clinical activity. Second-messenger signalling pathways do not appear to be modulated by carbamazepine.

Pretreatment plasma GABA concentrations have been positively correlated with the magnitude of improvement in manic symptomatology with valproate (Bowden 1998, Petty *et al.* 1996), i.e. serum GABA concentrations predict responsivity of acute mania to valproate.

CARBAMAZEPINE

In 1970, Japanese psychiatrists discovered that carbamazepine had antimanic properties (Takezaki 1971). Prior to this observation, carbamazepine was considered only for use in epilepsy and trigeminal neuralgia (Okuma *et al.* 1973).

More than 14 double-blind, controlled studies, including a total of approximately 300 patients, have demonstrated superiority of carbamazepine over placebo and its approximate equivalence to lithium for control of acute mania (Gaulin 1996). The average response rate in these studies was 55–70%. The use of carbamazepine for the treatment of bipolar disorder is decreasing because of a relatively unfavourable side-effect profile and the increased use of valproate (Freeman and Stoll 1998).

VALPROIC ACID

Valproic acid is the only medication other than lithium to be approved in the United States for the acute treatment of bipolar disorder. The role of GABA in mood disorders provided the basis for investigation of valproate in bipolar disorder (Guay 1995).

Its use in the treatment of bipolar disorder has increased significantly in recent years (Fenn *et al.* 1996). Although many patients receive valproate for maintenance treatment, its efficacy for long-term use has not yet been established. The addition of valproate to lithium is considered a first-line treatment for mania refractory to lithium monotherapy (Freeman and Stoll 1998). This combination (lithium and valproate) increased response in patients with rapid cycling or mixed episodes (Freeman and Stoll 1998). Valproate is also associated with side-effects including haematological, pancreatic, hepatic, hair loss and appetite stimulation leading to weight gain (Guay 1995). There is also an association with neural tube defects in the developing fetus, menstrual disturbances, polycystic ovaries and hyperandrogenism with valproate (Isojarvi *et al.* 1993, 1998), though the latter findings have not been confirmed by Altshuler and colleagues (1998). Reproductive disorders are more common in women with epilepsy than in matched, healthy controls. These disorders may be attributed to epilepsy itself, but further studies are necessary to evaluate the effect of antiepileptic drug therapies (including valproate) on reproductive function in women (Guay 1995). Recently our group has reported that, in rats, oral valproate treatment that results in plasma concentrations of valproate similar to those observed in patients treated for mania, results in reductions in regional brain concentrations of CRF, as well as reductions in CRF mRNA expression in the central nucleus of the amygdala (Stout *et al.* 2000). This may underlie the often-observed antidepressant effects of valproate in patients with bipolar disorder.

OTHER MOOD STABILIZERS

Emerging evidence indicates that gabapentin, lamotrigine and topirimate hold considerable promise as adjunctive and/or alternative treatments in refractory bipolar disorder.

Gabapentin

The rationale for using gabapentin as a mood stabilizer differs from that of other mood stabilizers. Beneficial effects of gabapentin on mood and quality of life were observed in the original treatment population of patients with epilepsy (Dimond *et al.* 1996). Several studies have suggested the efficacy of gabapentin in patients with mania, hypomania or mixed states (McElroy *et al.* 1997, Ryback *et al.* 1997, Schaffer and Schaffer 1997). The most common side-effects reported in these trials were oversedation, overactivation and neurological. Data from a double-blind, randomized, placebo-controlled study have failed to establish the efficacy of gabapentin in the treatment of acute mania.

Gabapentin was originally synthesized as a GABA analogue, but in fact it does not modulate GABA receptor function. Gabapentin was developed by integrating GABA into a lipophilic cyclohexane moiety in order to transport GABA across the blood–brain barrier. The goal was for this analogue molecule to inhibit seizures by binding to the GABA receptor. Gabapentin does have anticonvulsant activity but, in fact, does not adhere to the GABA receptor; instead it is believed to bind to a novel receptor site (Suman-Chauhan *et al.* 1993). It is believed to have indirect effects on GABA such as affecting the GABA transporter, leading to increased levels of GABA in the central nervous system (Beydoun *et al.* 1995). This is a dose-related effect (Taylor *et al.* 1998). The precise mechanism of action remains unknown. Gabapentin has been shown to decrease glutamate levels in the rat brain (Taylor *et al.* 1998). Gabapentin is not metabolized in humans and has no known pharmacokinetic interaction with other anticonvulsants (Taylor *et al.* 1998).

Pregabalin

Preliminary evidence suggests that pregabalin, a gabapentin analogue, has anxiolytic, anticonvulsant and analgesic properties. It has not yet been systematically evaluated in psychiatric disorders. Pregabalin is structurally similar to gabapentin, binds to the gabapentin-specific receptor, and may prove to be a more potent and longer-lasting analogue (Taylor *et al.* 1993).

Lamotrigine

Lamotrigine is currently indicated as adjunctive treatment for partial seizures. The probable mechanism of action is inhibition of release of excitatory

amino acids such as glutamate; this mechanism could account for its purported mood-stabilization properties (Sporn and Sachs 1997). Lamotrigine is a phenyltriazine derivative that inhibits voltage-gated sodium channels and reduces the release of glutamate. The anticonvulsant spectrum of lamotrigine, however, is far broader than that of phenytoin and carbamazepine which also act at sodium channels (Brodie *et al.* 1995). Additionally, lamotrigine has a mechanism of action not shared by other antiepileptic or mood-stabilizing drugs. Lamotrigine inhibits sodium channel activity subsequently linked to glutamate activation, but limited to the use-dependent, not resting sodium channel activity (Grunze *et al.* 1998). Moreover, use-dependent inhibition of calcium channel activity may occur (Goa *et al.* 1993). Recent studies have suggested that lamotrigine might be effective for the depressive phase of bipolar disorder (Calabrese *et al.* 1996a, Kusumakar and Yatham 1997a,b) and refractory bipolar illness (Sporn and Sachs 1997). Approximately 10% of patients treated with lamotrigine develop rash, which in rare cases can lead to Stevens–Johnson syndrome or toxic epidermonecrolysis Patients should be monitored closely. Rash is more likely when lamotrigine is given in combination with valproate or titrated rapidly in the presence of valproate (Gilman 1995).

Topiramate

Topiramate is a sulphamate-substituted monosaccharide indicated for adjunctive treatment of adult-onset partial epilepsy with influence at several neurological sites. Pharmacological properties that may contribute to its effects include a modulatory effect on sodium conductance by inhibiting rapid firing of voltage-dependent sodium channels and enhancement of GABA activity at the GABA A receptor. Topirimate is an antagonist of the kainate aminomethyl phosphoric acid subtype of the glutamate receptor, antagonizes kainate at the alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) receptor, and inhibits carbonic anhydrase (Markind 1998, Shank *et al.* 1994). Preliminary reports indicate that topiramate may be useful in refractory mood disorders (Calabrese *et al.* 1998, Marcotte 1998).

The most frequently reported side-effects with topiramate are somnolence, dizziness, ataxia, speech disorders, cognitive dysfunction, psychomotor slowing, headache, nausea, nystagmus, tremor, fatigue, gastrointestinal upset, visual disturbances and renal calculi (Markind 1998). Weight loss occurs in most patients; interestingly, greatest weight loss appears to occur in patients with the highest body mass index (BMI). The efficacy, safety and dosing of topiramate for bipolar disorder remains to be established in further studies.

ANTIDEPRESSANTS

Only limited studies of currently approved antidepressants in bipolar depressed patients are available. All seem to pose risks for inducing mania and hypomanic episodes and for causing more mood instability and rapid cycling (Bauer *et al.* 1994), though the SSRIs and buproprion seem the most efficacious and the least likely to cause a switch into mania. This issue is in need of further study.

Clonazepam and other high-potency benzodiazepines

In the 1970s, investigation of clonazepam for mania was based on its known anticonvulsant properties (Brown 1978). The overall antimanic and mood-stabilizing effects have not been adequately delineated. Generally, clonazepam is used as an add-on therapy. Efficacy and tolerability in controlled trials has not been studied, as monotherapy or as augmentation of valproate or carbamazepine for bipolar disorder. Sedation, cognitive and psychomotor impairment and potential for abuse are side-effects associated with clonazepam, and may limit its use.

Dihydropyridine L-type calcium channel blockers

The efficacy of verapamil in acute mania (Hoschl and Kozeny 1989, Janicak *et al.* 1998, Walton *et al.* 1996) is still not well accepted. Preliminary data suggest there may not be a cross-responsivity among all of the L-type calcium channel blockers. The dihydropyridines, such as nimodipine, with their different sites of action inside the calcium channel and different biochemical properties (Triggle 1992), may be preferable to the phenylalkalamines such as verapamil (Pazzaglia *et al.* 1993, 1998). Nimodipine has a different profile of anticonvulsant effects in animal models and, in contrast to verapamil, blocks cocaine-induced hyperactivity and its associated dopamine overflow (Pani *et al.* 1990).

ANTIPSYCHOTICS

Prior to the lithium era, the pharmacological strategies for management of bipolar disorder primarily included antipsychotics and antidepressants. Antipsychotic agents have been used in the treatment of bipolar disorder for over 40 years. Atypical antipsychotic agents such as clozapine, risperidone, olanzapine and quetiapine are being used more widely in the treatment of bipolar disorder. Some success has been noted in treating dysphoric mania, rapid-cycling bipolar disorder, and refractory bipolar patients with clozapine (Calabrese *et al.* 1996b, Calabrese and Woyshville 1995, Frye *et al.*

1996, Suppes *et al.* 1992). Although seizures are a side-effect of clozapine, it is interesting that one study reports that clozapine might have some effects in inhibiting kindled seizure evolution (Graham and Kokkinidis 1993). Others (Denney and Stevens 1995) have postulated that the microconvulsive properties of clozapine could be related to its clinical efficacy profile, and have noted that patients co-treated with valproate appear to have less robust responses than those not so treated. Newer atypical antipsychotics are currently being studied as monotherapeutic agents in the treatment of acute mania, with the olanzapine data the most comprehensive.

OTHER TREATMENTS FOR BIPOLAR DISORDER

Numerous other treatments for bipolar disorder have been reported. These include hypermetabolic doses of L-thyroxine, high doses of lecithin (phosphatidylcholine) and omega-3 fatty acids.

Omega-3 fatty acids may inhibit neural signal transduction pathways in a manner similar to that of lithium and valproate. A preliminary study found that omega-3 fatty acids were well tolerated and improved depression and mania in the short-term course of bipolar disorder (Stoll *et al.* 1999). Further evaluation will be needed to explore this innovative concept.

Another, clearly effective treatment for bipolar disorder is electroconvulsive therapy (ECT). Efficacy of ECT in treating both bipolar mania and depression has been clearly shown.

SUMMARY

The past several decades have produced experimentation that has begun to unravel the complexities underlying the biology of bipolar disorder. In order to continue expanding our understanding of this disorder it will be necessary to integrate findings from a wide variety of disciplines. The new millennium holds promise for breakthroughs in neuroimaging as methods are refined and ligands with improved specificity are developed. Several large studies focusing on the genetics of bipolar disorder are under way which will build on current thoughts that bipolar disorder vulnerability may lie on several chromosomes and involve many genes. Neuropharmacologists and molecular biologists are making progress in elucidating various second-messenger pathways and gene-regulation pathways altered by various mood stabilizers. An improved understanding in this area will pave the way for a new generation of mood stabilizers, a few possibilities have been discussed herein. Lastly, as human brain banks continue to expand, investigation of the biology of bipolar disorder will grow.

Acknowledgements

We are grateful to H. Manji, MD of Wayne State University for providing materials for inclusion in this review.

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Chapter fifteen

Cyclicity and manic-depressive illness

Athanasios Koukopoulos, Gabriele Sani,
Alexia E. Koukopoulos and Paolo Girardi

"The soul itself is not unlike a heaving wave".

J. C. Heinroth

INTRODUCTION

Manic-depressive illness is essentially a cyclic phenomenon. Its cyclicity is not simply a type of course such as can be observed, for instance, in malarial fevers or epileptic attacks, but is probably its fundamental constituent because the disorder in its core manifestations appears closely related to cyclical biological rhythms such as sleep, and to environmental, circadian and seasonal variations. From a clinical point of view it is the single most distinguishing feature of the disorder and is more important than any symptom or cluster of symptoms.

The word "cycle" was used for the first time in psychiatry by W. Griesinger (1845), in his *Mental Pathology and Therapeutics.* "Not rarely the whole disease consists of a cycle of both forms (mania and melancholia), which often regularly alternate with each other." Before the words "cycle" and "cyclical" were established, the term "periodic" was in use, from the Greek *periodos,* "to go for a walk around the streets", which went on to increasingly mean, "to go back to the place one started from", like the orbit of a heavenly body. The Romans later translated *periodos* into *circuitus* and *circularis,* which have been widely used to mean cycle and cyclical. The

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 315–334.

perception of the course of time of the Ancient Greeks and Romans was cyclical. Ulysses set out from Ithaca and returned to Ithaca.

The concept of period in medicine was used for the first time by Hippocrates (1967b) in the description of the course of fevers, mainly malaria: fevers were continuous, quotidian, tertian and quartan. Aretaeus (1735) states that mania occurs at intervals. Alexander of Tralles (1878), a Byzantine physician who lived in the 6th century AD, held that manics "present intervals and attacks such as occur in fevers that recur periodically". The word attack, originally used to describe attacks of fever, has become commonly used in psychiatry. Similarly, the terms remission and intermission, coined to describe the course of the fever, are in common use in psychiatry. Even at the beginning of the 19th century Esquirol (1838), one of the fathers of modern psychiatry, spoke of *folie continue, remittente ou intermittente*. The intermittent course may be a regular one with quotidian, tertian, quartan, monthly, annual or pluriannual recurrences, or an irregular one.

Many centuries after Alexander of Tralles, Georg Stahl wrote in 1701 "De affectibus periodicis", F. Hoffmann (1740) wrote in 1740 about "Melancholia hypochondriaca cum mania periodica alternans", and in 1764 Medicus spoke of periodicity in his work "On diseases which maintain periods". From that time on, the word "period" became fundamental in psychiatry and was gradually replaced by cyclical from the second half of the 19th century onwards (Kirn 1878, Pilcz 1901). Circular, the Latin version of the word, came into use for bipolar courses while periodic remained in use for unipolar manias or depressions. Today, the term "periodic" has been abandoned in favour of the term "recurrent", which was adopted by the DSM system. This change also reflected a shift away from the old cyclical perception of time.

In the 20th century the concept of cyclicity of mood disorders declined and then reemerged in the past 20 years. As early as 1904, in the seventh edition of his textbook, Kraepelin writes that "the more or less regular return of certain alterations is a general characteristic of all those forms of insanity which stem from a state of permanent nervous weakness and to this state return", and that in "periodic disturbances, such as epileptic fits, all the underlying conditions are present in the organism itself". He highlights only the endogenous nature of the disease but misses the close relation of human physiology and manic-depressive cyclicity to the environmental cycles of day and night, cold and heat, and summer and winter as various authors had observed over the centuries.

For centuries, mania and melancholia were considered two distinct diseases, although a close correlation between the two was always observed. Aretaeus (1735) said that "once the attack of mania is over the sick persons become slowed down, docile, taciturn and sad, and when they recall the illness they have been through they feel anguish at their wretchedness".

On melancholia he writes: "It seems to me that melancholia is the beginning and part of mania".

Alexander of Tralles (1878) maintained that "nothing else is mania than the mounting of melancholia towards aggressive excitation". Thomas Willis (1676) writes the following striking phrase: "These two, melancholy and mania, mutually exclude and replace each other like smoke and flame". A century earlier, Marsilio Ficino (1995), a neoplatonic philosopher at the Medici court, wrote something remarkably similar: "the melancholic humour lights and burns, producing that excitement which the Greeks call mania and we *furor.* But when it dies out, only a black soot is left … which makes people foolish and sluggish. This state of mind is properly called melancholia, dementia and madness". Morgagni (1761), Lorry (1765) and Chiarugi (1794) made similar observations. Since then, however, the alternation between the two phases was never seen as a regular occurrence, intrinsic to the disease. It was viewed as accidental or random. Esquirol (1838), for example, said: "It is not rare to see mania alternating, sometimes in a regular fashion, with *phthisis,* hypochondria and *lypemania* [the term he used for melancholia]". Griesinger (1845) certainly realized that the alternation of the phases was regular and linked to the cycle of the seasons. There are dozens of descriptions in which this alternation is repeatedly cited without the physician suspecting it might be a single process. It was probably the description of arachnitis (arachnoiditis) luetica by A. L. J. Bayle (1822) which made it possible to conceive that mania and depression might be parts of the same disease. Just as lues can produce an extremely wide range of clinical pictures including melancholia, excitation, delirium, dementia and so on, mood disorders, in their nosological unity, can manifest themselves in various clinical forms.

The credit for first describing a single disease entity must go to Falret (1851) who, first in his lessons at the Salpetriére and then in an article dated 24 January 1851, published in the Paris hospitals gazette, spoke of *folie circulaire,* characterized by an alternation between mania and melancholia followed by a free interval, intervalle lucide, more or less long. On 3 February 1854 Baillarger (1854) presented to the Imperial Academy of Science his *folie à double forme* in a work entitled "Note on a kind of insanity in which the attacks are marked by two regular periods, one of depression and the other of excitation". Unlike Falret's *folie circulaire,* the *folie à double forme* does not includes a free interval after each cycle (*accès)* but only intermissions between the two episodes (*periodes*). The contributions of Falret and Baillarger to the understanding of bipolar disorder were fundamental, both because they established once and for all the single nature of the disease and because they conferred precise nosological characteristics onto it, essential for distinguishing it from psychotic pictures of differing natures.

Subsequently, other authors contributed to the development of the concept of manic-depressive illness. Of these we shall mention particularly Kahlbaum (1863), who distinguished between cyclical forms with benign outcomes, which he called *vercordie,* and those leading to dementia, which he called *vesania tipica.* and which later became Kraepelin's dementia praecox. In 1882 Kahlbaum published a work on cyclothymia, that is the milder forms of the illness. Kraepelin presented, in the sixth edition (1899) of his handbook, the manic-depressive entity. Here he calls it manic-depressive insanity, and includes on the one hand the so-called periodic and circular insanity and on the other simple mania, usually kept distinct from it. In the eighth edition Kraepelin (1913) includes in manic-depressive illness also the temperamental forms, which he calls "fundamental states" and which correspond to today's hyperthymic, cyclothymic, dysthymic and irritable temperaments. It was Karl Kleist (1953) in his monograph "The classification of neuropsychological diseases", and his pupil Karl Leonhard (1957) in the book *Endogenous Psychoses* (1957), who distinguished simple unipolar forms from bipolar forms and cycloid forms corresponding to mixed states. Subsequently Angst (1966) and Ferris (1966) clearly divided manic-depressive illness into monopolar and bipolar forms on the basis of hereditary data.

Today there is a great deal of discussion about the actual rate of occurrence of unipolar forms. While formerly they were believed to be prevalent, debate has now developed to the point at which their very existence is being questioned. Many authors, including the authors of this chapter, believe that recurrent depressions preceded or followed by mild hypomanias, including those triggered by antidepressants (BP III) (Akiskal and Pinto 1999), and patients with cyclothymic or hyperthymic temperaments (BP IV) belong to the bipolar group together with the BPII (Dunner *et al.* 1976) patients (the so-called soft bipolar spectrum). It is generally accepted today that the ratio of unipolar to bipolar is 1 : 1. In our sample (Koukopoulos 1997) of 1257 affective patients, 80% were bipolars including soft bipolar cases. It should be emphasized that the Centro Lucio Bini is a facility for mood disorders, and the affective patients who attended suffer from more severe forms. We feel it is useful to recall that, while for unipolars it is possible to have just one or only a few episodes during a lifetime, this is virtually impossible for bipolars. Currently the DSM-IV (American Psychiatric Association 1994) divides unipolar forms into single or recurrent major depression and dysthymia, and bipolar forms into cyclothymia, bipolar I and II and mixed states. As we said before, manic-depressive illness is probably a disturbance of normal physiological cycles, which are in turn influenced by the environment and the seasons. We can observe it in the form of multi-year cycles, hard to understand; annual cycles with excitation in summer and depression in winter; 6-month cycles that already represent rapid cycling; seasonal cycles, closely linked to climate or environmental

Table 1 Lithium response and cycle pattern

	MDI (%)	*DMI (%)*
Koukopoulos *et al.* (1980)	61	32
Grof *et al.* (1987)	94	56
Haag *et al.* (1987)	90	48
Maj *et al.* (1989)	74	37
Faedda *et al.* (1991)	73	50
Koukopoulos *et al.* (1995)	43	29

changes; monthly cycles, very frequent in women and linked to the menstrual cycle; and 48-hour or circadian cycles with mood swings between the morning and the evening. Finally, we have ultradian cycles with swift changes in mood, even in the space of a few minutes, particularly frequent in the elderly, perhaps because of the impaired regulatory capacity of their central nervous systems. This is also called mood instability.

In order to better understand the intimate relationship between the two opposing phases of the manic-depressive cycle, it may be useful to introduce the concept of energy and the underlying biological processes that create and regulate it. Undoubtedly there is in mania an increased energy level with hyperactivity and decreased need for sleep. Periods of nervous excitement certainly consume great amounts of energy and may exhaust the biological processes that create it. Postmanic depression appears as an exhaustion of these processes. A genetic flaw may prevent the prompt recovery of this energy and give rise to a long-lasting depressive period.

This is probably the concept that Willis and Ficino expressed by comparing mania to a burning fire and melancholia to its soot or smoke. Heinroth's (1818) statement is also remarkable: "Exaltation is not a mere somatic accessory but is the fundamental affection of the psyche". A confirmation of the primacy of mania in the cycle is the fact that all prophylactic treatments against manic and depressive recurrences or episodes, such as lithium, anticonvulsants and neuroleptics, are fundamentally antimanic agents which, by preventing or suppressing mania, also prevent depression. This explains the better response to prophylaxis of those cases that start with mania (Faedda *et al.* 1991, Grof *et al.* 1987, Haag *et al.* 1987, Koukopoulos *et al.* 1980, 1995, Koukopoulos and Reginaldi 1973, Maj *et al.* 1989) (Table 1).

Further evidence of the primary role of mania in the manic-depressive cycle comprises relapses after the interruption of lithium maintenance therapy (Faedda *et al.* 1993a, Suppes *et al.* 1991). Relapses that occur during the first few months are phases of excitation and not depression. Depressions occur later and follow the manic relapse or the natural course of the disesase. All cases of apparent depression are in our opinion in fact mixed states.

On the other hand, antimanic treatments, especially neuroleptics, deepen and prolong depression that follows mania.

If the cycle starts with a depression, and we treat it with antidepressants, a rebound into mania may occur. As we shall discuss later, these patients are mainly of hyperthymic and cyclothymic temperament, i.e. persons of great vitality. Antidepressants probably activate the biological processes that tend to raise energy levels. It is conceivable that in genetically predisposed persons the energy levels may overshoot.

Our organism, in general, strives to maintain its homeostasis. Cardiovascular regulation, for instance, is a good example of this complex function. In particular the central nervous system spontaneously tends to push depressed mood back up towards euthymia, and to level off excitement. Our antimanic and antidepressant treatments certainly interfere with this process, and this explains at least part of the increase in circular cases and cyclicity in general, in recent years. Heinroth's (1818) intuition seems all the more prescient when he states: "The physician must be particularly careful not to go to extremes. For he may easily drive the patient to extreme depression by treating temporary fits of rage, or, alternatively, he may overexcite the patient whose prevailing mood is melancholic".

CYCLICITY AND THE SEASONS

The seasons, with their complex climatic changes in light, temperature, humidity, along with circadian variations, determine the cyclicity of biological rhythms and are the decisive factors in creating the cyclic patterns of manic-depressive illness. F. A. Carus (1846) said that "the nervous system decidedly partakes in the periodicity of the external world". Kay R. Jamison (1999) states:

> "We are, with the rest of life, periodic creatures, beholden for our rhythms to the rotations of the earth around the sun and the moon around the earth. The chemistry of our brains and bodies oscillates in adaptation to the earth's fluctuations in heat and light, and probably its electromagnetic fields as well. Like other mammals, our patterns of eating, sleeping, and other physical activities sway with the seasons, varying in accordance with changes in day length and temperature. A master biological clock, genetically determined, controls the cycling of our brain's constituent chemicals and shapes our responses to our physical environment."

This correlation was clear to the Ancient Greeks and the theory of the four humours – blood, yellow bile, black bile and phlegm – was based on close relations with the four seasons, the four ages and the four qualities: warm, cold, dry and humid. Each humour prevailed according to the season and in each age. Individuals adapted to each season or became sick according to their temperament. In the Hippocratic writings one reads observations such as the following: "But if the weather [in autumn] be northerly and

dry … it is very harmful to the bilious … and some of them become ill with melancholia", or "such diseases as increase in the winter ought to cease in the summer and such as increase in the summer ought to cease in the winter" (Hippocrates 1967b).

This conception remained vivid until the 19th century. Pinel (1809) states that "manic attacks begin immediately after the summer solstice, continue with more or less violence through the heat of summer, and commonly terminate towards the decline of autumn". Esquirol (1838) describes many cases with a seasonal pattern. It is significant that Griesinger (1845), after naming as Cyclus the alternation of mania and melancholia, goes on to say: "Other observers and ourselves have seen cases where at a particular season a profound melancholia supervenes and this in spring passes into mania, which again in autumn gradually sinks into melancholia".

Emil Kraepelin (1913) describes cases with seasonal patterns and Johannes Lange (1928) compares winter depression with hibernation.

In the course of the 20th century, however, these views have been neglected and almost fallen into oblivion. Thomas A. Wehr (1989a) gives a series of reasons for this, including "the cultural shift from a cyclic to a linear perception of time, so that psychiatrists and patients may be more likely to perceive affective recurrences as a succession of separate events than as a seasonal cycle of events". Norman Rosenthal (1993) agrees with the importance of this perception of time as linear or historical rather than cyclic. He also attaches great importance to the influence of psychoanalysis, citing Freud's belief that "the processes of the system Ucs. (the unconscious) are timeless; i.e. they are not ordered temporally, are not altered by the passage of time, in fact bear no relationship to time at all". ECT and pharmacological treatments act on affective conditions almost independently of the season. This may have contributed to the decline in interest in seasonal factors.

New interest in the cyclicity of seasonal affective disorders has emerged, especially thanks to the work of Wehr, F. K. Goodwin and Rosenthal (Rosenthal *et al.* 1984, Rosenthal 1993, Wehr and Goodwin 1979, Wehr *et al.* 1988, Wehr 1989a,b) at the NIMH. In this development, lithium treatment and studies on the longitudinal course of the disease played a major role in highlighting its relation to the seasons, although continuous lithium treatment often changes the seasonal pattern of the cycles (Koukopoulos *et al.* 1975).

Seasonal affective disorder (SAD) entered the DSM-IIIR (American Psychiatric Association 1987) as a seasonal pattern of the disorder. Given the importance of the seasons on the incidence of mania and depression, it appears correct to assume that light and heat may trigger and induce a seasonal pattern in the course of the disease. Wehr and Rosenthal (Wehr *et al.* 1988) further speculate that these factors may be "clues to the nature of affective illness; it might be a disorder of systems that mediate the

organism's adaptation to changes in the physical environment". Certainly the relationship between affective illness and the seasons is more profound than a mere modulation of its course.

The prevalence of seasonal patterns among patients who attended specialized clinics was found to be 16% by Thase (1988), 29% by Monplaisir (1990), 38% by Garvey *et al.* (1988), and 15% by Faedda *et al.* (1993b).

Of great interest is the group of patients with spring–summer depression. This season has the highest peak of suicides while in autumn–winter there is another, smaller peak. One explanation for this may be that winter depressions are generally retarded while spring–summer ones are anxious or agitated, often true mixed depressions. Agitation is certainly a major risk factor for suicide (Koukopoulos and Koukopoulos 1999).

ONSET OF THE DISORDER AND FREQUENCY OF CYCLES

Jules Angst (1986) in his classic studies on the course of affective disorders found that the median age at onset is 45 years for unipolar depression and 29 years for bipolar disorder. In more recent studies other authors have found that the onset occurs earlier in life, especially for bipolar disorder, and this could be explained by the increasing use of substances by young people, and by their change of lifestyle, such as going to sleep much later than earlier generations. The earlier onset of bipolar cases is an important fact and the depression that occurs at a young age is very likely to develop into bipolar disorder. Angst states:

"It is obvious that many bipolar cases start in preadolescence or adolescence. They are frequently misdiagnosed as 'reactive depression', 'neurosis', 'personality disorder', 'borderline disorder', or 'schizophrenia'. Obviously, many cases start with very mild or inapparent mood swings. Relapsing again and again, the amplitudes get higher and higher until the threshold of a clear disorder is reached. It is important to diagnose such cases as early as possible in order to put them on a long-term prophylaxis and to avoid a disastrous development of personality and social adjustment, frequently observed in adolescents."

Bipolar patients suffer from more occurrences than unipolar depressives. In Angst's sample of patients, depressives had four episodes versus 10 for the bipolar patients. About 47% of unipolar depressives suffer only one to three episodes while 95% of bipolar patients suffer more than four episodes. Angst also found that, annually, unipolars have 0.22 episode while bipolars have 0.37.

It may be that the unipolars with higher frequency whom one often encounters in clinical practice are probably pseudo-unipolars; that is they also have undetected periods of sub-threshold hypomania. Indeed, real unipolars have very long intervals of several years and it is doubtful whether they should undergo long-lasting prophylactic treatment.

Table 2 Manic-depressive patients ($n = 1257$) (from Koukopoulos 1997)

	Episodes/year	*RC (%)*
Dysthymic D.	0	0
UPD	0.33	2.4
BP I	0.63	8.5
BP II	1.80	28.0
RC	7.20	100

Marneros (1999) also found that the annual frequency of episodes of unipolars is 0.12 versus 0.22 for bipolars. The authors of this chapter found, in a sample of 1257 affective patients, the frequency of episodes per year to be: 0.33 in unipolar depressives, 0.63 in bipolar I patients, and 1.80 in bipolar II patients. This last high frequency should be attributed to the inclusion of 114 rapid cyclers, the majority of whom (93) were bipolar II (Table 2).

Tondo *et al.* (1998) found, in a sample of 317 lithium-treated bipolar patients, that before lithium maintenance treatment the recurrences per year were 1.65 for bipolar I and 2.30 for bipolar II. These high frequencies are certainly explained by the more severe course of the patients who are selected for lithium maintenance treatment, but they still show how malignant the course of this illess can be in many cases, and how much the frequency of recurrence has increased in recent years. Many authors, including the authors of this chapter, have emphasized the importance of antidepressant treatments in accelerating the cyclicity of manic-depressive illness. At Kraepelin's (1913) time there was no distinction between unipolar and bipolar patients, but he still finds 13% of prevalently depressive patients to have three or more attacks during their lifetime, while 37% of the bipolars had three or more attacks.

Given the tendency of affective disorders to recur several times during the course of a person's lifetime, and given the severity of the illness, due not only to the gravity of the symptoms and their duration but also and especially to the frequency with which they present themselves over a lifetime, it is of the utmost importance to ascertain this frequency and make a prognosis; that is to identify which forms tend to recur more frequently, and which less frequently.

This issue is crucial in deciding the prophylactic treatment against future recurrences. Unfortunately, these pharmacological treatments are not free from undesirable side-effects, and it is psychologically burdensome for the patient to undergo such therapy for years on end. It is therefore of the utmost importance to be able to form a prognosis of the probable frequency of future relapses on the basis of type of the index episode and the previous course of the disease.

SEQUENCE OF THE MANIC-DEPRESSIVE CYCLE

Angst in 1978 suggested a typology of manic-depressive illness distinguishing patients into predominantly manic, predominantly depressive, and a "nuclear" type with severe mania and severe depression. This corresponds to the distinction in BPI and BPII proposed by Dunner *et al.* (1976), which was accepted by the DSM system and is now in established use. We examined the manic-depressive cycle also from the point of view of the sequence of the two opposite phases and the interval. We were prompted to do so because of the differing responses to treatment of the different sequences of the cycle. We found that the sequence of the phases of the manic-depressive cycle presented the following patterns:

1. Mania–depression–interval (MDI)
2. Depression–mania–interval (DMI)
3. Continuous circular course (CC). This latter type of course can run in long cycles, one or less per year, or in short cycles of two or more per year, today called rapid cycles (Dunner and Fieve 1974, Dunner *et al.* 1977).
4. Irregular course of the sequence of the cycle (IRR). In this type of course there is no regular sequence of mania and interval and subsequent cycles.

Some patients follow one of the above patterns from the beginning of their disease. Frequently the disease starts with isolated episodes or with an irregular pattern which is followed after some years by a course with regular sequences of mania and depression and interval. Later, this regular course may become irregular again. In our studies we established the pattern of the cycle of our patients according to the sequence of the last four phases before the index one, which also corresponded to the start of lithium treatment.

In an investigation into the course of the manic-depressive cycles and the changes caused by treatment, published in 1980, involving 294 bipolar patients, we found the following patterns.

1. Mania–depression–free interval course (MDI)

In 119 patients (28%) the cycle started with a manic episode which was followed by a depressive episode and then by a free interval which lasted until a new cycle began with mania. A total of 181 cases (85%) had at least one severe mania that required hospitalization. The vast majority of these patients thus belonged to the BPI type. The onset of these severe manias was often preceded by a few days of anxiety and dysphoric mood. The mean duration of the manias was 3.3 months with a range of 1–9 months. The transition to depression was gradual, extending over several days or

weeks. The depression that followed a severe mania was moderate in most cases, with prevailing inhibitory symptoms, with little or no anxiety, and with a low score on the Hamilton Scale (Hedlund and Vieweg 1979) (ranging from 10 to 16). This type of cycle could be represented by the acronym MdI. The mean duration of these mild depressions was 4.3 months with a range of 1–24. In only 25 cases was a severe mania followed by a severe depression, in which the inhibitory symptoms still prevailed. The depression of this type of cycle carries a high risk of suicide. Eighteen patients (15%) with MDI course had only hypomanic episodes. Cases of this course with hypomanias are not always detected, because a mild hypomania is not always noticed by the patients or their families, and the patient is not yet under the care and observation of a physician. This type of cycle could be represented by the acronym mDI. It is worth noting that the depressions which followed the hypomanias in this type of course were all severe and characterized by anxiety, thus resembling recurrent depressions and depressions of the depression–hypomania–free interval course.

In 75 patients the disease took the MDI cycle pattern from the beginning. In the other patients the disease took a different course for many years before the MDI cycle was established. Also in the further course of the disease the intensity of the mania or the depression changed in some cases.

2. Depression–mania–free interval course (DMI)

In 106 patients (25% of all bipolars) the cycle started with a depression, which was then followed by a mania or hypomania, and then by a free interval, which lasted until a new cycle began again with a depression. The depression was almost always severe (only two patients suffered from mild depressions). It resembled unipolar depression, with anxiety prevailing over the inhibitory symptoms, and with a high score on the Hamilton Scale. The mean duration of the depressions was 5.1 months with a range of 1–22. The transition to mania or hypomania was often rapid, with the characteristics of the switch. The depression often became more severe on the day before the switch. In the majority of the cases (78%) the excitement that followed the depression was a hypomanic one, the mean duration of which was 3.1 months with a range of 1–15. Only in 23 cases (22%) was the depression followed at least once by a manic episode. Thus the vast majority of these patients belong to the BPII type. Only one third of these cases had the DMI course from the very beginning. In all the other cases one or more simple depressions preceded the DMI cycle. As will be discussed later, this evolution of the course of the disease and the acceleration of the cyclicity is often associated with antidepressant drug treatment (Figure 1).

3. Irregular pattern of cycle (IRRC)

In 39 patients there was no regular sequence of mania–depression–free interval. Thirty-one of them suffered from severe manias, while only eight

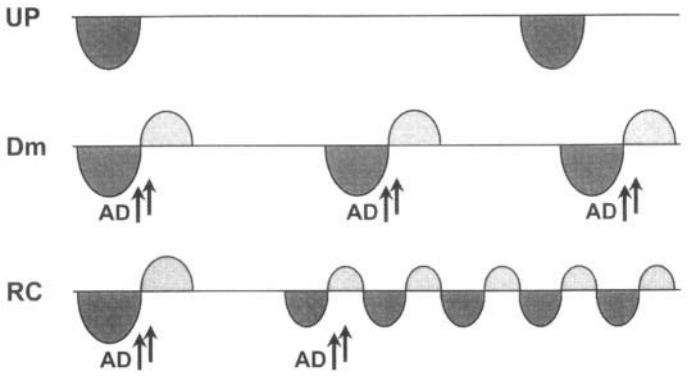

Figure 1 The onset of rapid cyclicity.

had hypomanic episodes. This brings them close to the MDI group and to the BPI type. We also include in this group three cases of recurrent mania.

4. Continuous circular course (CC)

Continuous circular course signifies that type of course in which episodes of depression and mania or hypomania alternate without real free intervals. We consider a period of less than 1 month of apparent well-being as a transition from one phase to its opposite, and not as a free interval.

We distinguish the cases with continuous circular course into those with long cycles (less than two per year) and those with short cycles (two or more per year, or four or more episodes per year). Patients with the latter type of course are called rapid cyclers. We make the distinction between the continuous circular course with long cycles (henceforth to be referred to as CC–LC) and the continuous circular course with short, rapid cycles (to be referred to as CC–RC) not only for descriptive reasons but because of other substantial differences and because of the special therapeutic problems that rapid cyclers present.

Continuous circular course with long cycles

Eighty-three patients (19% of all bipolars) had this type of course, divided about equally between men and women. Thirty-six of them (17 men and 19 women) had at least one severe mania. The majority of the group (47 patients: 26 men and 21 women) had hypomanic episodes between depressions. They correspond to the cyclothymic patients described by Kahlbaum (1882). The most typical patients of the group had an annual cycle, with depression in autumn and winter and mania (more often hypomania) in spring and summer. However, all combinations of lengths of the two phases

were seen. Both depression and mania could be as long as 2 years, but the depression was generally much longer than the mania.

Continuous circular course with rapid cycles

Eighty-seven patients (20% of all bipolar patients) had a continuous circular course with rapid cycles (two or more per year). In this group the number of women was more than twice that of men (61 women and 26 men). Only 16 patients had one or more severe manias, while 71 had only hypomanic episodes.

The depression was usually severe, with both inhibitory and anxiety symptoms. The depression was moderate and of the inhibitory type in only 11 cases, all of which had severe manias. The duration of the episodes was usually of 1–3 months, and depressions were slightly longer than hypomanias. The transition from depression to mania was often very rapid, like a switch, while the transition from mania or hypomania to depression was often very gradual. In 20 patients (10 men and 10 women) the disease took the rapid circular course from the very beginning. In the other 67 cases the disease started with a different course, which lasted from 1 to 40 years before the establishment of the rapid circular course. As we shall discuss later, this change of course was in most cases associated with the use of antidepressants.

CYCLE PATTERN AND RESPONSE TO TREATMENT

The intrinsic link between mania and depression which many physicians have intuited over the ages (Aretaeus 1735, Alexander of Tralles 1878, Thomas Willis 1676, Morgagni 1761, Chiarugi 1794) becomes manifest in the response of the different types of cycle to treatment. In general it could be stated that treatment with an antidepressant action shortens the duration of the depressive phase but may trigger or accentuate a hypomanic or manic phase and shorten the following interval (Altshuler *et al.* 1995, Arnold and Kryspin-Exner 1965, Hoheisel 1966, Koukopoulos *et al.* 1983, Lauber 1964, Till and Vuckovic 1970, Wehr and Goodwin 1979). This effect is more marked in those cycles where the depression is followed by an excited phase (DMI cycle) and may eventually result in rapid cycling (see later on rapid cyclers). On the contrary, in the MDI cycles this risk is much less because the depression is separated from the mania of the new cycle by a long interval. Patients with this type of cycle rarely become rapid cyclers but if continuous antidepressant treatments are administered they may cause an anticipated provocation of a mania and eventually rapid cyclicity.

Antimanic treatment suppresses the excited phase of the cycle but may aggravate the following depression. This phenomenon is more evident with

neuroleptics than with lithium and anticonvulsants. Neuroleptic treatment of mania is probably responsible for many of the post-manic depressions seen today, and it could explain the discrepancy in frequency of recurrent mania between studies carried out before the neuroleptic era and more recent ones. Today's greatly feared bipolar depression probably owes part of its seriousness to anti-manic treatments.

The underlying link between mania and the following depression was well understood by Aretaeus (1735), as seen in the quotation above, and by Pinel (1809) who writes:

"The attacks [of mania], after lasting through the hot season and ending towards the end of autumn, cannot fail to bring on a sort of exhaustion marked by a general feeling of lassitude, prostration that sometimes goes as far as syncope, an extreme confusion of ideas and in some cases a state of stupor and insensibility, or rather a gloomy moroseness and the deepest melancholy."

One could say that in the MDI cycle there is a primacy of the mania over the depression. This is clearly seen in the effect of lithium prophylactic treatment. Patients with the MDI cycle generally respond better to lithium than the other cycles (see Table 1). In these cases it is clear that lithium prevents depression by suppressing or preventing the onset of mania.

Patients with a cycle that starts with a depression (DMI course) respond less well to lithium than those with the DMI course: only one-third of them reached full prophylaxis within the first year of treatment, while two-thirds had recurrences for a long time. This poor response should be attributed in large measure to the action of antidepressant drugs given during the depressive phase; this action often causes a rapid switch from depression to mania or hypomania, and a temporary refractoriness to lithium of the mania or hypomania.

Patients with the continuous circular course are known to respond less well to treatment than patients with more or less long intervals. This could be attributed to the effects of the treatment of one episode upon the subsequent one. Anti-manic treatment aggravates the following depression, and antidepressant treatment accentuates the following mania or hypomania. However, one should recall Falret's (1851) observation: "Remarkable thing! These two varieties of mania and melancholia which when they run isolated are usually more curable than the others, present the greatest severity when they run together to form the *folie circulaire.*"

Of all cyclical cases the most difficult to treat are rapid cyclers; that is patients who suffer two or more cycles per year or four or more episodes per year. These cases have become more frequent in recent years, in the years of antidepressant drug treatment, than before. Rapid cyclers today represent about 15% of bipolar patients. In most cases (70%), rapid cyclicity is not spontaneous but develops later in the course of the illness, in association with treatment by antidepressant drugs. Patients with the DMI cycle

Table 3 Outcome of 96 RC patients >5 years follow-up: mean: 14 years (5–32) (from Koukopoulos 1997)

	No.	*Percentage*
Complete remission	31	32
Partial remission	19	20
Persisting RC course	33	34
Changed in long cyclers	13	14
Suicides	3	3

are the most prone to become rapid cyclers. Other patients start with recurrent depression and, in association with antidepressant treatment, become bipolar and eventually rapid cyclers. The common feature of the transformation of previous courses into rapid cyclic ones is the appearance for the first time in the course of the disease of a hypomanic episode after the depression, or the accentuation of a hypomania that had been of a milder intensity in previous recurrences. It is after one or more such depression–hypomania cycles (more rarely, depression–mania) that the following depression occurs without interval and that continuous circularity is established.

Rapid cyclers are very resistant cases to mood-stabilizing treatments. Table 3 shows the outcome of 96 rapid cycling patients after more than 5 years of follow-up (range 5–32 years); 34% of them were still cycling rapidly while another 14% had became long cyclers but still very resistant to stabilizing treatments. By 1997 only 32% had reached full remission (Koukopoulos 1997) after many years of intensive mood-stabilizing treatments.

TEMPERAMENT AND CYCLICITY

"There are men" [Heinroth (1818) states], who, though not quite indifferent or dull, are not markedly affected by joy or sorrow. Others will shout with joy or dissolve in tears at the slightest provocation, and others again are moved by a few things only, but these the more deeply and lastingly. All this indicates that there is something that decides the moods of the soul: this is the degree of vitality of the temperament."

This variation in response to emotional stimuli and the different degree of vital energy of people has been noticed and described in the theory of temperaments since Hippocrates (1967a), Aretaeus (1735) and Galen (1550). The four basic temperaments were the melancholic, the sanguine (hyperthymic), the choleric (irritable) and the phlegmatic. Through the contributions in modern times of Kraepelin (1913), Kretschmer (1929), Schneider (1962), and in recent years of Akiskal *et al.* (1979), the basic temperaments

are today considered the depressive or dysthymic, the hyperthymic, the irritable and the cyclothymic. The cyclothymic is certainly not the equivalent of the phlegmatic one; indeed, it is its opposite in every respect. The phlegmatic temperament, while still surviving in popular use, has lost its clinical interest. This is probably of significance and appears to provide further confirmation that affective disorders predominantly arise in persons with great emotional reactivity. There is little doubt about the importance of the temperaments in the onset of affective disorders. Indeed, they are also called affective temperaments. Akiskal maintains that each temperament is at the root of the various affective disorders.

We have observed a correlation between temperament and cyclicity and also between temperament and the sequence of the manic-depressive cycle. The most characteristic and evident relationship between temperament and cyclicity is seen in bipolar II patients; that is, those who suffer serious depressions but present only hypomania. The premorbid temperament of the majority of these persons is marked by considerable psychic energy, vivacity and notable emotional reactivity, sometimes with volatile behaviour, restless lifestyles and stormy love lives. Akiskal *et al.* (1979, 1998) have described these temperaments in various articles. Some of them are of the hyperthymic type, where hyperactivity and emotional vivacity do not present major variations over time. Others, the more characteristic ones, are of a cyclothymic type with an alternation between excited periods very close to hypomania and slowed-down periods in which relationships and activities are restricted. Often these oscillations in vitality follow a seasonal course with the highs coming in spring and the lows in autumn and winter. The correlation between these oscillations and the seasons comes as no surprise, of course, given the corresponding variations in daylight length and temperature.

BPI patients, the majority of whom present with an MDI cycle, are preponderantly of hyperthymic temperament. A smaller part have dysthymic premorbid temperament and often suffer from mixed dysphoric manias (Akiskal *et al.* 1979). Unipolar depressives are of dysthymic temperament and should be considered as true unipolars. Those with hyperthymic temperament are considered as bipolar III.

SUMMARY

In an historical overview of the development of the concept of cyclicity and its fundamental significance in manic-depressive illness, we underscore how the concept fell into neglect only to re-emerge in recent years. We then look at the intimate relationship between cyclicity and the seasons, before moving on to examine the frequency of cycles and the varying patterns of the disease, as well as their different responses to treatment. Finally, we

emphasize the crucial importance of the role of temperament and its interplay with biological and seasonal cycles. Our chapter stresses the centrality of mania both in the rise of manic-depressive cycles and as the prime target of prophylactic treatments.

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Chapter sixteen

Bipolar shifts as disorders of the bi-hemispheric integration of language: implications for the genetic origins of the psychotic continuum

Timothy J. Crow

THE KAEPELINIAN DICHOTOMY AND KRETSCHMER'S ALTERNATIVE

One hundred years after his seminal work Kraepelin dominates the nosology of psychiatry. In so far as this reflects the influence of the "Kraepelinian binary system" – the division of the psychoses into schizophrenia (dementia praecox) and manic-depressive insanity – one may say that the measure of his stature is the extent to which he has delayed progress since his death. This verdict we may be sure is not one with which he would be satisfied. He had himself developed doubts about the binary system. In 1920 he wrote "Perhaps it is also possible to tackle the difficulties which still prevent us from distinguishing reliably between manic-depressive insanity and dementia praecox. No experienced psychiatrist will deny that there is an alarmingly large number of cases in which it seems impossible, in spite of the most careful observation, to make a firm diagnosis. Nevertheless, it is becoming increasingly clear that we cannot distinguish satisfactorily between these two illnesses, and this brings home the suspicion that our formulation of the problem may be incorrect" (Kraepelin 1920).

A. Marneros and J. Angst (eds). Bipolar Disorders: 100 years after manic-depressive insanity, 335–348.

Endicott *et al.* (1982) demonstrated the inadequacies of the Kraepelinian concept by applying seven different sets of operational criteria for schizophrenia to 46 cases that met any one of the sets, consecutively admitted to the Psychiatric Institute in New York. By the most restrictive criteria (Taylor and Abrams 1978) six cases were diagnosed as suffering from schizophrenia; by the most liberal (Astrachan *et al.* 1972), 44 did so. Presumably the authors of each of these systems would regard them as being based upon a Kraepelinian concept. Comparison with the modal system (the Research Diagnostic Criteria) reveals a possible explanation for the discrepancies. Of the 44 who received a diagnosis of schizophrenia by the criteria of Astrakhan *et al.* (1972) eight would have been diagnosed as suffering from affective psychosis and 10 from schizo-affective disorder. The concept of schizophrenia expands or contracts by including more or less of the affective psychoses. The findings are entirely consistent with the concept of a continuum of psychosis rather than of categories (Crow 1995, 1998a).

The key question for a continuum concept, however, as its critics, e.g. Kendler and Walsh (1998) justifiably ask, is what is it a continuum of ? For if we are to abandon Kraepelin's original position in favour of his 1920 concept it seems there is little to prevent us from reaching Kretschmer's (1925) radical conclusion that:

"We can never do justice to the endogenous psychoses so long as we regard them as isolated unities of disease, having taken them out of their natural heredity environment, and forced them into the limits of a clinical system. Viewed in a large biological framework, however, the endogenous psychoses are nothing other than marked accentuations of normal types of temperament."

The implications are considerable. The conclusion is consistent with the concept that the origin of psychosis is intrinsic, i.e. that there are no exogenous aetiological agents but that these disorders arise as a component of variation that is inherent to the species (the "natural heredity environment"). It raises the question of the nature of this variation (i.e. its "large biological framework") and the dimensions of which it is composed, a particular instance of the more general evolutionary question concerning the nature of variation between individuals that is intrinsic to a species. What sort of genes are associated with variations in temperament and why does this variation (including its extreme manifestation in psychosis) persist across populations? With what function is it associated? The solution offered is that the variation relates to the function that defines the species – in the case of *Homo sapiens* it is language – and to "epigenetic" modifications of the genes that enabled the species transition. It is argued that the phenomena of psychosis are an essential element in the solution of the problem of the origin of the species – they are pointers to the neural structure of language, and a reflection of its genetic origins.

One component of the variation relates to the rate of development of the nervous system (it will be argued the cerebral cortex) – as demonstrated

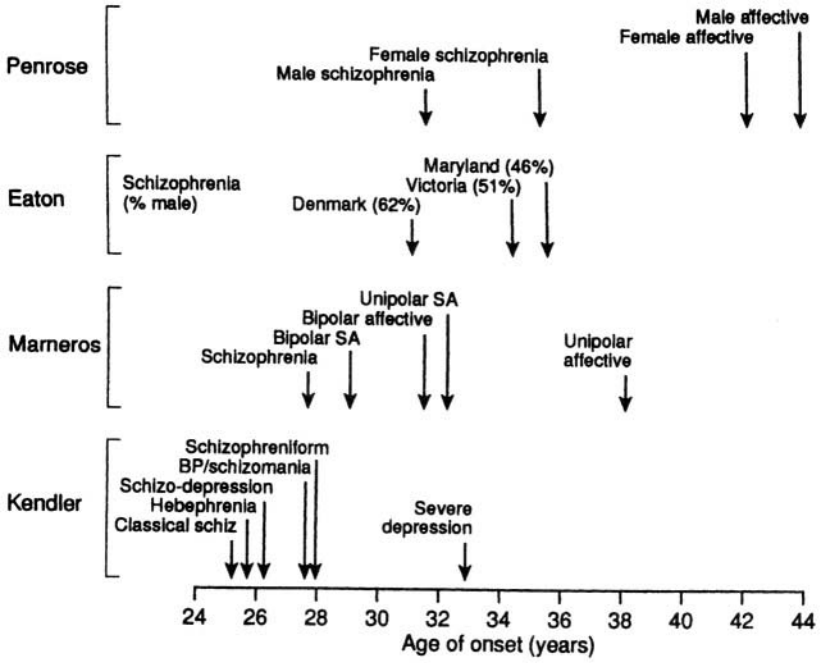

Figure 1 Age at first onset of categories of psychotic illness in four series (Penrose 1991, Eaton *et al.* 1992, Marneros *et al.* 1995, Kendler *et al.* 1998). Penrose's data relate to 5456 pairs of relatives with mental illness admitted to the Ontario (Canada) hospitals between 1926 and 1943. Eaton *et al.* included case-register data on schizophrenia from three centres (a fourth was omitted as it included onsets in old age). Marneros *et al.* included 355 cases of psychosis in a long-term follow-up study in Cologne, Germany. Kendler *et al.*'s data are from the Roscommon family study (Kendler *et al.* 1998) (figure from Crow 1998a).

by the impact of age of onset on form of psychosis (Figure 1). However the boundaries are drawn, earlier onsets are associated with illnesses that are more "schizophreniform" in character and later onsets with illnesses that are more likely to be described as affective. Moreover there is a sex difference – earlier onsets are more likely to occur in males and later onsets in females. Sex is thus a key to understanding the genetic origins of the developmental variable as is reflected in Eaton *et al.'s* (1992) analysis of age of onset and sex across case registers. Outcome is worse in males and with earlier onset, and sex and age of onset are interdependent. When controlled for age of onset sex no longer has an influence. A parsimonious explanation is that there is a single variable with a distribution that differs quantitatively but not qualitatively between the two sexes. We may assume that the rate of development of the cerebral cortex is variable between individuals, the

distribution of this variation is modestly different in the two sexes, and one boundary of the variation is demarcated by the phenomena of psychosis.

UNIVERSALITY OF INCIDENCE

An epidemiological approach illuminates the bipolar as well as the "schizophrenic" component. According to Weissman *et al.* (1996) the lifetime rates for bipolar disorder are similar across populations – ranging from 0.3/100 in Taiwan to 1.5/100 in New Zealand – amongst the seven countries included in this survey. From their review of community surveys Bebbington and Ramana (1995) estimated a lifetime prevalence of between 0.3% and 1.1% when the diagnosis was based upon a history of a manic episode. These figures are similar to those of Robins and Regier (1991) for lifetime prevalence of bipolar disorder in the US Epidemiologic Catchment Area study of 0.4–1.2%, or between 0.8% and 1.7% if bipolar II disorder is included. Relative constancy of rates reflects the comparison across case registers of Leff *et al.* (1976) that ascertained "virtually identical" incidences of mania of 2.6 per 100 000 population in London and Aarhus, Denmark.

Apparent uniformity of incidence of bipolar disorder echoes the findings of the WHO Ten Country Study of the incidence of schizophrenia as defined by the presence of nuclear symptoms (Jablensky *et al.* 1992): "Schizophrenic illnesses are ubiquitous, appear with similar incidence in different cultures, and have clinical features that are more remarkable by their similarity across cultures than by their difference."

Viewed in the light of a continuum concept these conclusions lead inexorably to the generalization that the phenomena of psychosis, including bipolar disorder, are a characteristic of human populations. But if the variation is genetic, and it is associated with the biological disadvantage of psychosis, why is it not selected out? This question, first clearly identified by Huxley *et al.* (1964), is at the heart of the problem. A solution requires a re-formulation of the question. To identify the genetic origins of psychosis I suggest that it is necessary to ask what relationship do the phenomena of psychosis have to the speciation of *Homo sapiens*?

THE SPECIATION OF MODERN *HOMO SAPIENS*

According to the Out of Africa theory (Stringer and McKie 1996) modern *Homo sapiens* originated in East Africa some time between 100 000 and 150 000 years ago, and the dispersal across the surface of the globe of the populations that constitute this single species followed that origin. One can ask – if the genetic variation that underlies psychosis is present in all populations at this point in time when did it enter the "gene pool"? Clearly it cannot have been later than the origin of the species. I offer the further

hypothesis that the variation did not precede the origin – but that it was generated in the change that instituted the transition to modern *Homo sapiens.* According to this theory the genetics of psychosis and the origin of the species are inextricably linked in what we can describe as the "speciation event", the genetic change that led to the biological success of the species and separation from the precursor hominoid lineage. The phenomena of psychosis (as an extremity of variation intrinsic to the species) and the speciation event are two aspects of a single problem. To understand one it is necessary to simultaneously consider the other.

But if psychosis is a biological disadvantage carried by the species what is its corresponding advantage? This (following the arguments of Bickerton 1995) I have suggested is language. The human capacity for language, by contrast with other putative defining characteristics such as intelligence, complex social ability or "consciousness", has obvious biological utility. Moreover it has distinctive features. Both the arbitrary relationship between the "signifier" and its "signifieds" (Saussure de 1916) and the "infinite" capacity for generating sentences (Chomsky 1985) have been suggested as species-specific characteristics. "Proto-language" (lacking grammatical features) may have existed earlier, but the capacity to use symbols in a structured manner followed the origin of the species and is a universal of human populations (Sapir 1921). The capacity for language apparently evolved abruptly. The conclusion that the transition occurred at the point of origin of the species is difficult to avoid. It must have been dependent upon a genetic change; but what sort of change might this have been? It must have been simple, but it accounted for a revolution in brain function.

LATERALIZATION OF THE HUMAN BRAIN

There is only one suggestion – that the brain lateralized in a way that was not previously the case. As has been known since the work of Dax and Broca some component of the capacity for language is localized in one hemisphere, and in more than 90% of the population this is the left. That this is an innovation in the hominid lineage is suggested by observations that population-based directional handedness (Marchant and McGrew 1996) and asymmetry of Wernicke's area at the level of the pyramidal cell columns (Buxhoeveden and Casanova 1999) are absent in the chimpanzee. There is the possibility therefore that this change represents a discontinuity in hominid evolution.

The relevance of lateralization to psychosis is attested by a number of findings. Individuals who later develop schizophrenic psychoses are more likely to be described as ambidextrous at the age of 7, and there is a trend in this direction for affective psychosis (Crow *et al.* 1996). The asymmetries of cortical structure that are present in most individuals are diminished or

even reversed in at least some patients with psychosis (Crow 1990, 1997). This evidence relates to the finding that degrees of asymmetry predict verbal and non-verbal ability and that delays in development are associated with failure to establish strong lateralization in one or the other hemisphere (Crow *el al.* 1998). Thus the dimension of lateralization is a major determinant of the rate of development of human cerebral capacity and a predictor of predisposition to psychosis. Inheritance of handedness can be accounted for by a single gene (Annett 1985), and that gene is a candidate to be associated with the speciation event and the specific capacity for language (Crow 1998c,d).

LANGUAGE AS BI-HEMISPHERIC

How could lateralization have accounted for the evolution of language? The form of the asymmetry of the brain – a "torque" from right frontal to left occipital (Bear *et al.* 1986) must be relevant. This torque allowed the two hemispheres to develop with a degree of independence, and some aspect of growth on one side of the brain was enhanced relative to the other side. This bias had the consequence that the terminal distribution of callosal fibres was modestly different in the two hemispheres, with the difference being in opposite directions in the anterior (motor) and posterior (sensory) divisions of the cerebrum. One can speculate that the immediate processing of any given pattern of neural activity was different in each hemisphere – for example that in one hemisphere the activity had a greater potential to spread. Thus processing might be more "linear" or "serial" in character in one hemisphere and more "parallel" in the other.

Taken in conjunction with the arguments of Cook (1986) that language is bi-hemispheric one can postulate that processing of two aspects of a single engram would be different in the two hemispheres. This would allow a segregation of function such that the "representation" of the engram converged from parallel to linear in the transition from right to left frontal, and from left to right occipito-temporo-parietal (Figure 2). Thus "thought" in the right frontal lobe might be transformed into motor speech represented in the left frontal lobe, and sensory "meaning" might be extracted in the right posterior association areas from incoming speech initially processed on the left side. This theory is compatible with the concept of Paivio (1991) that each word has a phonological and a spatial representation in the brain. The present theory attributes these representations to the two hemispheres and postulates that the motor transitions are separated from the senory transitions by the antero-posterior orientation of the torque.

PSYCHOTIC SYMPTOMS AS DISORDERS OF LANGUAGE

Within this framework the totality of psychotic symptoms can be conceived as deviations of language. Thus one group of nuclear symptoms (thought

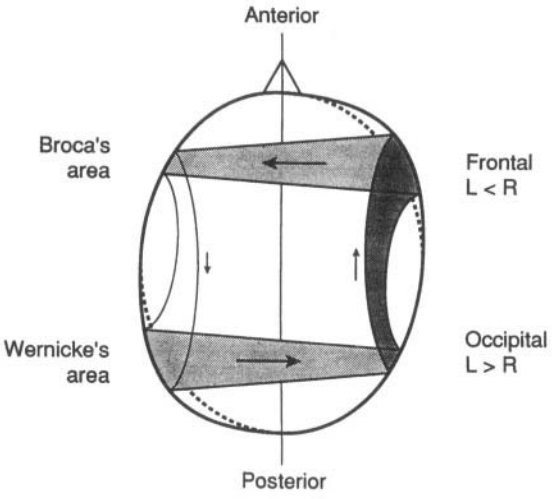

Figure 2 The fronto-occipital axis of asymmetry of the human brain. An (inter-individually variable) increase in the right frontal "hetero-modal" association cortex relative to the left, and of the left occipito-parieto-temporal association cortex relative to the right implies a convergence of callosal fibres from left to right in sensory (posterior) association cortex and from right to left in motor (anterior) association cortex. The intra-hemispheric antero-posterior connections carry reciprocal convergences and divergences (figure from Crow 1998b).

insertion, withdrawal and broadcast) can be considered as disorders of the transition from thought to speech and another (the auditory hallucinations) as anomalies of speech perception. Delusions arise as exaggerated associations between a "signifier" and its "signifieds", and the nuclear symptoms as a group reflect the necessity of a reference system as suggested by Buehler (1934) that relates the components of language to a deictic origin in the self and the present time and point in space (Crow 1998b).

How do affective symptoms fit into this framework? Some affective symptoms can be seen as disorders of speech production. Pressure of speech and the mutism of depressive stupor, for example, represent anomalies at the extremes of the motor function of word and sentence generation. They tell us that affect is an integral component of the normal mechanism. At a different level mood-congruent delusions reflect deviations in the interpretation of incoming information. They indicate that affective set is an aspect of the transition from the visually and acoustically experienced message to meaning. The key question is how do these phenomena relate to hemispheric differentiation?

A body of evidence (see e.g. chapter 11 in Goodwin and Jamison 1990) indicates that affective disorders are associated with dysfunctions, e.g. of spatial orientation and face recognition generally attributed to the right or

non-dominant hemisphere. Such problems might relate to posterior heteromodal association areas including the temporo-parieto-occipital junction region and fusiform gyrus. One can speculate that if spatial analysis is essential for a word to acquire meaning (or a face to acquire a name and its associations), and at a higher level for sentences to acquire grammatical structure (see e.g. Anderson 1971, Bybee *et al.* 1994, Bloom *et al.* 1996 for a discussion of some relevant analyses) then differential processing in the two hemispheres will be necessary to this process, and that it is at the stage of transition from "linear" to "parallel" processing, and vice-versa, that the affective component is introduced.

The phenomena of dyslexia are relevant. Learning to read depends upon the ability to convert graphemes to phonemes, a process that may be assumed to require an analysis in terms of spatial into linear (phonetic) engrams. Those who are delayed in developing hemispheric lateralization (indexed by a measure of relative hand skill) are delayed in learning to read (with a greater deficit in males than females) and also in the rate at which they acquire words and their associations (Crow *et al.* 1998).

Individuals who develop schizophrenic psychoses in adult life are more likely to be described as ambidextrous at age 7, and pre-affective psychotic individuals show a trend in the same direction (Crow *et al.* 1996). Pre-schizophrenic children are impaired in reading ability at the ages of 7, 11 and 16 years, and again pre-affective psychotic children also show deficits, although of lesser magnitude (Crow *et al.* 1995). Thus the rate at which hemispheric dominance is established for components of language is relevant to the phenomena of schizophrenic and affective psychoses as well as to dyslexia.

WHERE IS THE GENE?

If the process of lateralization is critical to predisposition to psychosis then the genetics of cerebral asymmetry become central to a genetic understanding of the problem. What has to be explained are the brain changes, the sex differences (e.g. in age of onset and form of psychosis) and the relationships to language and reading delay. The genetics of cerebral asymmetry as reflected in handedness has been much discussed (see e.g. Annett 1978, 1985, McManus 1985, 1991). There is a sex difference – females are modestly more likely to be right-handed than males (Annett 1994, Crow *et al.* 1998) – and the male brain is probably more asymmetrical than that of the female (Bear *et al.* 1986). I have suggested that these sex differences reflect the operation of a gene that is present in homologous form on the X and Y chromsomes, and that such a gene accounts for the well-known sex difference in verbal ability as well as for those that relate to psychosis.

Key evidence comes from observations on individuals with sex chromosome aneuploidies (Netley and Rovet 1982, Netley 1998). Lack or excess of

an X chromosome is associated with relative delays in development of the non-dominant and dominant hemispheres respectively. This suggests that the gene is present on the X chromosome. The absence of right hemisphere deficits, such as seen in Turner's (XO) syndrome, in males indicates that a homologue is present on the Y chromsome (Crow 1993, 1994a). If such a gene were present in a non-recombining portion of the chromosomes there is the possibility of sequence divergence (in a coding or control element) that could account for a sex difference in expression.

Although sex-linkage of affective disorders has been suggested (Winokur *et al.* 1980) the possibility that an X–Y homologous gene might play a central role has not been widely considered. Three sex-related observations may be relevant:

1. *Same-sex concordance.* The tendency for relatives both affected by psychotic illness to be somewhat more often of the same sex than would be expected was discussed by Penrose (1991) and Rosenthal (1962). Because a component of the risk will be transmitted from the father on an X or Y chromosome, such an effect will be predicted for a gene in the X–Y homologous class (whether in the pseudo-autosomal or sex-specific regions) although the size and parental origin of the effect will be dependent upon the mode of transmission (see e.g. Crow *et al.* 1990, Crow 1994a). The phenomenon has been noted in bipolar illness. For example in their study of 617 first-degree relatives of 95 probands with bipolar manic-depressive disorders Angst *et al.* (1980) concluded that "the relatives of the female probands tended to have a higher morbidity risk than the relatives of the male probands. The female relatives of the male probands did not have a higher, but a lower, morbidity risk than the male relatives. The possibility has to be considered that relatives of the same sex as the proband show a somewhat higher morbidity risk than those of the opposite sex." Similarly in an analysis of 187 families of bipolar probands (149 with a diagnosis of bipolar I disorder and 38 with a diagnosis of schizo-affective illness of manic type) Rice *et al.* (1987) wrote "multifactorial analysis found significant heterogeneity for sex-specific sibling correlations (with brother–sister smaller than same-sex correlations)". Both sets of authors argued that an environmental influence was relevant, but an influence of an X–Y homologous gene should also be considered.
2. *The sex-polarity effect.* Winokur and Crowe (1983) drew attention to an apparently consistent sex bias in the first-degree relatives of probands with bipolar affective disorder. Female relatives were more likely to be affected than males, and whereas amongst affected males the ratio of unipolar to bipolar illness was approximately 1:1, amongst affected females it was 2:1.
3. *Maternal transmission.* In their survival analysis of data from the NIMH-CRB Collaborative Psychobiology of Depression study Rice *et al.* (1984)

found that illness in the mother had a greater influence on liability in the child than illness in the father.

Each of these findings suggests an unaccounted-for effect of sex on the risk of bipolar or unipolar affective illness. Whilst this might relate to environmental factors, as some authors have suggested, it might also, as Winoker and Crowe emphasized, provide a key to unlocking the genetic mechanisms. In particular the same-sex concordance effect is consistent with the influence of an X–Y homologous gene. Such genes are subject to relatively rapid change on an evolutionary time scale.

Of particular interest is the region of homology generated by an X to Y translocation occurring after the separation of the chimpanzee and hominid lineages that was subject to a subsequent paracentric inversion (Sargent *et al.* 1996, Mumm *et al.* 1997, Schwartz *et al.* 1998). These changes created sequences on the Y chromosome that are *Homo sapiens*-specific, and therefore relevant to those characteristics such as the capacity for language that distinguish us from other surviving primate species (Crow 1998a–d).

Because most genes on one X chromosome are subject to inactivation, any genes within a segment translocated to the Y will be expressed at double dosage in males. Such genes become subject to new evolutionary selective pressures possibly acting through modification of the inactivation process (Jegalian and Page 1998). The phenomena of Turner′ s syndrome reflect losses of genes that are at least in part protected from X inactivation, and for some of these features parent-of-origin effects have been demonstrated (Skuse *et al.* 1997). This suggests that an imprinting (or inactivation) process is involved, and therefore that epigenetic mechanisms are relevant to the normal expression of these genes. If one such gene determines cerebral asymmetry the variants of its expression that are postulated in psychotic illness may also be dependent upon epigenetic rather than strictly genetic processes (Crow 1999).

CONCLUSIONS

The categorical classification that is implicit in the original Kraepelinian dichotomy of schizophrenic and affective psychoses has obscured the continuity of the basic phenomena across conventional diagnoses and with variation in the population as a whole. Kraepelin′s 1920 modification and its implications for developmental and evolutionary theories of the origins of psychosis deserve particular attention. They are consistent with aspects of Kretschmer′s formulation and with what is now known about the epidemiology of the psychoses – that these are phenomena that are intrinsic to human populations. They reflect on the genetic origins of *Homo sapiens* and the cerebral organization of the function that characterizes the species – language. The generally later onset of affective psychoses and the association

of affective symptoms with functions associated with the non-dominant hemisphere provide a lead to the role of affect and non-dominant hemisphere function in the organization of language. Sex differences in the spectrum of psychosis and in its correlates are consistent with the hypothesis that a determinant of cerebral asymmetry is located within the Xq21.3/Yp region of homology that was generated by a translocation that occurred after the separation of the chimpanzee and hominid lineages. It is suggested that the critical species-specific variation is subject to epigenetic modification.

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Chapter seventeen

Mood stabilizers in bipolar disorder

Mario Maj, Alfonso Tortorella and Luca Bartoli

INTRODUCTION

This chapter reviews the currently available evidence concerning the efficacy/effectiveness and tolerability of lithium and anticonvulsants in the treatment of manic and depressive episodes of bipolar disorder and in the prevention of the recurrences of the disorder. The focus of the review is strictly clinical; the extensive literature on the mechanisms of action of the above-mentioned drugs is not reviewed. Moreover, no mention is made of the special issues related to the use of lithium and anticonvulsants in the elderly, in children, and during pregnancy, because these topics are covered in other chapters of the present volume. The teratogenicity of lithium and anticonvulsants is, however, briefly dealt with.

LITHIUM

Treatment of manic episodes

The efficacy of lithium in the treatment of manic episodes has been documented by five placebo-controlled trials (Schou *et al.* 1954, Maggs 1963, Goodwin *et al.* 1969, Stokes *et al.* 1971, Bowden *et al.* 1994). The percentage of patients with at least moderate improvement after 2–3 weeks of treatment ranged from 40% to 80%. In the most recent of those studies (Bowden *et al.* 1994), the only one using operational diagnostic criteria and standardized rating scales, 49% of lithium-treated patients presented an improvement of at least 50% on a mania rating scale, compared with 25% of patients receiving placebo, a statistically significant difference. More than one-third

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 349–372.

of patients recruited for that study had psychotic symptoms, and no additional medication (except for low-dose lorazepam or chloral hydrate during the first 10 days) was allowed. The superiority of lithium over placebo was limited to patients with classic (euphoric) mania, while in patients with mixed mania (i.e. patients who also had depressive symptoms) no difference between lithium and placebo was observed (Swann *et al.* 1997).

Several double-blind trials (Johnson *et al.* 1968, 1971, Platman 1970, Spring *et al.* 1970, Prien *et al.* 1972, Takahashi *et al.* 1975, Braden *et al.* 1982, Shopsin *et al.* 1975, Post *et al.* 1980) have compared lithium with an antipsychotic drug (usually chlorpromazine) in the treatment of acute mania. They have almost constantly found lithium to be superior in terms of overall improvement of symptoms and improvement in mood and ideation, whereas chlorpromazine was sometimes found to be more effective than lithium on motor hyperactivity. The onset of the effect of lithium has usually been found to be slower than that of chlorpromazine. Two double-blind trials (Johnstone *et al.* 1988, Garfinkel *et al.* 1980) have failed to show a superiority of the association lithium–antipsychotic (haloperidol or pimozide) over the antipsychotic alone in the treatment of acute mania, but their very small sample size does not allow any definite conclusion.

The currently predominant consensus (Expert Consensus Panel 1996, Suppes *et al.* 1995) is that lithium should be regarded as the first-choice drug in the treatment of classic (euphoric) mania. The addition of intramuscular or oral neuroleptics and / or benzodiazepines may be necessary for behavioural control until marked improvement is achieved, especially in the presence of psychotic symptoms, agitation or insomnia. A number of studies have supported the safety of the lithium–neuroleptic combination, although some cases of neurotoxicity, especially in patients with a pre-existing encephalopathy, have also been reported (see Freeman and Stoll 1998 for a review). Plasma lithium levels suggested for the treatment of manic episodes are between 0.8 and 1.2 mmol/L. Levels below 1.0 mmol/L are advisable when a neuroleptic is associated.

Treatment of depressive episodes of bipolar disorder

During the 1960s and 1970s, eight trials (Goodwin *et al.* 1969, 1972, Greenspan *et al.* 1970, Stokes *et al.* 1971, Noyes *et al* 1974, Baron *et al.* 1975, Mendels 1977, Donnelly *et al.* 1978) have compared lithium with placebo in the treatment of bipolar depression. A crossover design was applied (i.e. each patient received in sequence lithium and placebo). Seven of those studies, including 116 patients (40 bipolar I, 23 bipolar II and 53 bipolar, not specified) found lithium to be significantly more effective than placebo, whereas one (Goodwin *et al.* 1972), including 18 patients (all bipolar I), reported no difference between the two treatments. In this last study, however, lithium was administered for only 7–10 days, as opposed to the

14–28 days of all but one of the other investigations. Five of the above studies also included unipolar depressed patients, thus allowing a comparative estimate of the response rate in bipolars versus unipolars: overall, a complete or partial response to lithium was observed in 79% of bipolars and 36% of unipolars.

Only two controlled trials (Fieve *et al.* 1968, Watanabe *et al.* 1975) have compared a tricyclic antidepressant (imipramine) with lithium in the treatment of bipolar depression. In the former, both imipramine and lithium were superior to placebo, but the mean decrease in depression scores was significantly more pronounced with lithium than with imipramine (58% versus 32%). In the latter study, carried out in only five patients, no significant difference between lithium and imipramine was observed.

According to currently predominant consensus (Expert Consensus Panel 1996, Suppes *et al.* 1995, Maj 1997), in bipolar patients who develop a depressive episode during long-term treatment with a mood-stabilizing drug, it is advisable in the first place: (a) to check the dosage of the drug and the patient's compliance; (b) to look for possible coexisting problems, such as general medical disorders (e.g. clinical or subclinical hypothyroidism), alcohol or drug abuse, or recent loss of a significant relationship. If the mood-stabilizing drug is lithium, the adequacy of plasma levels should be verified. If the dosage of the mood-stabilizing drug or the patient's compliance is inadequate, or if any of the above-mentioned coexisting problems is present, a specific intervention should be accomplished. If the patient is not on a mood-stabilizing drug, this treatment should be started, and lithium should be the first option. If depression is mild, or the patient has a history of antidepressant-induced mania or rapid cycling, it is advisable to use lithium alone. Plasma levels should be in the range from 0.8 to 1.2 mmol / L, and response should be expected by 4–6 weeks. If the patient does not respond to lithium, an antidepressant should be added. If depression is moderate or severe, or if the patient has a history of previous depressive episodes successfully treated with antidepressant drugs, the combination of lithium and an antidepressant should be used from the beginning.

Prevention of recurrences of bipolar disorder

The efficacy of lithium in preventing the recurrences of bipolar disorder is documented by several double-blind placebo-controlled trials, all published during the 1970s (Baastrup *et al.* 1970, Melia 1970, Coppen *et al.* 1971, Cundall *et al.* 1972, Hullin *et al.* 1972, Prien *et al.* 1973a,b, Stallone *et al.* 1973, Dunner *et al.* 1976a, Fieve *et al.* 1976). All these studies, except one (Melia 1970) carried out in a very small patient sample (seven patients treated with lithium and eight with placebo), found a statistically significant superiority of lithium over placebo in reducing the frequency of recurrences

during the observation period. Overall, the 1-year recurrence rate detected in those trials was 34% in patients treated with lithium and 81% in those receiving placebo (Goodwin 1994), a statistically significant difference. Of the seven studies reporting separate data for manic and depressive episodes, four found a statistically significant superiority of lithium over placebo in preventing manic recurrences, and only one a significant superiority of lithium in preventing depressive recurrences.

Of the above-mentioned 10 double-blind studies, four were discontinuation trials, i.e. trials in which a sample of patients already on treatment with lithium was randomly subdivided into two subsamples, one of which continued to take lithium and the other was switched to placebo. This design may have artificially inflated the recurrence rate in patients receiving placebo, and consequently the difference between lithium and placebo, since lithium discontinuation is followed by a period of high risk of recurrences, especially of manic episodes (see below). In support to this idea, in one of those studies (Cundall *et al.* 1972), the ratio between the number of manic and depressive episodes was 0.67:1 before the beginning of lithium treatment and became 3.5:1 after lithium withdrawal. The above criticism may be extended to some of the other studies (parallel-group prospective trials), in which some patients were or had been recently treated with lithium at the moment of recruitment (Moncrieff 1995).

Moreover, in some of those parallel-group prospective studies, the treating physicians knew which patients were taking lithium, and were allowed to increase the dosage of the drug in the presence of prodromal manic symptoms. This may have artificially reduced the recurrence rate in patients randomized to lithium. In fact, in one of those studies (Prien *et al.* 1973a), it is reported that some of the patients classified as lithium responders had had prodromal symptoms of mania during the observation period.

Other limitations of the available trials comparing lithium and placebo in the prophylaxis of bipolar disorder are the extensive use of additional drugs (in at least one of the trials (Coppen *et al.* 1971), unrestricted use of neuroleptics, antidepressants and electroconvulsive therapy was allowed), the focus on patients completing the treatment period (disregarding dropouts), the short follow-up period (no more than 6 months in four of the studies), the inclusion of schizoaffective patients, and the fact that operational criteria for patients′ diagnosis and standardized rating scales were not used.

During the 1980s and the 1990s no further double-blind placebo-controlled trials testing the prophylactic effect of lithium were published, but several naturalistic follow-up studies of bipolar patients receiving lithium prophylaxis under routine clinical conditions have appeared. Markar and Mander (1989) studied retrospectively 83 bipolar patients who had recovered from a manic episode, 41 of whom had received prophylactic lithium for at least 6 months after the episode and 42 had not, and did not find a

significant difference between the two groups with respect to the number of hospitalizations and the time spent in hospital during a 6-year observation period. Harrow *et al.* (1990) studied prospectively, after discharge, 73 patients hospitalized for a manic episode, and found that those who took lithium throughout the 1-year period following discharge did not differ significantly from those who did not receive the drug throughout that period, with respect to several outcome measures. Sachs *et al.* (1994) followed up retrospectively 100 bipolar patients, of whom 67 had received lithium, alone or in combination with other drugs, and 33 had not, and detected no significant difference between the two groups with regard to the recurrence rate during a 1-year period. On the other hand, some epidemiological studies have reported that the frequency of hospitalizations for mania has not decreased, but actually increased, in the years following the introduction of lithium (Symonds and Williams 1981, Dickson and Kendell 1986). All these observations have led to the conclusion that the impact of lithium on the course of bipolar disorder in ordinary clinical conditions is less significant than that expected on the basis of the results of controlled trials.

However, the above-mentioned clinical and epidemiological studies have some important drawbacks. In the study by Markar and Mander (1989), although the observation period was of 6 years, the lithium-treated group also included patients who had received the drug for only 6 months: these patients may well have relapsed after lithium discontinuation. In the study by Harrow *et al.* (1990), the periodic check of plasma lithium levels was not ensured, so that several lithium-treated patients may have not been adequately exposed to the drug. Moreover, under naturalistic conditions the illness course is a determinant as well as a consequence of the choice of treatment, so that the lack of a significant difference with respect to outcome, between patients who have received lithium and those who have not, cannot be regarded as an evidence that the drug is not effective. On the other hand, the above-mentioned epidemiological studies have not documented that patients who were hospitalized during the observation period had actually received lithium prophylaxis; in fact, there are other studies (Grof and Fox 1987) showing the same increase in the hospitalization rate for mania in the years following the introduction of lithium (ascribed to the change in diagnostic habits, with the broadening of the concept of mania), but a decrease of that rate in patients treated with lithium. Finally, it is important to emphasize that a gap between the efficacy of a treatment (i.e. its therapeutic potential, as resulting from controlled trials) and its effectiveness (i.e. its impact on the target disorder in ordinary clinical conditions) is a common observation in medicine (Guscott and Taylor 1994), being due to such factors as patients′ incomplete compliance, physicians′ inadequate supervision of treatment, and underdiagnosis / undertreatment

of the target disorder. All these factors are significantly at work in the case of lithium prophylaxis.

Incomplete or intermittent compliance is indeed very frequent among bipolar patients on lithium prophylaxis, with prevalence rates up to 60% (Keck *et al.* 1996). The factors involved can be subdivided (Jamison *et al.* 1979) into patient-related (younger age, being male and single, lower educational level and socioeconomic status, insufficient knowledge about the illness; refusal of the role of chronic mentally ill, or of the idea that one's mood is controlled by a drug, or of the perspective of a pharmacological treatment to be continued for an indefinite period of time); illness-related (missing hypomanic or manic "highs", rapid cycling, concomitant personality disorders, alcohol or drug abuse, higher number of hospitalizations); drug-related (perceived inefficacy, side-effects) and physician-related (physician's insufficient endorsement of treatment, lack of continuity of care). It is useful to point out that non-compliance cannot be excluded even if plasma lithium levels are constantly within the prophylactic range (see below), because some patients learn after some time to deceive their physician by taking a loading dose of the drug in the day(s) preceding each blood check.

In our prospective study (Maj *et al.* 1998) carried out in all bipolar patients who had started lithium prophylaxis at a lithium clinic over more than 15 years, we found that 27.9% of the enrolled patients were no longer on lithium after 5 years. Among patients who had interrupted prophylaxis on their own initiative, the most frequently alleged reasons for discontinuation were perceived inefficacy, trouble related to side-effects, the conviction of being cured and of needing no more drugs, the annoyance of taking medicines, and the loss of energy or productivity. In that prospective study, among patients who were still on lithium after 5 years, 38.1% had had no major depressive or manic episode during the treatment period; 46.6% had had at least one episode, but with a reduction of at least 50% in the mean annual time spent in hospital during the treatment period compared to the 2-year period preceding the index episode and the start of prophylaxis; and 15.4% had had at least one episode without the above-mentioned reduction of at least 50% in the mean annual time spent in hospital. These findings apparently support the clinical perception that lithium, if taken regularly for several years, has a substantial impact on the course of illness in most bipolar patients. However, the bias of self-selection should not be overlooked: the figures cited above refer only to a subgroup of the enrolled patients (Figure 1), whose permanence on the prophylactic regimen may have been a consequence as well as a determinant of the favourable response, and who may not be representative of the initial study group. Patients with psychotic features in the index episode (a possible predictor of poor outcome in bipolar disorder) were overrepresented among those who stopped lithium before the 5-year term.

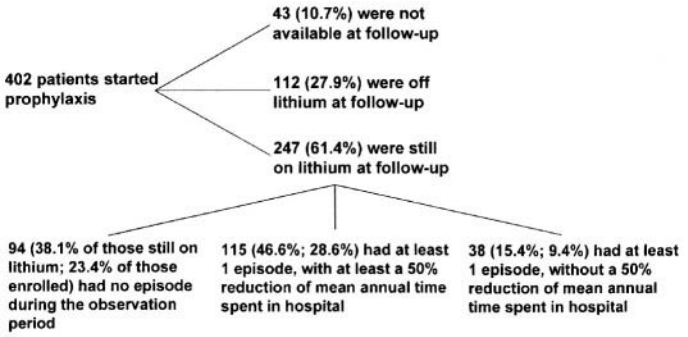

Figure 1 Results of the 5-year follow-up of bipolar patients who started lithium prophylaxis at a lithium clinic (data from Maj *et al.* 1998).

Overall, lithium does not seem to lose its prophylactic effect over time. In the 10-year follow-up of our prospective study (Maj 1999b), we found that the mean number of affective episodes and the mean time spent in hospital were not significantly different during the second versus the first 5-year observation period. However, 13% of patients who had had no recurrence during the first period had at least two episodes during the second period without a reduction of at least 50% in the mean annual time spent in hospital compared to the 2-year pre-treatment reference period. Whether this observation indicates a loss of effect of lithium over time in at least a minority of patients, or simply reflects the capricious natural course of the illness, remains uncertain.

Prediction of response to lithium prophylaxis in bipolar disorder has been the subject of an extensive literature (see Maj 1992 for a review). Among putative predictors of a favourable response are a family history of bipolar disorder (Mendlewicz *et al.* 1973, Prien *et al.* 1974, Maj *et al.* 1985, Mander 1986) and a course of the MDI type (mama-depression-free interval sequence) (Koukopoulos *et al.* 1980, Haag *et al.* 1986, Grof *et al.* 1987, Maj *et al.* 1989, Faedda *et al.* 1991), whereas putative predictors of a poor response are a previous higher frequency of episodes and hospitalizations (Gelenberg *et al.* 1989, O'Connell *et al.* 1991), rapid cycling (Dunner *et al.* 1976b, Bauer and Whybrow 1991) and concomitant drug abuse (Himmelhoch *et al.* 1980). In our above-mentioned 5-year prospective study (Maj *et al.* 1998), we found that a higher number of pre-treatment episodes and hospitalizations and rapid cycling were associated with the least favourable patterns of outcome of prophylaxis. However, these variables are likely to be predictors of poor outcome of bipolar disorder *per se* independently from treatment, rather than specific predictors of an unfavourable response to lithium. This applies at the moment also to rapid cycling, in the absence of double-blind randomized trials showing the superiority of other drugs over lithium in bipolar patients presenting that pattern.

The abrupt discontinuation of lithium prophylaxis is followed by a period of high risk of recurrences. According to a meta-analysis of the relevant literature (Suppes *et al.* 1993), a new episode occurs within 5 months from lithium withdrawal in 50% of patients. The risk for a manic recurrence is significantly higher than that for a depressive one (the computed time to 25% risk of recurrence is 2.7 months for mania and 14 months for depression). The risk of recurrence after lithium withdrawal is significantly higher than that of bipolar patients never treated with lithium: in 16 bipolar patients the shortest inter-episodic euthymic period before starting lithium prophylaxis was 11.6 months, whereas the mean euthymic period between lithium withdrawal and a new affective episode was 1.7 months (Suppes *et al.* 1993). However, the recurrence risk is significantly lower if lithium is discontinued gradually: the median time to recurrence has been found to be 2.5 months for rapid discontinuation (over 1–14 days) versus 14 months for gradual discontinuation (over 15–30 days) (Baldessarini *et al.* 1997).

Some patients may present a secondary refractoriness to lithium prophylaxis after one or more discontinuations (Post *et al.* 1992, 1993, Bauer 1994, Koukopoulos *et al* 1995, Baldessarini 1996, Maj *et al.* 1995), which may be reversible in some cases (Maj *et al.* 1995). A recent study attempting to verify this phenomenon in a large sample of bipolar patients (Suppes *et al.* 1997) actually found a statistically significant increase of morbidity during a second versus a first period of lithium treatment. This difference, however, failed to reach statistical significance in a smaller sample studied by the same group (Tondo *et al.* 1997) and was not observed in another investigation carried out in a very small patient sample (Coryell *et al.* 1998). The statistical power of these last two studies was probably insufficient to detect the phenomenon (Maj 1999b).

Lithium prophylaxis is associated with a marked decrease of suicide risk in bipolar patients, whereas lithium discontinuation is accompanied by a pronounced increase of that risk (Schou 1998). Baldessarini *et al.* (1999) found that suicidal acts per year were reduced 6.5-fold during lithium treatment, and that suicide risk increased 20-fold in the first year off lithium, being 2-fold lower after slow versus rapid discontinuation.

On the basis of currently available evidence (Hullin 1980, Maj *et al.* 1986, Goodnick *et al.* 1987), plasma lithium levels between 0.5 and 0.8 mmol / L should be regarded as the most appropriate for the prophylactic purpose. In our prospective study (Maj *et al.* 1986) comparing different ranges of plasma lithium levels, we found that levels between 0.30 and 0.45 mmol / L were associated with a marked decrease of the efficacy of treatment, whereas levels above 0.75 mmol / L were associated with an increase in the frequency and intensity of side-effects, in particular polyuria.

Lithium administration in a single daily dose, rather than in two or three doses, may be useful to improve compliance, while lithium administration every second day, repeatedly proposed in the past, is associated with a

three-fold increase in the recurrence risk and should therefore be avoided (Jensen *el al.* 1995).

At the present state of knowledge lithium should be regarded as the first-choice drug in the prevention of the recurrences of bipolar disorder. According to currently predominant consensus (Expert Consensus Panel 1996), lithium prophylaxis should be started after the second manic episode, or after the first if this has been extremely severe or destructive, or if family loading for bipolar disorder is pronounced.

Side-effects

Polyuria, often accompanied by polydipsia, is the most frequent side-effect of lithium, being found in at least 50% of patients at some stage of long-term treatment. It is usually mild and reversible, but can be persistent and reach the intensity of a nephrogenic diabetes insipidus. The primary mechanism responsible for this polyuria is the inhibition of antidiuretic hormone-stimulated cyclic AMP production, with the consequent reduction of water reabsorption, in the renal distal tubules and collecting ducts (Dousa and Hechter 1970). Polydipsia is usually secondary to polyuria, but a direct effect of lithium on central mechanisms of thirst regulation has also been documented.

In 5–10% of patients on long-term lithium treatment the impairment of renal concentrating ability may be irreversible or only partially reversible after lithium discontinuation (Bendz 1983). This is more frequent in patients exposed to periods of lithium intoxication or to concomitant treatment with neuroleptics. In some of these cases, renal biopsy may show morphological changes (interstitial fibrosis, tubular atrophy, and more rarely glomerular sclerosis) (Hestbech *et al.* 1977). These changes, however, have also been observed in psychiatric patients never treated with lithium (Walker *et al.* 1982).

Lithium does not seem to interfere significantly with glomerular filtration. Although some cases of nephrotic syndrome or renal insufficiency apparently related to lithium treatment have been reported (Gitlin 1993, Walker 1993), the risk for the development of these conditions should be considered extremely low, and the nephrotoxicity of the drug does not seem to influence the mortality of the patients who take it (Norton and Whalley 1984). The impact on renal function of periods of overdose may be much more significant, and it is possible that in some clinical conditions, where treatment monitoring is not adequate, lithium nephrotoxicity represents a more serious problem than appears from currently available research.

A fine hand tremor is probably the second most frequent side-effect of lithium prophylaxis, being found in 30–70% of patients in some phase of treatment. Advanced age, male sex, personal or family history of essential

tremor, and concomitant assumption of tricyclic antidepressants have been regarded as risk factors (Vestergaard 1983).

Patients treated with lithium often report feelings of mental slowing or memory and concentration disturbances. Some groups have detected a reduction of objective cognitive performance in patients treated with lithium, but this has not been confirmed by others (Jefferson *et al.* 1987). The frequent lack of information about patients′ cognitive functioning before starting treatment, and the effect of mood pathology on that functioning, complicate the interpretation of research findings. On the other hand, studies on normal controls provide information which is only partially extensible to the clinical situation.

Weight gain is another frequent side-effect of lithium, being found in a percentage of treated patients ranging between 11% and 65% (Chen and Silverstone 1990). The concomitant treatment with other psychotropic drugs, particularly antipsychotics and antidepressants, may increase the risk. Four main mechanisms have been called upon to explain lithium-induced weight gain (Baptista *et al.* 1995): (a) the increased intake of high-calorie beverages; (b) the increase of appetite caused by the mood-stabilizing action of the drug; (c) the reduction of metabolism probably determined by the drug; (d) the lithium-induced increase of the plasma levels of insulin.

Clinical signs (euthyroid goiter, myxoedema) or laboratory indicators (increase of TSH plasma levels, enhanced response of TSH to TRH) of hypothyroidism occur in 5–15% of patients on long-term lithium treatment. Women are more frequently affected. The main mechanism through which lithium exerts its antithyroid effect is the decrease of the release of thyroid hormones. Moreover, the drug competitively interferes with iodine captation by the thyroid, inhibits several stages of thyroxine and triiodothyronine synthesis, inhibits thyroglobulin synthesis, and interferes with cyclic AMP-mediated effects of TSH.

Lithium can cause an increase of plasma levels of parathormone, calcium and magnesium, usually without clinical manifestations. This effect has been ascribed to an alteration of the set point of parathyroids for serum calcium, so that higher levels of calcium are needed to inhibit the secretion of parathormone (Haden *et al.* 1997).

The most common cardiovascular effect of lithium (13–100% of treated patients) is a benign, usually reversible, dose-dependent flattening or inversion of the T-wave of the electrocardiogram. In the literature there are several anecdotal reports of sinus node dysfunction or sinoatrial block, as well as of ventricular rhythm disorders, in patients treated with lithium (Mitchell and Mackenzie 1982), but in most cases the dysfunction predated treatment. The mortality for cardiovascular disease in patients with affective disorders treated with lithium is not different from the general population, while in non-selected patients with affective disorders such mortality is significantly higher (Ahrens *et al.* 1995).

Gastrointestinal effects (anorexia, nausea, vomiting, diarrhoea, abdominal pains) are not uncommon in the initial phase of lithium treatment, but are usually mild and reversible. A serious, but rare, dermatological effect of lithium is the worsening of psoriasis, while more common is an aspecific, reversible acneiform eruption. Lithium often produces a reversible benign neutrophilic granulocytosis. An oedema, generally localized to the feet and ankles, usually temporary and intermittent, has sometimes been reported. Some patients who take lithium complain of a persistent metallic taste, while others report a mouth dryness that might be due to a reduction of saliva flow caused by the drug.

Teratogenesis

Concern about the cardiac teratogenicity of lithium was raised by the Lithium Register study (Weinstein 1980), which reported, in 225 lithium-exposed children, an incidence of heart malformations of 8% (versus 0.8% in the general population) and of Ebstein's anomaly (a defect of tricuspidal valve) of 2.7% (versus 0.005% in the general population). The incidence of non-heart abnormalities was similar to the general population (3.1% versus 3.5%). However, a subsequent prospective cohort study of 138 women who reported use of lithium during the first trimester of pregnancy found only one case of Ebstein's anomaly and no other case of heart malformation (Jacobson *et al.* 1992). Moreover, some case–control studies (Kallen 1988, Edmonds and Oakley 1990, Zalzstein *et al.* 1990) have found no case of Ebstein's anomaly in a total of 162 women exposed to lithium during pregnancy. These data suggest that the cardiac teratogenicity of lithium has previously been overestimated.

CARBAMAZEPINE

Treatment of manic episodes and of depressive episodes of bipolar disorder

The efficacy of carbamazepine in the treatment of manic episodes has been tested by several double-blind trials, five of which (Ballenger and Post 1978, Okuma *et al.* 1979, Grossi *et al.* 1984, Lerer *et al.* 1987, Small *et al.* 1991) – one versus placebo, two versus lithium and two versus chlorpromazine – did not include patients concomitantly treated with other drugs. The only placebo-controlled study (Ballenger and Post 1978, Post *et al.* 1984) did not clarify whether the superiority of carbamazepine over placebo was statistically significant, but reported several cases of recurrences on placebo substitution and re-responsiveness after carbamazepine reinstitution on a blind basis. Of the two studies versus lithium, one found a superiority of this drug over carbamazepine (response rate: 79% versus 29%) which, however,

did not reach statistical significance, and the other reported no difference between the two drugs. Both studies versus chlorpromazine found no difference between this neuroleptic and carbamazepine.

A double-blind study has shown that a lithium-carbamazepine combination is as effective as the association of lithium and haloperidol in the treatment of a manic episode (Small *et al.* 1995). The former less frequently produces extrapyramidal effects, but more often requires the addition of a benzodiazepine during the first week.

According to currently available knowledge, carbamazepine should be regarded as a valid alternative to lithium in the treatment of manic episodes. The suggested dosage is between 600 and 1800 mg / day. There is no convincing evidence of a superiority of carbamazepine over lithium in the treatment of mixed mania.

The evidence of an efficacy of carbamazepine in depressive episodes of bipolar disorder is much weaker. In a placebo-controlled crossover study, Post *et al.* (1986) reported a marked improvement in 12 (34%) of 35 patients with treatment-resistant depression, with a trend towards a better response in bipolars than in unipolars, and a clinical deterioration in some carbamazepine-responsive patients switched to placebo. Some other very small controlled trials and several open studies do not add significantly to the above evidence.

Prevention of recurrences of bipolar disorder

At present there is only one double-blind placebo-controlled trial of carbamazepine in the prevention of recurrences of bipolar disorder (Okuma *et al.* 1981), which found a 1-year recurrence rate of 40% in patients treated with the drug and of 78% in those receiving placebo (a non-significant difference). Moreover, there are several double-blind trials versus lithium (Placidi *et al.* 1986, Watkins *et al.* 1987, Lusznat *et al.* 1988, Coxhead *et al.* 1992), whose interpretation is made difficult by the heterogeneity of the enrolled patients (only one of them included exclusively bipolar patients) and the peculiarity of the designs (one of them was a discontinuation trial, while in another the length of the observation period in some patients was less than 6 months). Of these studies, three found carbamazepine to be as effective as lithium, while one (Watkins *et al.* 1987) found lithium to be significantly superior in increasing the time in remission.

A recent multicentre randomized open trial (Greil *et al.* 1997), comparing carbamazepine and lithium in 144 bipolar patients, found a non-significant superiority of lithium in terms of recurrence rate during the 2.5-year observation period (28% versus 47%). However, the difference in favour of lithium became significant when, in addition to recurrences, the need for neuroleptics and / or antidepressants for at least 6 months was considered as failure. The mean carbamazepine dose was 621 mg / day, i.e. very close

to the lower limit of the suggested prophylactic dose range (600–1200 mg/day).

It has been maintained that bipolar patients who respond to carbamazepine prophylaxis, compared with those responding to lithium, less often have a positive family history of bipolar disorder and are more frequently rapid cyclers (Kishimoto *et al.* 1983). However, a retrospective study conducted in 215 bipolar patients treated with lithium or carbamazepine for 2 years (Okuma 1993) found that rapid cycling predicts a poor response to both drugs. It has been reported that at least half of patients who respond initially to carbamazepine have a recurrence after 3–4 years (Post *et al.* 1990), which has been ascribed to the development of tolerance.

The combination of lithium and carbamazepine may be useful in some bipolar patients who do not respond satisfactorily to either drug. In a double-blind crossover study, Denicoff *et al.* (1997) found that the total number of recurrences was significantly lower in the period in which patients were on the combination compared with the lithium and carbamazepine phases. The mean survival time to the first manic episode was 179.3 days on the combination, 89.8 days on lithium alone and 66.2 days on carbamazepine alone (a statistically significant difference). The difference among the three regimens with respect to the percentage of patients who had a marked or moderate improvement on the CGI scale did not reach statistical significance in the whole patient sample (55.2% on the combination, 33.3% on lithium and 31.4% on carbamazepine), but became significant in the subsample of rapid cyclers (56.3% on the combination, 28% on lithium and 19% on carbamazepine).

The combination of lithium and carbamazepine is usually safe, although one case of neurotoxicity has been reported. A history of brain pathology seems to be a risk factor.

Via the cytochrome P450 3A3 / 4 system, carbamazepine induces its own metabolism (so that its half-life may decrease during long-term treatment from 18–55 to 5–26 hours, requiring dosage adjustment) and that of several other drugs, including valproate, haloperidol, clozapine, imipramine and oral contraceptives, whose plasma levels are therefore reduced. Several drugs inhibiting the above cytochrome may slow carbamazepine metabolism, increasing its plasma levels: they include valproate, selective serotonin reuptake inhibitors and some antibiotics.

Side-effects

The most common side-effects of carbamazepine are neurological: fatigue, blurred vision, nausea, dizziness, headache, motor incoordination, diplopy, nystagmus. They are dose-related, usually transient and reversible with dose reduction. Their frequency increases with carbamazepine plasma levels higher than 12 μg/ml.

A transient leukopenia has been found in about 10% of patients treated with carbamazepine. It does not predispose to infections and usually resolves spontaneously or after dose reduction. More seldom, a mild reversible thrombocytopenia may occur. In about five cases out of 1 million, carbamazepine may cause aplastic anaemia and in about 1.5 cases out of 1 million, agranulocytosis. These reactions are potentially fatal and are not predictable by monitoring drug plasma levels or by the occurrence of the above-mentioned mild haematological side-effects. In most cases these severe adverse reactions occur in the first 3–6 months of treatment.

Hyponatraemia has been reported in 5–30% of patients treated with carbamazepine, and is likely to be a consequence of the drug's antidiuretic effect (both direct and mediated by a potentiation of the action of antidiuretic hormone). It seems to be dose-related and more frequent in old people. It can manifest itself with symptoms (nausea, headache, dizziness) and require treatment discontinuation.

An asymptomatic increase of liver enzymes has been found in 5–10% of patients treated with carbamazepine. It has no relationship with the rare, idiosyncratic and unpredictable hepatic failure, usually occurring during the first month of treatment, which may be fatal.

Skin rashes have been reported in 2–15% of patients treated with carbamazepine. In most cases they are mild and not accompanied by other symptoms, and resolve spontaneously. In rare cases a skin rash may be part of a widespread reaction caused by hypersensitivity to the drug, including fever, hepatosplenomegaly and lymphadenopathy, with a possible involvement of other organs (myocarditis, interstitial pneumonia, pseudolymphoma, interstitial nephritis). In very rare cases carbamazepine may cause serious and potentially fatal skin reactions such as exfoliative dermatitis, Stevens–Johnson syndrome, and Lyell syndrome.

Carbamazepine has been involved in rare cases of pancreatitis, heart failure, hypertension, cardiac conduction disturbances and renal failure, and in sporadic cases of psychosis.

The use of carbamazepine during the first trimester of pregnancy has been associated with an increased risk of neural tube defects and craniofacial malformations. The frequency of neural tube defects can be reduced by prophylactic treatment with high doses of folate.

VALPROATE

Treatment of manic episodes and of depressive episodes of bipolar disorder

The efficacy of valproate in the treatment of manic episodes has been tested in three double-blind trials, controlled with placebo (Pope *et al.* 1991), lithium (Freeman *et al.* 1992), or lithium and placebo (Bowden *et al.* 1994).

The drug has been found to be significantly superior to placebo, and as effective as lithium. Pooling the results of the three studies, 54% of patients treated with valproate showed a reduction of at least 50% of manic symptomatology. In the study by Bowden *et al.* (1994), the superiority of valproate over placebo was already significant at the end of the first week of treatment. Contrary to lithium, valproate was equally effective in mixed and classic mania (Swann *et al.* 1997).

In a randomized trial of valproate oral loading (20 mg / kg per day) versus haloperidol (0.2 mg / kg per day), a comparable reduction was observed of both manic and psychotic symptoms. The greatest rate of improvement for both treatments occurred during the first three full days of administration (McElroy *et al.* 1996).

According to currently predominant consensus (Expert Consensus Panel 1996, Suppes *et al.* 1995), valproate should be regarded as the first-choice drug in the treatment of mixed mania, and as a valid alternative to lithium in that of classic mania. The recommended dose range is 750–3000 mg / day.

There is no controlled trial of valproate in the treatment of depressive episodes of bipolar disorder, and open trials have reported response rates consistent with a placebo mechanism of action (American Psychiatric Association 1994).

Prevention of recurrences of bipolar disorder

No controlled trial of valproate in the prevention of recurrences of bipolar disorder has been published as yet, but the preliminary results of a 1-year double-blind placebo-controlled trial (Bowden 1997) suggest a significant superiority of the drug over placebo in increasing the time in remission, and several open trials indicate that the drug may reduce the frequency and severity of affective episodes, also in rapid cyclers (McElroy *et al.* 1989, Calabrese *et al.* 1992). In a randomized trial in which 12 bipolar patients received either valproate or placebo in association with lithium, those treated with lithium and valproate were significantly less likely to suffer a recurrence (Solomon *et al.* 1997).

The lithium–valproate combination is reported to be safe. Lithium's pharmacokinetics is not affected by the co-administration of valproate (Granneman *et al.* 1996). The valproate dose range recommended for the prophylactic purpose is 750–2000 mg/day.

Side-effects

Common, dose-related side-effects of valproate are gastrointestinal disturbances (nausea, vomiting, anorexia, dyspepsia), observed in up to 25% of treated patients; a transient asymptomatic increase of hepatic transaminases; tremor, drowsiness; trombocytopenia, leukopenia and inhibition of blood

platelet aggregation; increased appetite and weight gain. Some patients present with hair loss. Rare, idiosyncratic and potentially fatal adverse reactions are irreversible hepatic failure, acute haemorrhagic pancreatitis, and agranulocytosis. The exposure to valproate during the first trimester of pregnancy has been associated with an increased risk of neural tube defects.

OTHER ANTICONVULSANTS

Lamotrigine

The largest available open trial of lamotrigine in bipolar disorder (Cookson *et al.* 1996) was carried out in 75 treatment-resistant patients, of whom 60 received the drug as add-on to other psychotropics and 15 in monotherapy, for a total of 48 weeks. Of the 41 patients who were currently depressed, 18% displayed moderate and 53% marked improvement. Of the 31 patients who were currently in a manic, hypomanic or mixed episode, 3% showed moderate and 81% marked improvement. Improvement was significant among both rapid cyclers and non-rapid cyclers; however, while in patients who were currently depressed the improvement in depressive symptomatology was equivalent in the two groups, in those who were in a manic, hypomanic or mixed episode the improvement in manic symptomatology was more pronounced in non-rapid cyclers (Bowden *et al.* 1999). Dizziness, headache and skin rashes were the most frequent side-effects, and led to treatment discontinuation in 10 patients (13%). In seven cases discontinuation was caused by a rash.

According to the preliminary results of an ongoing double-blind placebo-controlled trial (Frye *et al.* 1998), eight out of 13 (61.5%) treatment-refractory patients with bipolar I or II disorder showed a moderate or marked response to a 6-week treatment with lamotrigine.

Concomitant treatment with valproate increases the blood levels of lamotrigine, which may cause an increased frequency and severity of skin rashes (Peck 1991). One study (Warner *et al.* 1992) has found that lamotrigine increases carbamazepine metabolite concentration, resulting in neurotoxicity, whereas other studies have found the combination to be safe. No problems have been reported with the lithium-lamotrigine association.

Gabapentin

The largest available open trial of gabapentin in bipolar disorder (Shaffer and Shaffer 1997) used the drug as add-on or in monotherapy in 28 bipolar patients refractory to treatment with lithium, valproate or carbamazepine. A ″positive response as judged by both the treating psychiatrist and the patient″ was observed in 18 cases. Eight patients interrupted treatment

because of intolerable side-effects (of which the most common were oversedation and overactivation) and two due to inadequate response.

An ongoing double-blind placebo-controlled trial (Frye *et al.* 1998) found that seven out of 13 (53.8%) patients with bipolar I or III disorder presented a moderate or marked response to a 6-week treatment with gabapentin.

The combination of gabapentin with lithium, valproate or carbamazepine appears to be safe.

FURTHER READING

The reader is referred to the papers by Miklowitz *et al.* (Miklowitz 1996) and Miklowitz and Frank (1999) for a review of psychoeducational and psychotherapeutic interventions which are often integrated with lithium and anticonvulsant treatment in the long-term management of bipolar disorder. An update on the biological effects of lithium and anticonvulsants which may be relevant to their clinical activity can be found in Manji *et al.* (1999). Lithium intoxication and its treatment have been reviewed by Tyrer (1966).

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Chapter eighteen

Antipsychotics in acute mania

Mauricio Tohen

INTRODUCTION

The use of antipsychotic agents in the treatment of mania was first reported by Delay *et al.* (1952) almost half a century ago. In their original publication, Delay and co-workers (1952) described the benefits of chlorpromazine in five patients who were severely agitated, three of them suffering from psychotic mania. They suggested that antipsychotic agents were "life-saving", as their use prevented the exhaustion and dehydration secondary to severe agitation. Antipsychotic agents therefore represent the oldest pharmacological treatment for acute mania, not only for those suffering from schizophrenia, but also those suffering from bipolar disorder. In the 1950s and 1960s chlorpromazine was instrumental in the treatment of the severely mentally ill.

Prior to 1980, when DSM-III was published, the boundaries between schizophrenia and bipolar disorder in the United States were unclear. The US/UK diagnostic study highlighted the lack of clarity in the differential diagnosis of schizophrenia and bipolar disorder (Cooper *et al.* 1972). It is possible that many patients treated with antipsychotics at that time would be diagnosed as bipolar using modern criteria.

In the 1970s, when lithium became available in the United States, the use of antipsychotics became a second option, primarily because of their adverse effect potential. In the late 1980s and early 1990s the use of the anticonvulsant divalproex sodium further relegated the use of antipsychotic agents. More recently, with the availability of new atypical antipsychotic agents, a renewed interest in antipsychotic agents has evolved in the field. This chapter will review the use of both typical and atypical antipsychotic agents in the treatment of acute mania.

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 373–385.

TYPICAL ANTIPSYCHOTIC AGENTS IN ACUTE MANIA

Chlorpromazine has been widely studied in the treatment of acute mania, starting with the original publication by Delay *et al.* (1952). The only placebo-controlled study of a typical antipsychotic agent was conducted by Klein (1967) in the 1960s. This study clearly demonstrated the efficacy of a conventional antipsychotic in acute mania. The authors compared chlorpromazine (1200 mg/day) with imipramine (300 mg/day) and placebo in a 7-week study. Response was measured with a global scale. The major finding was the superiority of chlorpromazine over both placebo and imipramine.

A number of head-to-head comparisons between chlorpromazine and lithium were published in the 1970s. Most studies found no difference in terms of overall response and onset of response when chlorpromazine was compared to lithium (Tran *et al.* 1997). A study by Platman (1970) found that lithium was superior to chlorpromazine. Specifically, patients who were randomized to lithium in a six-point severity scale improved 18% during the first week of treatment and 46% by week four. In comparison, patients randomized to chlorpromazine improved only 2% by the first week and 36% at week three. In a similar study, Takahashi *et al.* (1975) found clinical improvement in 50% of patients randomized to lithium by week one, compared to only 32% of those randomized to chlorpromazine ($p = 0.03$). Other investigators found that chlorpromazine has a faster onset of action. A well-known study conducted by Prien *et al.* (1972) found that chlorpromazine is effective in decreasing psychomotor activity in patients who were classified as highly active. However, in those patients who were classified as mildly active the response to lithium appeared more robust. The investigators concluded that lithium appeared more effective in the improvement of affective symptoms, but that chlorpromazine was more effective in agitated patients.

HALOPERIDOL

In the United States, haloperidol is the most frequently utilized antipsychotic agent in the treatment of mania. The popularity of haloperidol can be attributed to its fast onset of action, and its availability as a short-acting intramuscular and long-lasting depot formulations. Its short-acting intramuscular injection has a peak plasma concentration of 20 minutes. Having less anticholinergic side-effects than chlorpromazine, it has become a popular treatment in emergency rooms. The first study that compared haloperidol with lithium was conducted by Garfinkel *et al.* (1980) at the Clarke Institute of Psychiatry in Toronto. Patients were randomized to haloperidol alone, lithium alone, or the combination of the two. After 8 days of treatment a significant improvement was observed with haloperidol alone, and with

haloperidol and lithium, but no improvement was observed in the patients treated with lithium. In addition, the combination of lithium and haloperidol did not appear to be superior to the use of haloperidol monotherapy. Importantly, the faster onset of action of haloperidol was seen specifically in the decrease of motor activity and agitation. However, by the end of the 3-week period the improvement noticed in patients receiving lithium was superior to those receiving haloperidol. Most likely this report was influential in the practice of treating patients with both medications and discontinuation of haloperidol 3–4 weeks after treatment initiation.

An interesting study published by McElroy and colleagues (1996) compared divalproex oral loading with haloperidol. The investigators studied 36 patients, of whom 21 were randomly assigned to divalproex oral loading 20 mg/kg per day, and 15 were randomized to haloperidol 0.2 mg/kg per day. The investigators found that divalproex oral loading and haloperidol were equally effective in improving manic symptoms. As measured by the mean change in Young Mania Rating Scale (Y-MRS) scores, the investigators found that 37.6% of divalproex-treated patients and 33.3% of the haloperidol-treated patients were considered acute responders, as determined by a 40% decrease in total Y-MRS improvement. The findings of this study suggested that divalproex sodium was as effective as haloperidol, not only in terms of reductions in manic symptoms, but also of psychotic symptoms; with both drugs showing significant improvement after 3 days of treatment. The investigators concluded that divalproex sodium was as effective as haloperidol, but offered a more benign adverse effect profile.

COMPARISONS BETWEEN TYPICAL ANTIPSYCHOTIC AGENTS

Shopsin and colleagues (1975) reported a double-blind study comparing haloperidol, chlorpromazine, and lithium in the treatment of acute mania. The investigators found that, by week one, 32% of patients randomized to haloperidol and 23% randomized to chlorpromazine showed significant improvement. By week three a 50% improvement was seen in 45% of haloperidol-treated patients and a 32% improvement in chlorpromazine-treated patients, as measured by Brief Psychiatric Rating Scale (BPRS) scores and Clinical Global Impression (CGI) scores. In another study, Rifkin *et al.* (1994) found that haloperidol administered at doses of 10, 30, and 80 mg per day was equally effective, and concluded that higher doses did not reduce onset of action latency.

ZUCLOPENTHIXOL

Zuclopenthixol, which is not available in the United States, is widely used in Scandinavia (Gouliaev *et al.* 1996). A comparison study between zuclo-

penthixol and haloperidol found that the two drugs were equally effective in overall efficacy and action in acute mania (Baastrup *et al.* 1993). There was also no difference in terms of adverse events.

Other typical antipsychotics

Thiothixene

Janicak *et al.* (1988) compared the high-potency thiothixene with the low-potency chlorpromazine, and found no difference between the onset of action between the two drugs.

Primozide

One of the most potent typical antipsychotic drugs, primozide, has also been studied in the treatment of acute mania. Cookson and colleagues (1979, 1981) compared primozide to chlorpromazine. The investigators found an initially faster response with the use of chlorpromazine, as measured by the Beigel–Murphy Mania Rating Scale. By day seven, primozide appeared to produce a greater improvement. The authors concluded that the initial effects of chlorpromazine appeared to be related to sedative effects.

In summary, typical antipsychotic agents have been used in the treatment of mania since they first appeared in the early 1950s. High-potency typical antipsychotics such as haloperidol or primozide appear to be more effective and have a faster onset of action than chlorpromazine. A major concern that remains regarding the use of typical antipsychotics is their adverse effect profile, including tardive dyskinesia, hyperprolactinaemia, and neuroleptic malignant syndrome. In addition, typical antipsychotics have been found to be depressogenic (Kukopulos *et al.* 1980).

Considering their possible depressogenic effects, the use of typical antipsychotics in acute mania appears limited as they have only a unidirectional therapeutic effect. The latter is defined as an improvement of the symptoms of acute mania, but lack of improvement in the symptoms of depression or even worsening of depressive symptoms. This limitation has restricted the use of typical antipsychotic agents to the acute phase of the condition. Nonetheless, their use remains prevalent. It has been estimated that more than 85% of patients with acute mania receive a typical antipsychotic agent (Tohen *et al.* 1998, Chou *et al.* 1996). Its use is surprisingly high in spite of the fact that it has been discouraged by the American Psychiatric Association (APA 1994).

With the availability of the newer antipsychotic agents that provide a more benign adverse effect profile, and possibly mood-stabilizing proper-

ties, there has been renewed interest in the use of antipsychotic agents in the treatment of acute mania.

Some investigators have suggested that bipolar patients may have an increased risk of developing acute dystonia, akathisia, and tardive dyskinesia (Nasrallah *et al.* 1988, Kane 1988). An additional risk associated with the typical antipsychotic agents is neuroleptic malignant syndrome.

A possible association between affective disorders and tardive dyskinesia has been reviewed by a number of investigators. Kane and Smith (1982) found that the cumulative risk of developing tardive dyskinesia after being exposed to neuroleptics for at least 6 years was 26% for bipolar patients, compared to 18% for patients with schizophrenia. On the other hand, other investigators have not found a higher risk treating affective disorder patients. Specifically, Morgenstern and Glazer (1993), in a 5-year, follow-up study of close to 300 patients, found that psychiatric diagnosis was not a risk factor. Furthermore, Jeste *et al.* (1995) observed, in a 3-year study of patients over 45 years old, that a mood disorder was not a risk factor in developing tardive dyskinesia. Moreover, Chakos *et al.* (1996) found in a sample of first-episode psychotic patients, followed for $8\frac{1}{2}$ years, that psychiatric diagnosis was not a risk factor for tardive dyskinesia. In terms of severity of tardive dyskinesia, Glazer and Morgenstern (1988) discovered that patients with affective disorders had a more severe form of tardive dyskinesia.

To summarize, although there is some literature suggesting that affective disorders may be a risk factor for developing tardive dyskinesia in patients exposed to typical antipsychotics, the findings are not compelling. Another consideration is to consider outcome as the severity of tardive dyskinesia rather than the relative risk of developing the condition. In this regard it is possible that patients with affective disorders who may develop tardive dyskinesia may be more incapacitated. Nonetheless, with the availability of other compounds such as lithium, anticonvulsants, or the atypical antipsychotic agents, the use of typical antipsychotics in affective disorders needs to be clearly justified.

ATYPICAL ANTIPSYCHOTIC AGENTS

A number of studies have documented the superiority of atypical antipsychotic agents over the older typical agents with regard to both efficacy and safety. The superiority of the atypical agents also includes a more benign adverse effect profile with a lower risk of extrapyramidal side-effects, lower risk of tardive dyskinesia, lower risk of hyperprolactinaemia, and lower risk of anticholinergic side-effects. In addition to safety concerns the atypical agents appear to have a wider therapeutic spectrum in patients with schizophrenia. Importantly, a number of studies have suggested that the atypical

agents, due to an affinity to serotonin and norepinephrine receptors, may have mood-altering properties.

Clozapine

Reports of the efficacy of clozapine in bipolar and schizoaffective disorder first appear in literature in the early 1970s (Faltus *et al.* 1973, Rodova *et al.* 1973, van Praag *et al.* 1976, Battegay *et al.* 1977). A number of publications have found clozapine to be highly effective in the treatment of bipolar disorder. However, the vast majority of those studies have been case reports or open-label trials. The only double-blind designs have included very few patients (Rodova *et al.* 1973, Pickar *et al.* 1992a, Barbini *et al.* 1997). However, a comprehensive review conducted by Zarate *et al.* (1995a) from a Medline database found that, up to 1995, there were no large double-blind studies of clozapine in the treatment of bipolar disorder. The authors identified a limited number of controlled studies that included patients with psychotic mood disorders or schizoaffective disorders. Of note, a double-blind comparison study was recently published by Barbini *et al.* (1997), who conducted a 3-week, double-blind, randomized study comparing clozapine with chlorpromazine, both in concomitant use with lithium carbonate. The authors concluded that patients receiving clozapine had a faster onset of action than those receiving chlorpromazine. The difference was statistically significant at the first assessment at week two, and remained significant at week three.

In the comprehensive review conducted by Zarate *et al.* (1995a), a total of 30 reports were identified in Medline where clozapine was used in the treatment of psychotic mood disorders. The review included two double-blind studies, eight open-label, 10 retrospective studies and 10 case reports. Of those 30 studies, 10 provided information that enabled the authors to estimate an overall assessment of the efficacy of clozapine in terms of the percentage of patients responding to clozapine (McElroy *et al.* 1991, Banov *et al.* 1994, Faltus *et al.* 1973, Rodova *et al.* 1973, van Praag *et al.* 1976, Battegay *et al.* 1977). Of those 10 studies a total of 350 patients with psychotic mood disorders were treated with clozapine; of which these patients had a bipolar disorder and 221 had a schizoaffective disorder in the bipolar phase of the illness. The authors estimated that 71.2% of the 94 bipolar and 69.6% of the 221 schizoaffective patients were classified as responders to clozapine. When those patients were compared with schizophrenic patients in seven of the 10 studies ($n = 692$), the response of the schizophrenic patients was 61.3%, which statistically was significantly lower than the 71.2% response of the affective disorder patients ($\chi^2 = 7.42$, $p = 0.006$. This suggested that clozapine appeared to be more effective in severe mood disorder than in schizophrenia, a finding previously reported by McElroy *et al.* (1991).

Two studies have looked at the use of clozapine in treatment-resistant mania. The first one, conducted by Calabrese and colleagues (1996), reported

the use of clozapine in 25 patients with acute mania, non-responsive to lithium, valproate, and typical antipsychotics. Criteria for non-response included the use of lithium carbonate at a blood level of 0.8 mg/L, carbamazepine 6 mg/ml, and valproate 50 mg/ml for at least 6 weeks. In addition, patients were required to have a history of not responding to a 6-week trial of a typical antipsychotic at a dose equivalent of 20 mg of haloperidol. The authors found that, in 22 of the 25 patients who completed the trial, 72% (18) had a marked improvement, and statistical significance was attained in the first week of treatment.

A similar study, conducted at McLean Hospital (Tohen and Zarate 1998), included 24 patients who had a previous history of failing to respond to typical antipsychotics (chlorpromazine 500 mg or equivalent or lithium 0.8 mg/ml) for at least 6 weeks. Patients received clozapine monotherapy, 550 mg/day for at least 13 weeks. Fifteen patients were able to complete this 13-week trial, of whom 87% were classified as very much or much improved. In the Young Mania Rating Scale a 50% improvement was achieved in 93% of the patients. The studies conducted by Calabrese and colleagues, and at McLean Hospital, suggest that clozapine may be effective in treatment-resistant manic patients.

Although the efficacy of clozapine in acute mania appears convincing, less evidence is available for its effects as a mood stabilizer. Suppes *et al.* (1992) reported seven patients who were treated with clozapine in combination with mood stabilizers and three of them with clozapine monotherapy, who were treated for a mean period of 4 years. Similarly, Zarate *et al.* (1995a) reported that 11 of 17 patients (65%) were stable for 16 months with the use of clozapine monotherapy, reducing the number of hospitalizations. After the patients were treated with clozapine the mean number of hospitalizations was 0.4 for 6 months, which was significantly lower than 6 months prior to clozapine therapy ($0.8 \pm 1.2p = 0.025$). The study by Calabrese *et al.* (1996) reported that 11 bipolar patients and 11 schizoaffective patients were stable on clozapine after being followed up for an average of 15 months.

In another report by Suppes and colleagues (1999), there was a significant improvement in psychotic and affective symptoms 6 months after being randomized through either clozapine or usual treatment. Banov *et al.* (1994) also reported efficacy in the long-term use of clozapine in treatment-refractory patients.

In a retrospective review that included 52 patients with bipolar disorder, 81 with schizoaffective disorder, and 14 with psychotic depression, the authors found that psychotic mania and schizoaffective bipolar patients had significantly better outcomes than patients with psychotic depression or schizoaffective-depressed type; suggesting that the index episode of mania or schizoaffective bipolar type predicted a better outcome. In addition, patients with a psychotic affective disorder had a better outcome in social

functioning compared to 40 patients with schizophrenia who were followed as a comparison group.

Risperidone

Hillert and colleagues (1996) were the first to report risperidone's mood-altering properties in patients with major depression with psychotic features and schizoaffective disorder depressive subtype. A number of other case reports have also suggested that risperidone has mood-altering properties (Hillert *et al.* 1992, Jacobsen 1995, Goodnick 1995). Tohen *et al.* (1996) conducted an open-label study of risperidone concurrent with stabilizing agents in patients with acute mania with psychotic features. Fifteen subjects were included, of whom 13 completed 2 weeks of treatment. Eight of the 13 had a 50% improvement on the BPRS and all 13 had at least a 25% improvement. Of eight patients who completed a 16-week trial, seven had a 50% improvement, and all eight had a 25% improvement with both the BPRS and the Young Mania Rating Scale. Risperidone was well tolerated, and no case worsened. Similarly, Keck and colleagues (1995), in a retrospective chart review, found that patients with bipolar disorder or schizoaffective disorder depressed type had a good response when risperidone was added to mood stabilizers. More recently, Segal *et al.* (1998) conducted a double-blind, randomized, controlled trial comparing risperidone to both lithium and haloperidol. The investigators studied 45 patients in a 4-week trial randomized to up to 6 mg of risperidone, up to 10 mg of haloperidol, and lithium 800–1200 mg daily, with blood levels 0.6 and 1.2 mg/L. Fifteen patients were assigned to each treatment group. In all three groups there was a significant improvement at the end of the trial and there were no significant differences between the three groups when assessed with the BPRS, the GAF, and the CGI. The authors concluded that monotherapy with risperidone was of comparable efficacy to that of lithium and haloperidol.

Olanzapine

Olanzapine, a novel antipsychotic agent, has affinity for D1, D2, D3, D4, 5HT2, 5HT3, 5HT6, alpha-cholinergic muscarinic, and 1 histaminic, and histaminic H1 receptors. The first report, including a large sample size, was reported by Zarate *et al.* 1997, in a review conducted at McLean Hospital, which suggested that olanzapine was effective in the treatment of psychotic mood disorders. This review included 150 patients with psychotic disorders, including 47 patients with bipolar disorder with psychotic features, 29 patients with schizophrenia, 23 patients with schizoaffective disorder bipolar type, 17 patients with schizoaffective disorder depressive type, 22 patients with major depression with psychotic features, and 12 patients with psychosis not otherwise specified. Of interest in this review is that

patients more likely to respond to olanzapine had a bipolar disorder diagnosis, were younger, female, and had a shorter duration of illness. McElroy and colleagues (1998) also reported that olanzapine was effective in treatment-resistant mania.

To date, two double-blind, placebo-controlled studies with olanzapine have been conducted. The first one (Tohen *et al.* 1999a) included 70 patients randomized to olanzapine and 69 to placebo. The starting dose of olanzapine was 10 mg/day. In this study, of 3 weeks duration, efficacy was assessed by mean change from baseline to end point. The mean difference between olanzapine and placebo groups was –5.38 points ($p = 0.01$). Of note, when patients with and without psychotic features were compared, no statistical difference was found in the difference of olanzapine relative to placebo. In a subgroup of patients with a rapid-cycling course there was a statistically significant improvement in those receiving olanzapine with a mean change from baseline to endpoint of –13.89 for olanzapine and –4.12 for placebo ($p = 0.03$). Clinical response was defined as a 50% improvement in the Y-MRS. By this definition 48.6% of olanzapine-treated patients were considered responders, compared to 24.2% of those randomized to placebo ($p = 0.01$).

In a second trial (Tohen *et al.* 2000) ($n = 115$), patients were randomized to olanzapine ($n = 55$), or placebo ($n = 60$). Olanzapine was started at 15 mg/day. Efficacy was also measured utilizing the Young Mania Rating Scale. Olanzapine-treated patients had a statistically significant superior efficacy. Furthermore, clinical improvement, defined as 50% improvement on the Y-MRS, was observed in 62% of patients receiving olanzapine and 42% of those receiving placebo ($p = 0.02$). Of note, the superiority of olanzapine over placebo was observed at week one. In order to assess an antidepressant response in this population of bipolar manic or mixed patients, a subgroup of patients who scored 20 or more in the Hamilton Rating Scale were compared. Patients receiving olanzapine had an improvement in the HAMD-21 scale of 12 points, compared to three points for those receiving placebo ($p = 0.4$). This study suggests that olanzapine has a fast onset of action, and also that it may have mood-stabilizing properties in patients with acute mania. However, antidepressant properties still need to be confirmed in a population with bipolar depression.

To summarize, antipsychotics in the treatment of mania have been utilized since they became available almost half a century ago. Although typical antipsychotics have proven to be a valuable treatment tool for acute mania, they have limitations regarding the adverse effect profile, and possible depressogenic effects. Novel antipsychotic agents appear promising. The role that these agents will have in the treatment of bipolar disorder, *vis-à-vis* mood stabilizers, remains unclear. Although the evidence of the efficacy in the treatment of acute mania has been demonstrated, studies assessing

its efficacy in bipolar depression and relapse prevention need to be conducted to determine their role in the therapeutic armamentarium in the treatment of bipolar disorder.

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Chapter nineteen

Antidepressant treatment of bipolar depression

Hans-Jürgen Möller and Heinz Grunze

INTRODUCTION

While in some countries, for example Germany, antidepressants have a long tradition of being the drug of first choice in the treatment of acute bipolar depression – a tradition which still has a strong impact on treatment decisions in current routine treatment – other countries, especially the United States, are increasingly restrictive concerning the use of antidepressants in this indication (Hirschfeld *et al.* 1994, Sachs 1996). This modern development is especially based on some risks induced by antidepressants in bipolar depression, such as switch into mania and rapid cycling. Some bipolar experts even question the generally held hypothesis that antidepressants which have been proven to be effective in unipolar depression are also effective in bipolar depression.

In the following, the possibilities, limitations and risks of antidepressants in the treatment of acute bipolar depression will be reviewed, focusing on bipolar I depression, since most of the findings in the literature refer to this group of bipolar depressions.

EFFICACY OF ANTIDEPRESSANTS IN ACUTE BIPOLAR DEPRESSION

Antidepressants were extensively studied in patients with unipolar depression and in mixed groups of patients with unipolar and bipolar disorder during the first decades after the introduction of the tricyclic antidepressants. At that time the efficacy of antidepressants in episodes of acute bipolar depression was not generally evaluated separately. Nowadays, the

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 387–403.

hypothesis that drugs which have been shown as effective in unipolar depression are also effective in bipolar depression is still commonly accepted. This position is especially based on broad and long-term clinical experience. For a long time it did not seem relevant or necessary to prove the efficacy of antidepressants in separate samples of bipolar depression. However, the situation is currently changing and arguments have been made that this view possibly does not hold true (Hirschfeld *et al.* 1994, Sachs 1996) as there is evidence from genetic (Souery *et al.* 1996) as well as neuroimaging studies (Soares and Mann 1997) which suggests that unipolar and bipolar depression are biologically different entities, and therefore possibly require differential treatment.

Proceeding from this position, over recent decades bipolar depressions were excluded from the phase II and phase III studies testing the efficacy of the newer antidepressants, to restrict variance of the efficacy data and to avoid the risk of switch and rapid cycling phenomena. In addition, this led to the performance of a small number of controlled trials on antidepressants in samples of acute bipolar depressive patients (Baumhackl *et al.* 1989, Cohn *et al.* 1989, Katz *et al.* 1987, Zornberg and Pope 1993).

Apparently, the sceptical view that antidepressants might not be effective in acute bipolar depression, which seems to be very extreme, or the position that they might not be as effective as in unipolar depression, or that the induced risk of switch into mania and rapid cycling might override the benefits of a good antidepressive response, which were expressed in this very sceptical and maybe over-critical tendency especially in the most recent years, is not supported by empirical evidence.

Zornberg and Pope (1993) reviewed seven controlled studies that examined the efficacy of tricyclic antidepressants in the treatment of bipolar depression. In general, the data indicate that tricyclic antidepressants are more effective than placebo for patients with bipolar depression. The relative efficacy compared to other antidepressants is not so clearly established. Their efficacy when combined with lithium, or alternatively with other mood stabilizers, has not been systematically studied, although this is the manner in which antidepressants are increasingly used in acute bipolar depression. Two controlled studies have tested monoaminoxidase inhibitors in patients with bipolar depression. One study found the reversible MAO-A inhibitor moclobemide to be equivalent to imipramine in a heterogeneous group of depressed patients, including 33 bipolar patients (Baumhackl *et al.* 1989). The other study showed that the classical MAO inhibitor tranylcypromine was significantly superior to imipramine in the anergic subtype of bipolar depression in patients with bipolar I and bipolar II disorder (Himmelhoch *et al.* 1991). Selective serotonin re-uptake inhibitors have not been well studied in a controlled manner in the treatment of acute bipolar depression. One controlled study found that fluoxetine was superior to imipramine and placebo in the treatment of acute bipolar depression (Cohn

et al. 1989). Two clinical trials suggested buproprione as effective in the treatment of episodes of bipolar depression (Fogelson *et al.* 1992, Sachs *et al.* 1994).

All of these studies have methodological limitations: most of them were conducted in only a small number of patients, a placebo control group was rarely used, and the risk and especially differential risk of switch into mania was apparently of greater interest in some of the studies than the proper evaluation of the antidepressive efficacy. Nevertheless, altogether the data appear to support to a certain degree the hypothesis that antidepressants are effective not only in acute unipolar depression but also in acute bipolar depression.

It has to be admitted, as already pointed out, that the database from controlled clinical trials is limited. Nevertheless, it gives no hint that antidepressants might not be effective in acute bipolar depression. Under this aspect it seems questionable whether we really need more formal studies on the efficacy of classical or new-generation antidepressants in bipolar disorders, with all the associated risks for the patients, or whether we should continue to believe in the traditional hypothesis that a drug which has shown efficacy in unipolar depression is also effective in bipolar depression. Based on the theoretical assumption that most psychoactive drugs are syndrome-orientated in their efficacy, and not cause-related, we suppose the efficacy of antidepressants not only in unipolar as well as in bipolar functional depression but even in organic depression. Especially the broad clinical experience from many years of treatment with antidepressants seems to validate this approach. Therefore, in the following section our own study based on controlled clinical experiences in the routine treatment conditions of a large sample of inpatients, which definitely shows that acute bipolar depressive patients respond as well as acute unipolar depressive patients, will be presented. The results are even more convincing because, given the fact that the sample was an inpatient sample, most of the patients suffered from a severe unipolar or bipolar depression. Thus, we avoided the uncertainty which is a risk when studying antidepressive efficacy in mild or moderate depression, where it has been shown that anxiolytics or other drugs can also turn out as "antidepressants" (Laakman *et al.* 1986, 1995, Möller *et al.* 1991).

In this study (Möller *et al.* 2000), the data from 2032 inpatients with unipolar or bipolar I depression, who had been consecutively admitted to the Psychiatric University Hospital, Munich, were compared concerning efficacy of antidepressants in both groups under naturalistic treatment conditions. The outcome was assessed by the Global Assessment Scale (GAS), the duration of hospitalization, and the depression, apathy and mania syndrome subscale of a comprehensive rating instrument, the AMDP system (AMDP = Association for Methodology and Documentation in Psychiatry) (AMDP System 1982, Pietzcker *et al.* 1983). The study is based

on the routine documentation in the Psychiatric University Hospital in Munich, which has been performed since the late 1970s, and which includes sociodemographic data, anamnestic data, treatment and psychopathological data. In those patients with multiple hospitalizations only the first stay in our hospital was considered for this study. Due to the fact that the cohort under investigation was treated in the years 1980–1992, the great majority of the patients were treated with tricyclics or tetracyclics, monoaminoxidase inhibitors were administered to a much lesser degree, while SSRIs were quite seldomly used.

The cohorts of unipolar and bipolar depressive patients were comparable with respect to psychosocial parameters, the severity of depression at admission and treatment regimens. At discharge there were no statistically significant differences between bipolar I and unipolar depression for the outcome criteria depressive syndrome, GAS score and days in hospital. Bipolar patients showed a slightly decreased apathy score at discharge, and a slightly elevated score of the manic syndrome. In addition to the main analysis on the outcome of unipolar and bipolar depressed patients, several additional analyses were performed:

1. Outcome in unipolar and bipolar depressed patients subdivided into four year cohorts (1980–1984, 1985–1988, 1989–1992), reflecting potential changes in treatment regimens.
2. Outcome in unipolar and bipolar depressed patients grouped for different degrees of severity of depression.
3. Outcome in unipolar and bipolar depressed patients for different age groups.
4. Outcome in unipolar and bipolar depressed patients for different gender groups.
5. Outcome in unipolar and bipolar depressed patients with and without neuroleptic treatment as add-on to antidepressant treatment.

None of these sub-analyses revealed any significant differences between the response of unipolar or bipolar depressed patients, and especially there was no difference between more or less severely depressed groups of patients.

These results seem to reject the hypothesis that antidepressants – in the case of this study, predominantly tricyclics – may be less effective in the acute treatment of bipolar I depressed patients compared to unipolar depressed patients. The large sample size of this study supports a high validity of this conclusion. This study did not check for differences in unwanted effects, such as switching or rapid cycling, which are commonly attributed to the use of tricyclic antidepressants in bipolar patients. Apparently these unwanted effects, for which data are available from a subgroup of 158 bipolar I depressed patients (Bottlender *et al.* 1998, see

below!), did not lead to a prolongation of the average duration of the hospital stay in the bipolar patients compared to the unipolar patients.

When all the evidence is taken together, there does not seem to be any question that antidepressants are effective in acute bipolar I depression, and that apparently the efficacy is equal to the response in unipolar depression. In this context the general need of antidepressant treatment in bipolar depression, at least in moderate and severe cases, should be emphasized to avoid the risk of suicide, the risk of chronicity, etc. Naturalistic studies show that bipolar depressions are an underestimated treatment challenge, not only with respect to the risk of switch into mania, rapid cycling, etc., but also with respect to treatment of the depressive syndrome itself, and there is a high proportion of chronicity (Hlastala *et al.* 1997). Such results should emphasize the need for the best effective treatment of the depressive syndrome. To date there are no data available which show comparable efficacy of drugs other than antidepressants in acute bipolar depressive patients (see below!). The opposite is true – most of the mood stabilizers have not been investigated in the adequate way, i.e. in double-blind, randomized, parallel group studies in comparison to placebo and/or standard antidepressants in acute unipolar or bipolar depression, and the evidence of efficacy is generally weak.

Apart from this positive statement for the use of antidepressants in bipolar depression, it should be considered that the use of antidepressants has its special limitations in bipolar depressions in rapid cycling conditions, and also in mixed mania or mixed depression. In the case of rapid cycling, treatment with an antidepressant should be generally terminated as early as possible to avoid the induction of further rapid cycling. In mixed mania/mixed depression, antidepressants have to be avoided because they are contraindicated in the presence of manic symptoms (Calabrese and Woyshville 1995, Sachs 1996). In cases of acute bipolar depression with psychotic symptoms such as delusions, etc., co-medication with a neuroleptic is necessary in most cases.

RISK OF SWITCH INTO MANIA/HYPOMANIA UNDER ANTIDEPRESSANTS

The risk rate of switch into mania shows a broad spectrum in the literature, from about 10% to 70% (Akiskal *et al.* 1977, Altshuler *et al.* 1995, Bunney 1978, Prien *et al.* 1984, Quitkin *et al.* 1981, Wehr and Goodwin 1979a). The early studies, which are mostly retrospective and related to the tricyclic antidepressants (TCA), seem to overestimate the switch risk, possibly due to selected samples (Grunze *et al.* 1999). A meta-analysis of 80 publications covering a total of about 4000 patients with bipolar depression or unipolar depression, not showing a bipolar history or feature at the time of the

study, found a switch rate of 9.6% for tricyclic antidepressants and for MAO inhibitors (Bunney 1978). In his meta-analysis on all available data from clinical trials comparing SSRIs, TCA and placebo, Peet (1994) differentiated between unipolar and bipolar depressive patients; while the switch rate of the unipolar patients under TCAs amounted to less than 1%, the switch rate among bipolar patients was about 10-fold higher at 11.2%. Peet also differentiated in his analysis between different treatment groups of bipolar depressive patients. While the risk rate of switch into mania under TCAs amounted to 11.2%, the respective risk rate under SSRIs was 3.7%, and under placebo 4.2%.

In a study comparing fluoxetine, imipramine and placebo (Cohn *et al.* 1989) in a smaller sample of acute bipolar depressive patients, the switch rate under imipramine was 9.5%, under placebo 7.7%, and under fluoxetine 0%. Other modern antidepressants such as the selective and reversible MAO-A inhibitor moclobemide (Baumhackl *et al.* 1989) or the dopamine agonist buproprione (Sachs *et al.* 1994) also showed a more favourable switch rate risk compared to TCAs.

In some of the studies mentioned above, the concomitant treatment with a mood stabilizer was not considered, which might lead to an underestimation of the switch rate under antidepressants. Thus, the study by Himmelhoch *et al.* (1991), in which concomitant mood stabilizers were not allowed, is of interest: this group found a switch rate of 38% for anergic bipolar I patients treated with antidepressants (imipramine or tranylcypromine) over a 16-week period.

In a naturalistic study on 29 bipolar I patients, Boerlin *et al.* (1998) found that switches to hypomania or mania occurred in 28% of the overall number of episodes. Depressive episodes treated with tricyclics or MAO inhibitors showed a higher risk for switching than those treated with fluoxetine. Based on a within-subject analysis between patients who received mood stabilizers and those who received mood stabilizers plus an antidepressant, Boerlin concluded that mood stabilizers may reduce the risk for switching. Patients who were treated with an antidepressant and a mood stabilizer in co-medication had no higher a risk of switch into mania than patients who were treated with a mood stabilizer alone. The protective function of mood stabilizers, in this case lithium, can also be derived from long-term studies on bipolar depression in which patients were treated with imipramine and lithium (Prien *et al.* 1984, Quitkin *et al.* 1981).

Rouillon *et al.* (1992) provided an overview of 15 long-term placebo-controlled studies in depressive patients. In patients specifically diagnosed as bipolar (n = 158), the incidence of maniform states was 51% in 49 patients treated with imipramine alone, 21% in 60 patients treated with lithium alone, 28% in 36 patients treated with lithium and imipramine, and 23% in 13 patients receiving only placebo.

In our switch rate study we collected the data from the records and investigated the switch rate of 158 bipolar I depressive inpatients of the Psychiatric University Hospital, Munich (Bottlender *et al.* 1998). In addition, we used the sociodemographic, anamnestic and psychopathological data from our routine documentation system (see above!). Thirty-nine patients (25%) of the sample switched to a maniform state during the treatment period in the hospital. Among that group the phenomenon occurred in 23 patients (15% of the total sample) as a hypomania and in 16 patients (10% of the total sample) as mania. This switch rate has to be interpreted considering that the majority of the patients were treated with TCAs. Differentiating for the different kinds of antidepressants, the switch rate for TCAs was 33.7%, for SSRIs 12% and for MAO inhibitors 8.3%. According to the naturalistic data set, mood stabilizers can reduce the risk for switching, especially in patients treated with tricyclics; however, the protection does not seem sufficient in all patients, since 59% of the switched patients received mood stabilizers. It is of great interest that apparently the switch into hypomania or mania has no significant influence on the duration of hospital treatment. However, under international perspectives this finding should be related to the long duration of hospital stay of about 60 days, which is not unusual for a German university psychiatric hospital, and which on the one hand demonstrates the quite luxurious treatment conditions in German psychiatry, and on the other hand gives a hint towards a selection of partially treatment-refractory patients. The following variables were tested and not found to be significantly associated with the risk of switch: gender, age, duration of illness, number of prior episodes of mania, number of prior episodes of depression, depressive syndrome at admission, hallucinatory syndrome at admission. However, low basal TSH serum levels appeared to be a risk factor for switches into hypomanic/manic states (Bottlender *et al.* 2000).

Contradictory to such findings, which show a link especially between treatment with TCAs and switch into mania/hypomania, on the basis of a retrospective analysis of patients′ records, Lewis and Winokur (1982) found that a switch into mania occurred in 23% of patients when tricyclics were used, and in 34% of patients when no treatment was given. Based on these findings the authors concluded that tricyclics do not increase the risk of switching into mania, and that the so-called switch effect due to tricyclics represents random manifestations of bipolar illness. Angst's (1985) findings concerning patients admitted to the Zurich psychiatric university hospital between 1920 and 1982 point in the same direction. After the introduction of antidepressants in 1958 there was no significant increase of switches of unipolar or bipolar patients compared to the earlier treatment periods.

Altogether there seems to be evidence available that antidepressant treatment can induce a switch into hypomania or mania (Grunze *et al.* 1999). According to recent studies the risk of switching into hypomania/mania is lower than described in earlier studies; it apparently amounts to about

10–30% under tricyclics, depending on the sample selection. Seemingly, tricyclics have the highest risk of inducing switch phenomena, while the risk under MAO inhibitors, and especially SSRIs, seems to be lower, for example for SSRIs in the range of about 4–12%. Lithium and other mood stabilizers have a protective effect concerning the antidepressant-induced switch risk; however, they fail in this respect in a relevant subgroup of patients.

RISK OF RAPID CYCLING UNDER TREATMENT WITH ANTIDEPRESSANTS

The hypotheses that antidepressants can induce switch into hypomania/mania are closely related to the hypothesis that antidepressants can induce rapid cycling (Wehr and Goodwin 1979a), and possibly also mixed states (Akiskal and Mallya 1987). In a retrospective study published by Altshuler *et al.* (1995), the longitudinal course of 51 patients with treatment-refractory bipolar disorders was examined. The switch rate of patients in depressive episodes undergoing antidepressant treatment was 35%. Cycle acceleration was likely to be associated with antidepressant treatment in 26% of the patients.

Another naturalistic study described an increase of the frequency of episodes up to the rapid cycling phenomenon (more than four episodes per year) under antidepressant treatment (Ghaemi *et al.* 1998). This tendency to an increased frequency of episodes was also found in some other studies (Reginaldi *et al.* 1982, Tondo *et al.* 1981, Wehr and Goodwin 1979a, Wehr *et al.* 1988).

Several authors (Kukopulos *et al.* 1980, Wehr and Goodwin 1979b) concluded that the best treatment against rapid cycling is the immediate withdrawal of the antidepressant medication.

However, there are also critical findings. Coryell *et al.* (1992) compared 919 patients with and without rapid cycling. The rapid cyclers were more frequent in those patients of female gender, with a depressive hypomanic index episode or with a fast cycling from depression to hypomania during the index episode. A causal relationship between the use of antidepressants and rapid cycling could not be demonstrated in this sample. To explain the results of other authors concerning the risk of antidepressants for inducing rapid cycling, the authors state that rapid cycling is significantly more often preceded by depression, which leads to treatment with an antidepressant, which leads in the end to the wrong causal attribution between antidepressant treatment and rapid cycling.

Altogether there seems to be a special risk of rapid cycling under antidepressant treatment (Grunze *et al.* 1999). Due to the open and naturalistic manner of the studies the results are not totally clear, and leave some questions unanswered. If the induction of switch into mania and the induction of rapid cycling are related phenomena, it could be supposed that

drugs with a higher risk rate of inducing switch into mania also have a higher risk rate concerning rapid cycling. Empirical findings which support this hypothesis sufficiently are not yet available.

DO MOOD STABILIZERS HAVE AN ESTABLISHED ANTIDEPRESSIVE EFFICACY?

Several experts and guidelines recommend mood stabilizers as the treatment of first choice in acute bipolar depression (Frances *et al.* 1996, 1998, Hirschfeld *et al.* 1994, Sachs 1996, Yatham *et al.* 1997). This recommendation has to be questioned as long as there is no definite proof that mood stabilizers have antidepressive efficacy in unipolar and/or bipolar depression, and that this efficacy is comparable to the antidepressive efficacy of traditional or modern antidepressants.

Traditionally, lithium is the most intensively evaluated mood stabilizer with respect to antidepressive efficacy (Adli *et al.* 1998, Mendels 1976, Souza and Goodwin 1991). In controlled studies, lithium showed a certain antidepressive activity. Altogether, the total number of patients included in these studies is very small. In most studies no differentiation is made between unipolar and bipolar depression. Several of the controlled studies are not randomized, parallel-group studies, but followed cross-over designs with all their known problems and limitations, including the problem of hangover and withdrawal phenomena. Most of the randomized, parallel-group studies compare lithium with a standard antidepressant, without a placebo arm. The sample size is extremely small in each of these studies, in general less than 20 patients per treatment group. The conclusion of equal efficacy is completely misleading under these conditions, given the fact of an enormous β-error problem. Furthermore, in most of the studies the daily dose of the standard comparator was inadequate, e.g. 100 mg/day of a tricyclic or less. Without mentioning the other methodological problems from a modern perspective, the essence of these studies with respect to efficacy is extremely weak, a critical position which cannot even be softened by positive-sounding meta-analytical approaches or review papers. Lithium seems to have some antidepressive efficacy – for example as shown in the very small placebo-controlled study by Khan *et al.* (1987) – however, the power strength of the antidepressive effects compared to antidepressants is widely unclear, but generally the data indicate an inferior efficacy. In a head-to-head comparison of lithium with imipramine under controlled treatment conditions, lithium was inferior to imipramine (Fieve *et al.* 1968). Many patients require lithium treatment for 6–8 weeks before a "full" antidepressive response becomes evident (Zornberg and Pope 1993). A recent study published by Nemeroff (1997), in which the combination of lithium with placebo, with paroxetine and with imipramine in the treatment of bipolar depression were compared under double-blind conditions, demonstrated

that co-medication with an antidepressant led to a significantly higher responder rate compared with monotherapy with lithium. To avoid misunderstandings these statements are related only to the question of acute antidepressive effects of lithium and not to the efficacy of lithium augmentation.

The respective database giving hints of an antidepressive property of carbamazepine is even worse. A meta-analysis of several open and controlled studies, all of which had a small sample size and often made no differentiation between unipolar and bipolar depressives, found a response rate of 56% for depressed patients in open trials and 44% for patients in the controlled studies (moderate and good response) (Post *et al.* 1997). Apparently, the responder rates between unipolar and bipolar depressive patients are not different, as demonstrated in the studies of Svestka *et al.* (1991) and Dilsaver *et al.* (1996), for example. In two double-blind studies (Ballenger and Post 1980, Post *et al.* 1986), evidence for a good treatment response was not found in patients under carbamazepine monotherapy.

As to valproate, the database is even weaker. In an open study Calabrese and Delucchi (1990) found a marked improvement in 57% of the patients. In the study with the largest sample of 103 patients, however, a moderate improvement was found in only 22% of the patients (Lambert 1984).

With respect to the current methodological standards in the field of the evaluation of antidepressive efficacy of mood stabilizers, the placebo-controlled study on lamotrigine, involving 195 patients, seems paradigmatic (Calabrese *et al.* 1999). The study was based on positive findings of some open clinical studies and observations giving a hint of an antidepressive property of lamotrigine. In this study 200 mg lamotrigine per day was compared to 50 mg lamotrigine per day and to placebo. Lamotrigine 200 mg/day demonstrated significant antidepressant efficacy on different outcome parameters such as the total score of the Hamilton Depression Scale (HAM-D) (only for observed points, not in the LOCF analysis), the total score of the Montgomery–Asberg Depression Rating Scale (MADRS), the score of the item depressive mood of the HAM-D and the Clinical Global Impressions (CGI) compared to placebo. Lamotrigine 50 mg/day demonstrated some efficacy compared to placebo but was inferior to the higher dosage of lamotrigine. Responder rates (CGI) were 51% in the lamotrigine 200 mg/day group, 41% in the 50 mg/day lamotrigine group and 26% in the placebo group. These positive findings need replication, hopefully in a three-arm study comparing 200 mg/day lamotrigine with placebo and an antidepressant, preferentially an SSRI or another modern antidepressant known to have a low switch-rate risk. From the tactical viewpoint it should be mentioned that lamotrigine must be increased very slowly, due to its known risk of severe dermatosis, not reaching the final dose of 200 mg/day before 6 weeks. This might limit the possibility of inducing an antidepressive response as soon as possible.

To prove the antidepressive efficacy of lithium or other mood stabilizers, at least two adequately designed, positive, double-blind, randomized, parallel group studies in comparison to placebo are necessary. In trials comparing a mood stabilizer to standard antidepressants the β-error problem has to be considered very carefully before the conclusion of equal efficacy can be made. The antidepressive property of mood stabilizers has to be proven in severe depression before a final judgement on antidepressive efficacy can be made (Laakman *et al.* 1986, Montgomery and Lecrubier 1999, Möller 1992).

To summarize, overall the antidepressive efficacy of mood stabilizers is not well proven, at least not following the same methodological standards as are commonly used for establishing the efficacy of antidepressants. Although there are some hints for an antidepressive efficacy of mood stabilizers, especially for lithium, and also for lamotrigine, when using the most adequate design, the question remains open whether this antidepressive efficacy is comparable to that of antidepressants. There are at least some data showing a lower efficacy of lithium compared to antidepressants or the co-medication of lithium with antidepressants. Especially this question needs further evaluation before a final conclusion can be drawn as to whether antidepressants should be replaced by lithium or other mood stabilizers generally, or under certain conditions, in the treatment of acute bipolar depressions. As to this question, of course the tolerability of traditional and modern antidepressants compared to the recommended mood stabilizers also has to be taken into consideration. Some of the mood stabilizers have an unfavourable side-effect profile, at least compared to modern antidepressants.

Although some modern treatment guidelines (see below!) recommend a restricted use of antidepressants in the treatment of acute bipolar depression, and define mood stabilizers as first-line treatment in this condition, it should be generally considered that mood stabilizers are neither licensed by the US-American nor by the European drug authorities for the indication acute bipolar depression. This is quite an unusual situation, meaning, among other things, that these treatment guidelines might be very premature and not covered by the official regulations of the drug authority, and therefore have a risk of insurance problems, for example, if a patient suffering from an acute bipolar depression commits suicide without having had the chance to receive proper treatment with antidepressants. All experts and consensus groups should take this aspect into serious consideration.

EXPERT OPINIONS, CONSENSUS PAPERS, GUIDELINES ON THE USE OF ANTIDEPRESSANTS IN ACUTE BIPOLAR DEPRESSION

Especially in American and Canadian psychiatry there is a strong tendency to avoid antidepressants in bipolar depression, to prefer a monotherapy

with mood stabilizers and, in the case of co-medication with mood stabilizers and antidepressants in severe depressions, to withdraw the antidepressants as early as possible. This tendency has been expressed in several expert opinions, consensus papers and guidelines (Frances *et al.* 1996, 1998, Hirschfeld *et al.* 1994, Kusumakar *et al.* 1997, Sachs 1996, Yatham *et al.* 1997). The so-called European Algorithm Project (based on the consensus of some European experts) also reflects this tendency (Goodwin and Nolen 1997).

The recommendations published in the different papers and guidelines are not identical but, with certain differences, they follow a similar general direction: avoid the use of antidepressants in mild, possibly also in moderate, depression, and in general use antidepressants only if they are "clinically necessary", whatever the latter term, which is not defined or operationalized in any way, means.

As already mentioned above, it is an unusual situation in medicine that drugs (mood stabilizers) are recommended as first-line therapy without having shown antidepressive efficacy in adequate clinical trials, and without having been licensed in this indication. Probably the risk of mania and risk of rapid cycling induced by antidepressants has been over-estimated in comparison to the risk of suicidal acts and chronicity. Of course, it is difficult to make the right decision between Scylla and Charybdis. Nevertheless, suicidality seems to be the more critical outcome. Coming from this position the questions have to be posed: Have we lost a well-balanced view? Have we gone too far in the restriction of antidepressants, possibly caused by findings on too-selected patients, e.g. patients in specialized bipolar clinics, where there might be an over-representation of complicated patients, including those with a higher risk of switch into mania and rapid cycling? Does the following paragraph from the "Practice guideline for the treatment of patients with bipolar disorder" (Hirschfeld *et al.* 1994) really take into account the hitherto-limited evidence for a sufficient antidepressive efficacy of mood stabilizers?:

> "The addition of an antidepressant medication to the mood stabilizing regimen is likely to be beneficial for the following groups of patients: patients who cannot safely tolerate or are unwilling to tolerate a 4- to 6-week delay before response to the initiation (or dosage adjustment) of a mood-stabilizing medication; patients who have a history of beneficial response to previous treatment with an antidepressant medication; or patients who have not responded to the combination of psychiatric management, a mood stabilizer, and, if indicated, a specific psychotherapy." (Hirschfeld *et al.* 1994, p. 21).

The subsequent paragraph describes the risk of mania under antidepressant treatment and the need to inform the patient about this risk and possible early signs of mania or hypomania. This is, of course, a very important paragraph; but should there not also be, similar to this paragraph, at least one sentence about the risk of suicide and possible chronicity, if the

depression is not treated as soon as possible with a well-established antidepressant?

Most experts′ recommendations and guidelines differentiate between different classes of antidepressants concerning the risk of inducing mania. There seems a broad consensus that SSRIs, and possibly other modern antidepressants, have a much lower risk than the tricyclics, possibly close to that of placebo. If this holds true, is it really acceptable that the treatment recommendations are so restrictive concerning the use of modern antidepressants as mentioned above? It at least seems meaningful, as is recommended in some of the guidelines, that the SSRIs or possibly other modern antidepressants should be the first choice in the treatment of acute bipolar depression. Further studies are needed to demonstrate in a conformative way that monotherapy with mood stabilizers is really as advantageous compared to SSRIs as apparently supposed by some experts in this field.

The recommendation that antidepressants should be used in co-medication with a mood stabilizer, common in most of the recommendations and guideline papers, seems plausible and clinically meaningful. However, as described above, the databases for this recommendation need additional studies. Of greatest importance is the question of when the antidepressant should be withdrawn. In some of the guidelines there is the tendency to withdraw the antidepressant as soon as possible, e.g. after 6–12 weeks (Sachs 1996). This proposal is in contrast to the convention – accepted up to now at least for the treatment of unipolar depression – that a continuation therapy of 6 months, or better 12 months, is necessary to avoid early relapse. Apparently the divergent recommendation for bipolar disorders is again based on an over-consideration of the risk of inducing mania compared to the risk of inducing relapse, and on the other hand on the assumption, which is not at all proven, that a mood stabilizer might be effective enough in the continuation phase to avoid early relapse of depression. A more classical and possibly more effective approach would be to continue the co-medication of a mood stabilizer and an antidepressant for at least 6–12 months. Although this strategy has not been tested sufficiently, at least the available data seem to give the impression that the risk of inducing mania is markedly reduced by this co-medication with lithium.

Following this general argumentation, the recommendations for the treatment of bipolar affective disorders of a German expert group (Walden *et al.* 1999) suggest, as a general rule, antidepressant treatment (preferably with SSRIs or other modern antidepressants) in co-medication with mood stabilizers for the treatment of the acute phase of a bipolar depression, and continuation of this combined treatment for at least 6 months after the remission of the acute depression, followed by another 6 months continuation of the mood stabilizer in monotherapy.

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Chapter twenty

The prognosis of bipolar disorders: course and outcome

Marc L. Bourgeois and Andreas Marneros

FROM THE "TERRIBLE ... INCURABLE FORM OF INSANITY"; OF FALRET'S *FOLIE CIRCULAIRE* TO KRAEPELIN'S "GOOD PROGNOSIS" MANIC-DEPRESSIVE INSANITY

Both Jean-Pierre Falret and Emil Kraepelin based their concept of *folie circulaire* or "manic-depressive insanity" not only on signs and symptoms but also on course and outcome. For Falret, signs and symptoms were not sufficient to characterize a mental disorder. Aetiology was essential but yet to be discovered. He emphasized the relevance of the course and outcome of the disease. In his opinion the *folie circulaire* (see also Chapter 1, by Marneros and Angst) the prognosis of the illness was considered very grave: "sounds desperate ... terrible ... incurable form of insanity".

Kraepelin also placed emphasis on course and outcome in defining mental diseases. Unlike Falret, however, Kraepelin assumed that manic-depressive insanity (see also Chapter 1, by Marneros and Angst) had a good prognosis and did not develop into severe residual states, although he described "asthenic states" (*"Schwächezustände"*) after recovery from the episodes (Kraepelin 1913, p. 1349).

As early as the 5th edition of his *Lehrbuch* (1896), Kraepelin stressed "the decisive shift from the *symptomatic approach* to the *clinical approach* of madness ... the importance of external signs and symptoms gave way to the importance of the conditions of onset, course, and prognosis". In this "clinical approach" the previously defined clinical syndromes (*"Zustandsbilder"*) became obsolete and useless. Therefore, Kraepelin denied most of the clinical interest of symptomatology (all symptoms could be

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 405–436.

seen in every psychiatric condition) and chose as his major criterion the longitudinal approach (course of the illness and prognosis). Different terminal states (*"Endzustände"*) could be foreseen. What defines an illness and lends it unity (evolution and consequences of the process, *"Vorgang"*) is a fundamental concept in German conceptualization of psychopathology (Géraud 1995), following the paradigm of Karl Kahlbaum (1863).

Moreover, mood, for Kraepelin, was not of extraordinary nosological value. Disturbance of psychic functioning, behaviour, thinking, willing and psychomotor activity prevailed in his definition of manic-depressive illness. Conversely, mood disorders can be observed in other mental disorders.

Manic-depressive illness, as opposed to *dementia praecox,* was supposed to have a good prognosis, which was a much more optimistic view than Falret's. In the chapter *"Das manisch-depressive Irresein"* ("Manic-depressive illness") of the 1913 edition of his *Lehrbuch,* Emil Kraepelin reunited "several pathological conditions with certain common traits (*gemeinsame Grundzüge*)". "In spite of numerous external differences, certain fundamental common traits (*gemeinsame Grundzüge*) are regularly identified". "What they have in common is the uniform course and prognosis" (*einheitliche Prognose*). "The acute episodes of manic-depressive insanity ... never lead to severe dementia (*tiefe Verblödung*), even when they almost continuously occupy the patient's entire life".

"Usually, all pathological manifestations completely disappear, but when exceptionally it is not the case, in particular rather mild psychic asthenic states (*'seelische Schwächezustände'*) occur, which are common to all regrouped forms and are unlike the *'dementia process'* (*dementification*) that appears in the course of other disorders" (Chapter 1, *Begriffsbestimmung*).

Chapter 9 addresses the problem of course and evolution (*Verlauf*), on the basis of 899 cases classified by mood "colouring" (*Färbung*). Kraepelin distinguished three clinical categories: depression, mania, mixed states. As the number of episodes increased there was increasing of alternation of *Färbung* and mixing (*Beimischung*).

Kraepelin could not find any regularity governing the course. "Episode type and length as well as intermediary phases are different in each particular case". As opposed to Falret's description of nearly perfect regularity: "the perfectly regular altering of pathological manic and depressive phases, which was what first attracted the alienists, is exceptional". "Duration of episodes is extraordinarily variable (1 to 2 days or even a few hours; usually 6 to 8 months, up to 7, 10, or even 14 years)".

Unlike Falret and Jules Baillarger, who described *clinical subtypes,* Kraepelin was convinced that attempts to classify such subtypes were doomed to fail.

Finally, the impact of stress and life events was almost denied. They could play a role in the very first episodes, but later "manic-depressive

Table 1

Onset of the disorder: kind of onset (*"prodromal"* signs, acuity), age at onset, precipitation
Episodes: type of episode, number, frequency, length, symptoms
Cycle: number, frequency and length
Intervals: length and symptoms, suicidal intentions, stability of symptom constellations, syndrome shifts
Activity of the disorder: the disorder is still clinically active (i.e. new remanifestation)
Inactivity of the disorder: the disorder is no longer active (i.e. no more remanifestations)
Outcome: psychopathological and psychological status stable over some years (i.e. 3 years) (existence of persisting alterations, changes of the personality, handicap of performance, subjective well-being, social and occupational mobility and status, autarky, etc.), suicide, mortality

episodes can be surprisingly independent from external events" (Kraepelin 1913, p. 1370).

In their comprehensive paper on "Natural history of bipolar disorder", Angst and Sellaro (2000) point out that notable contemporary authors disagreed with Kraepelin's Unitarian approach, and their studies of the natural history of affective disorders maintained the distinction between mania, depression and bipolar disorder (Pilcz 1901, Ziehen 1902, Ballet 1903, Wernicke 1900). Their data on the course of bipolar disorder in the 19th and the first half of the 20th century, before the introduction of modern antidepressants and mood stabilizers, are of special value in that they represent the disorder's untreated natural history (Angst and Sellaro 2000).

ONSET, COURSE AND OUTCOME OF BIPOLAR DISORDERS: DEFINITIONS AND TERMS

The course of every mental disorder contains all phenomena and symptoms that are manifested during the whole life of the patient after the onset of illness (Angst 1986a). It is not rare in the literature for the term "course" to be used synonymously with the term "outcome". This equivalence of the terms "course" and "outcome" is not legitimate, because outcome is only one of many elements of course (Marneros *et al.* 1990c, Marneros 1999). The most important features of the course can be found in Table 1. Sometimes "course" and "outcome" are grouped together under the heading "prognosis", but with a very global meaning. Sometimes "good progno-

sis" means few recurrences, and sometimes full remission or recovery (Boland and Keller 1996, Goodwin and Jamison 1990, Marneros *et al.* 1990c, 1991a, Marneros 1999, Zarate and Tohen 1996).

The MacArthur Foundation Research Network on the Psychobiology of Depression recommended some descriptive terms for use in assessing the course and outcome of depression which will also serve for bipolar disorders (Frank *et al.* 1991).

Episode: episodes are defined as consisting of a number of symptoms and lasting longer than some days.

Response and partial remission: A partial remission is a period during which an improvement of sufficient magnitude is observed that the individual is no longer fully symptomatic (i.e. no longer meets syndromal criteria for the disorder) but continues to evidence more than minimal symptoms. Treatment is not a requirement of the definition, partial remission can be spontaneous. A response can be thought of as the point at which a partial remission begins.

Full remission: a full remission is a period during which an improvement of sufficient magnitude is observed that the individual is asymptomatic (i.e. no longer meets syndromal criteria for the disorder and has no more than minimal symptoms). Full remission can be spontaneous or after treatment.

Recovery: this term is used to designate recovery from the episode, not from the illness *per se*. It is defined as full remission lasting for an indefinite period (minimum). Treatment is not always an assumption for recovery.

Relapse: relapse is a return of symptoms satisfying the full syndrome criteria for an episode that occurs during the period of remission, but before recovery.

Recurrence: recurrence is the appearance of the disorder, and thus can occur only during a recovery.

In spite of the obvious advantages of these recommendations, especially for statistical and pharmacological research, they do not cover all aspects of prognosis.

In the following we present the most important elements of course and outcome of bipolar affective disorders. This chapter concerns only bipolar affective, not schizoaffective disorders, which are described in Chapter 5.

Onset

Age at onset

The exact definition of age at onset is difficult, because the age when symptoms first appear is not always identical with the age at first medical

consultation or with the age at first admission to hospital. Symptoms generally appear some time before medical consultation is first sought (Weissman 1988, Egeland *et al.* 1987, Goodwin and Jamison 1990, Marneros *et al.* 1991a). In spite of this discrepancy, bipolar affective patients usually become ill at a younger age than unipolar patients. There is good agreement in the literature that the peak onset occurs in the 20s (between 25 and 30) for bipolar affective disorders and in the late 30s for unipolar affective disorders (Angst 1966, 1980, 1986b,c, Dell'Osso *et al.* 1993, Goodwin and Jamison 1990, Marneros *et al* 1990a,b,d, 1991a, Marneros 1999).

Type of onset

The type of onset of bipolar disorders depends on the initial episode, i.e. whether it is a depressive or a manic episode. An acute onset of depressive symptomatology, in which the symptoms develop from a healthy state to a full-blown disorder within a few days, is rare. Usually the onset of depressive symptomatology is subacute, with signs and symptoms beginning several weeks or months before the full manifestation of the illness. More than 20% of patients have a gradual onset with prodromal signs for anything between several months and some years before the full manifestation (Marneros *et al.* 1991a, Marneros 1999, Eaton *et al.* 1997, Hays 1964, Goodwin and Jamison 1990, Kendell 1968, Marneros *et al.* 1991a, Rennie 1942, Winokur 1976). The Epidemiological Catchment Area Study (Eaton *et al.* 1997) showed that the duration of prodromal signs depends on the groups of symptoms. Usually the average duration of prodromal signs was 1 year, but for dysphoria, as well as for anhedonia, psychomotor disturbances, feelings of guilt and insufficiency, 5 years are described (Eaton *et al.* 1997).

Manic symptomatology is usually acute in onset, over a number of days, although in some cases long-lasting prodromal signs have been observed (Kraepelin 1913, Carlson and Goodwin 1973, Jacobson 1965, Marneros *et al.* 1991a, Post *et al.* 1981, Sclare and Creed 1990).

Precipitants

Kraepelin's observation that the onset of affective episodes appears to be independent of external influences proved only partially correct. Research showed a partial relation of stressful life events and the manifestation of episodes (Goodwin and Jamison 1990, Marneros 1999). Some theories on the pathogenesis of affective disorders assign primary causal relevance to psychosocial environmental events (Paykel and Cooper 1992). It is, however, now generally accepted that psychosocial or physical events contribute more to the timing of an episode than to causing it. Causality is likely to be largely biological and, especially, genetic (Goodwin and Jamison 1990,

Marneros 1999). Precipitating events seemingly play an important role in the onset of the first episodes but not in the later ones (Angst 1987, 1988, Marneros *et al.* 1991a). The frequency of precipitating factors reported in the literature varies considerably, from 25% to 75% (overview in Goodwin and Jamison 1990, Marneros 1999). Many serious studies find no differences in precipitating factors between unipolar and bipolar patients. We found in the Cologne study that approximately 53% of the unipolar and 47% of the bipolar patients have stressful life events at the onset of an episode (the difference is statistically insignificant) (Marneros *et al.* 1990b, 1991a). However, many studies consider only cross-sectional manifestations. A review of all episodes of a long-term course (more than 25 years duration) indicates that only in approximately 13% of all episodes can stressful life events be found in a period of 6 months before onset of the episode (Marneros *et al.* 1991a). It is interesting that the difference between manic and melancholic episodes regarding the frequency of life events in a longitudinal perspective is not significant (Marneros *et al.* 1991a).

The kind of life event (bereavement, changing job, moving house, etc.) seems to be unspecific (Aronson and Shukla 1987). Wehr *et al.* (1985) found that the common denominator in all life events is sleep reduction. Not only depressive episodes but also manic episodes show a correlation between life events and first manifestation (Ambelas and George 1988).

Episodes

Number of episodes

Unipolar and bipolar affective disorders are usually recurrent. Monophasic cases or cases with only one episode are exceptions. Studies reporting low relapse rates have usually had methodological limitations such as short duration of the observation time, consideration only of severe episodes, and lack of knowledge of short intervals (Angst and Sellaro 2000, Marneros 1991a). The majority of unipolar and bipolar patients are polyphasic, which means they have more than three episodes within an illness duration of 20 years. Bipolar patients have significantly more episodes than unipolars (Angst 1966, 1992, Goodwin and Jamison 1990, Marneros *et al.* 1988d,e, 1989e, 1991a, Perris 1966). Some factors seem to have an influence on the number of episodes, e.g. occurrence of life events during the course, long observation time, lower age at onset and, of course, bipolarity (Marneros *et al.* 1991a).

Frequency of episodes and length of cycles

The frequency of episodes in unipolar and bipolar diseases can be estimated by evaluating the number and length of cycles (see Figure 1). A cycle is

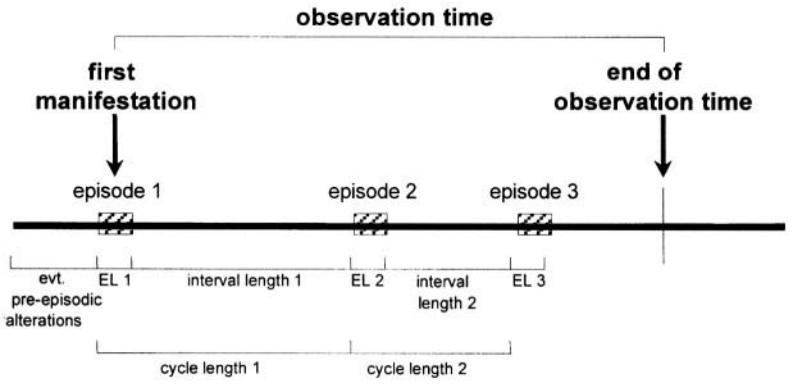

Figure 1 Elements of course (EL = length of episode). From Marneros *et al.* 1991a.

defined as the time from the onset of one episode to the onset of the next (Angst 1986a). A variation of cycle length usually reflects variations in the length of intervals between episodes, because the length of episodes commonly varies only insignificantly (Angst 1986a, Marneros *et al.* 1991a). Since the length of cycles in bipolar diseases is significantly shorter than in unipolar ones, the frequency of remanifestations of episodes in bipolar diseases is higher than in unipolar. Especially the length of the first cycle differs markedly. This means that in bipolar diseases the second episode occurs significantly sooner than in unipolar ones. Subsequent cycles are usually shorter, so that the remanifestation of episodes occurs more frequently in later periods of the course (Angst *et al.* 1973, Angst 1986a, Angst and Sellaro 2000, Marneros *et al.* 1988e, 1991a). In a survival analysis of the Zurich follow-up data (Angst and Preisig 1995a), the differences between cycles 1 and 5 were significant: difficult to interpret. The first cycle was longer and the second cycle shorter than all the others. In conclusion, Angst and Preisig (1995a) found a shortening of cycle length at the beginning of the disorder only; later episodes were persistently recurrent but came at irregular intervals without any systematic deterioration or amelioration, thus confirming the results of Winokur *et al.* (1993, 1994). The same factors that influence the number of episodes can also influence cycle length (Marneros *et al.* 1991a). Some bipolar patients (about 10–20%) and a smaller proportion of unipolars may display the phenomenon of rapid cycling. This phenomenon is characterized at least by four affective episodes per year (APA 1994). The phenomenon of rapid cycling is more frequent in females and usually occurs later in the course of the illness (Calabrese *et al.*, Chapter 4 in this book). This could reflect the impact of certain treatments accelerating the natural course of illness, or may reflect underlying pathophysiological mechanisms (Goodwin and Jamison 1990, Marneros 1999). Patients with rapid cycles are more likely to be unresponsive to prophylactic

lithium treatment than patients with no rapid cycling (Prien 1979, Koukopoulos *et al.* 1983, Marneros 1999, Calabrese *et al.,* Chapter 4 in this book).

Length of episodes

Angst and Sellaro (2000) reviewed the findings of studies on the natural length of episodes which were published prior to the introduction of effective treatments. The data of Mendel (1881), Panse (1924), Wertham (1929), Rennie (1942) and Kinkelin (1954) describe durations of episodes between 2 months and more than a year.

It can be concluded that since the introduction of effective treatment the duration of depressive episodes in both unipolar and bipolar patients exceeds that of manic episodes (Keller 1988, Silverstone and Hunt 1992, Zarate and Tohen 1996). It seems that the duration of an episode is dependent on various factors, of which the most important is the response to the pharmacological treatment. Some studies reported discrepant findings regarding the difference in length between initial episodes (longer) and subsequent episodes (shorter). The duration of an episode also seems to be exclusively dependent on the type of disorder, i.e. unipolar or bipolar (shorter), and not on its position in the course.

In spite of the discrepancies in the literature, it can be said that the duration of a full depressive episode is 2–5 months (Eaton *et al.* 1997, Marneros *et al.* 1991a); a longer duration is not exceptional (Angst and Preisig 1995a,b, Angst and Sellaro 2000, Boland and Keller 1996, Goodwin and Jamison 1990). The duration of manic episodes is on average 2 months (Keller 1988, Silverstone and Hunt 1992, Zarate and Tohen 1996, Marneros *et al.* 1991a).

Bipolar mixed episodes seem to be longer – on average from over more than 5 months to over a year (see Figure 2) (Marneros *et al.* 1991a, 1996a,b, Marneros 1999, Perugi *et al.* 1997, Zarate and Tohen 1996).

Stability of syndromes

We define as stable syndromes in which the same type of episode occurs consistently during a long-term course (more than 25 years). The stability is dependent on the kind of initial episode as well as on the duration of the illness, as shown in Figure 3 (Marneros *et al.* 1991b). Schizodepressive and depressive symptomatology is much more stable than that of manic symptomatology (see Figure 3).

Outcome

In evaluating the outcome of mental disorders we must consider the term "outcome" as problematic. Many studies have demonstrated that, as the

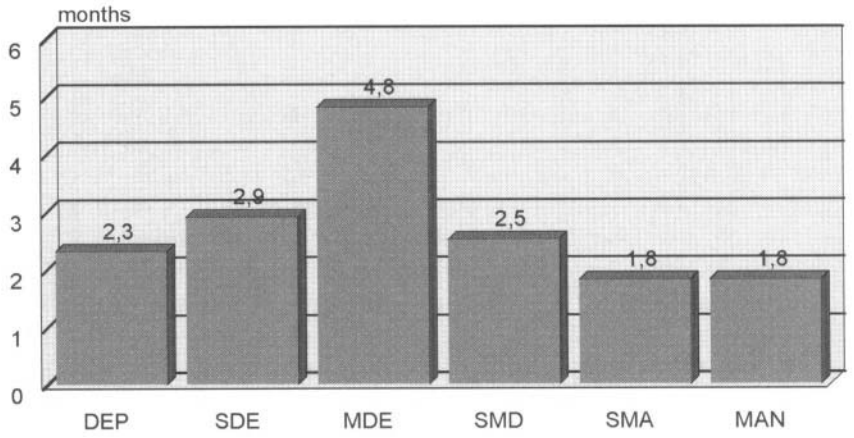

Figure 2 Length of episodes. DEP = depressive; SMD = mixed bipolar schizoaffective; SDE = schizodepressive; SMA = schizomanic; MDE = mixed bipolar affective; MAN = manic. From: Marneros *et al.* 1991a.

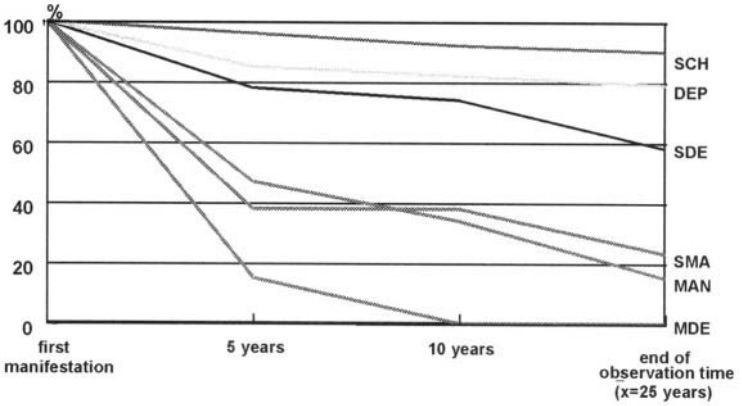

Figure 3 Longitudinal stability. SCH = schizophrenic episode; DEP = depressive episode; SDE = schizodepressive episode; SMA = schizomanic episode; MAN = manic episode; MDE = manic-depressive mixed episode. From: Marneros *et al.* 1991a.

ultimate stage of a mental disorder, "outcome" is seldom a final state without further psychological and interactional mobility. The term "outcome" should therefore be used only as a compromise to describe the psychopathological and social status of a patient after a certain duration of illness. Outcome is not a monolithic phenomenon but has many psychopathological, psychological, interactional and social aspects. All of these aspects can be affected by the illness in different ways and to different degrees. There is a paucity of long-term studies of affective disorders con-

sidering these aspects and applying operational criteria for evaluating the various aspects of outcome (Marneros *et al.* 1989a, 1990c, 1991c).

Kraepelin's assumption that affective psychoses always have a "good" outcome was untrue. Long-term investigations have shown that a significant proportion of patients with affective disorders have an unfavorable outcome (Angst 1987, Marneros and Deister 1990, Marneros and Tsuang 1990, 1991). However, studies investigating the outcome of affective disorders suffer from varying criteria and heterogeneous definitions of "unfavourable outcome". Although the term "chronic depression" is frequently used to indicate affective disorders with an unfavourable outcome, the criteria for it vary widely among studies (Angst 1987). The results reported in the literature, with their wide spectrum of findings regarding the frequency of persistent alterations in affective disorders [between 1% (Winokur and Morrison 1973) and 72% (Berti Ceroni *et al.* 1984)], are based on different definitions; the same broad variety of results could also be shown with the material of the Cologne Study if different definitions were applied (Marneros and Deister 1990). Different definitions yielded results which varied, from 1% of the patients being without a good outcome, a result similar to the findings of Winokur and Morrison (1973), to up to 72%, which is close to the findings of Berti Ceroni *et al.* (1984). Although favourable outcome in affective disorders is not the rule, affective patients had a much more favourable long-term outcome than schizophrenic and to some extent than schizoaffective patients (Marneros *et al.* 1989a, 1991a, Marneros 1999).

In summary, it can be said that the findings regarding long-term outcome of bipolar disorders are very inhomogeneous. Stenstedt (1952), for example, found persistent alterations in 4% of affective disorders. Angst and Preisig (1995a,b), however, found 26%, Kinkelin (1954) 39%, Tsuang *et al* (1979) 36% and Marneros *et al.* (1991a) 33%. Studies focusing on "disability" and disturbances of social adaptation reported that approximately one-third of bipolar patients do not have a "social full remission" (Angst 1987a, Bratfos and Haug 1968, Carlson *et al.* 1974, Cassano and Maggini 1983, Cassano and Savino 1997, Lehmann 1988, Marneros *et al.* 1991a, Marneros and Rohde 1997, Scott 1988, Wittchen and von Zerssen 1988).

Goodwin and Jamison's (1990) conclusion, that in studies of illness lasting more than 12 years approximately 25% of patients with unipolar and bipolar affective disorders have persisting alterations, emphasizes the point.

Phenomenology of persistent alterations in unipolar and bipolar affective disorders

Research on persistent alterations in affective disorders is usually limited to evaluation of the frequency of global types of "chronic depression", whatever that might mean. Modern descriptions of phenomenological aspects of persistent alterations (so-called residual states) in affective but also in schizoaffective and schizophrenic disorders often simply reflect

items, scores and variables of scales and evaluation instruments. However, the operational structure and intentions of such instruments have a limiting or even a negative impact on the phenomenological picture. It is difficult to describe phenomenological constellations of persistent alterations in functional psychotic disorders, mainly because of the high degree of individuality and changeability of patterns of course and elements of phenomenology. In earlier publications we described eight phenomenological constellations of persisting alterations in patients with psychotic disorders (Marneros *et al.* 1991a,c). There are interesting differences between affective, schizoaffective and schizophrenic disorders with regard to the phenomenology of persisting alterations. Only the slight asthenic insufficiency syndrome was found in all three groups investigated.

In affective disorders we found only the *slight asthenic insufficiency syndrome* (21%), the *chronic subdepressive syndrome* (13%) and the *chronic hyperthymic syndrome* (2%). The characteristics of the slight asthenic insufficiency syndrome are: slight reduction of mental energetic potential and, possibly, slight subjectively perceived impairments of concentration capacity, slight mood disturbances, fatigue, no productive psychotic symptoms. Chronic subdepressive syndrome is characterized by chronic subdepressive symptoms (in mood, interest, social interactions, etc.), and no productive psychotic symptomatology. The characteristics of the chronic hyperthymic syndrome are chronic hyperthymic symptoms (euphoria, hyperactivity, etc.), no affective flattening and no productive psychotic symptomatology. The "slight asthenic insufficiency syndromes" were distributed evenly between unipolar and bipolar affective diseases; however, as expected, we found a "chronic subdepressive syndrome" significantly more frequently in the unipolar group and a "chronic hyperthymic syndrome" only in the group of bipolar patients.

Suicidality and mortality

Patients with unipolar and bipolar diseases (affective and schizoaffective also) are far more likely to commit suicide than individuals in any other psychiatric risk group. Suicide in unipolar and bipolar patients is one of the most important problems of medicine in general. The mortality rate for untreated manic-depressive patients is higher than that of most types of heart disease and many types of cancer (Goodwin and Jamison 1990). At least one-fifth of manic-depressive patients die because of suicide. The rates reported in the literature vary from 9% to 60%. It seems that the frequency of suicide does not differ between unipolar and bipolar patients (overviews in Goodwin and Jamison 1990). Much higher than the mortality rate from suicide is the frequency of suicidal ideas and attempted suicide. About 60% of unipolar and bipolar patients have serious suicidal intentions at least once during their illness (Marneros *et al.* 1991a). The suicidal intentions in

bipolar patients are related to depressive episodes. The majority of patients with suicidal intentions in both groups are females (Marneros 1994).

Goodwin and Jamison (1990) pooled 29 studies and 9389 patients (unipolars and bipolars), and found a global mean suicide rate of 18.9%.

Contradictory data thwart the conclusions that suicidal risk is greater for unipolars or for bipolars. It is apparent that the risk for suicidality is higher during mixed or depressive phases than during pure manic phases (Dilsaver *et al.* 1994, Strakowski *et al.* 1996). The risk appears to be greater during the first few years after onset, with rates of completed suicide diminishing over time. There are many more suicides in cases of co-morbidity with substance abuse and alcoholism. Bipolar patients attempt suicide more often than do unipolar depressed patients (Lester 1993). In the Finnish National Study, stressful life events were found in more than 60% of cases in bipolar and unipolar patients, but in bipolar patients the majority of stressful life events are induced by self-damaging behaviours (Isometsa *et al.* 1995).

Recently, several studies have clearly demonstrated that lithium reduces six-fold the rate of suicide among bipolar patients (Tondo *et al.* 1998, Baldessarini *et al.* 1999). A large ongoing European study has forcefully confirmed the anti-suicidal effect of lithium (Müller-Oerlinghausen *et al.* 1994). According to Schou (1998), with lithium, "the number of patients attempting suicide was 6–15 times lower and the number of patients completing suicide was 3–17 times lower when they were on lithium than when they were not. Similar observations have not been reported for prophylactic treatment with other mood stabilizers".

In 1974, Barraclough *et al.,* in their famous 100-patient psychological autopsy, concluded that 20 lives could have been saved by lithium. Goodwin and Jamison (1990) reported only four suicides in a series of 9000 bipolar patients. Coppen *et al.* (1991) found a dramatic reduction of suicidal mortality in a group of unipolar and bipolar patients.

Additionally, lithium has a clearly demonstrated antiviral and immunomodulatory action, especially against herpes simplex, Epstein–Barr, and borna viruses. This could explain the reduction of mortality in bipolar patients, beyond its anti-suicidal and mood-stabilizing effects (Rybakowski 1999).

SELECTED LONG-TERM STUDIES ON BIPOLAR DISORDERS OF THE PAST DECADE

Naturalistic studies (from real-world clinical practice, with patients often presenting with coexisting pathology and uncertain treatment compliance) will now be compared with clinical trials (in academic and tertiary referral settings, with tight patient selection). This leads to the differentiation of effectiveness (real) and efficacy (theoretical) of treatment. Recent follow-up studies assess two distinct domains:

1. Clinical outcome: one can distinguish recurrences of full-blown affective episodes (syndromal), or subthreshold, subclinical psychopathology (subsyndromal), which can, however, be protracted. It seems that most patients are not in a symptom-free state.
2. Functional outcome: it now seems more important to evaluate the psychological, interpersonal, social, and occupational outcome instead of just symptoms, but these two aspects are interdependent.

One should also distinguish the length of follow-up: short-term (1 year); medium-term (5 years); or long-term (one to several decades) (Marneros *et al.* 1991a).

In a recently published book on the clinical course and outcome of bipolar disorders (Goldberg and Harrow 1999), the authors present several of the more recent studies: the Naples study (Maj *et al.* 1989, 1995); the UCLA study (Gitlin *et al.* 1995, Hammen *et al.* 1990, 1995); the Chicago Follow-up study (Goldberg and Harrow 1995); and the NIMH study (Keller *et al.* 1993, Coryell *et al* 1998). Table 2 (Goldberg and Harrow 1999 and Marneros 1999) summarizes some naturalistic outcome studies, showing that many patients have a poor prognosis.

The NIMH Collaborative Depression Study (CDS) (Katz and Klerman 1979, Keller et al. 1986, 1993, Coryell *et al.* 1998)

This long-term follow-up study of 955 inpatients and outpatients from five medical centres (New York–Columbia, Harvard, Iowa, Chicago, Saint Louis) has provided many articles on diverse aspects of affective disorders. For example, it demonstrated that, of 559 unipolar depressed patients, only 12.5% switched to a bipolar disorder over an 11-year period (Akiskal *et al.* 1995).

Of the first 155 subjects (type II patients were excluded; mean age 37 years) with bipolar disorder at the time of entry, 63 were manic, 25 were depressed, and 67 were mixed or rapid cyclers. After a manic index episode, recovery was faster. A longer duration of major depressive disorder predicted a longer delay to recovery, while a greater number of previous major affective episodes was associated with more subsequent relapses.

The course and outcome of bipolar disorder differed significantly, depending on the subject's initial symptoms: manic episode or mixed cycling episode. Recovery rate, rate of chronicity, rate of relapse, etc. were large enough to be of clinical relevance.

More recently, Coryell *et al.* (1998) gave the results of the 15-year follow-up of 113 bipolar patients followed semi-annually for 5 years, then annually for a subsequent 15 years. Two hundred and six patients with bipolar type I (RDC, Spitzer *et al.* 1978) disorder began this study. Twenty-six were known to have died; 113 of the other 180 (62.8%) were included

Table 2 Naturalistic outcome studies in bipolar disorders (Goldberg and Harrow 1999, Marneros 1999)

Investigators	*No.*	*Follow-up period*	*Comment*
Tsuang *et al.* (1979)	100	30 years	24% had poor work functioning; 29% had ratings of "poor" psychiatric symptoms
Dion *et al.* (1988)	67	6 months	67% had poor work functioning; those with multiple admissions had greatest impairment
Harrow *et al.* (1990)	73	1.7 years	34% had very poor global functioning; outcome was poorer for bipolar patients than for unipolar patients
Tohen *et al.* (1990)	75	4 years	28% were unable to work; 19% could not live independently at follow-up
Marneros *et al.* (1991a)	207 (106-affective) (101-schizoaffective)	27 years	Persisting alterations; affective: 36% (unipolar 36.8%/bipolar 33.3%); schizoaffective: 50% (unipolar 44.4%/bipolar 53.6%)
O'Connell *et al.* (1991)	248	1 year	19% had very poor overall outcome
Coryell *et al.* (1993)	29	5 years	31% never achieved sustained recovery ($\geq$ 8 weeks)
Goldberg *et al.* (1995a)	51	4.6 years	22% had poor outcome; 14% had persistent poor functioning at two follow-ups
Angst and Preisig (1995b)	220	27 years	5-year remission: 26% in unipolar/16% in bipolar
Gitlin *et al.* (1995)	62	4.3 years	35% had poor occupational functioning; 61% had only fair or poor social functioning
Strakowski *et al.* (1998)	109	1 year	65% failed to achieve functional recovery; all subjects had no prior hospitalizations
Keck *et al.* (1998)	134	1 year	76% failed to achieve functional recovery; patients with mixed or manic episodes at index did not differ in recovery rates at follow-up

in the study; 56.6% had no major depression, mania or schizoaffective symptoms during the final year; 22.1% had symptoms for less than 52 weeks. Altogether, 20.4% had symptoms of one or more disorders in all the weeks of year 15. This group of 23 patients (20.4%) had a poor long-term outcome (mania or major depressive disorder throughout the 15 years). They were compared to the 90 remaining patients (two outcome groups). Only active alcoholism and low levels of optimum functioning in the preceding 5 years characterized poor-outcome patients. The persistence of depressive symptoms in the first 2 years of follow-up predicted depressive symptoms 15 years later. The early persistence of manic symptoms seemed to have no predictive value. Cycling, particularly rapid cycling, has been associated with greater morbidity in the short term. In this study, however, cycling *per se* did not predict a poor 15-year outcome. Earlier analyses of data from this cohort have shown that, although rapid cycling anticipates greater morbidity in the ensuing year, its prognostic significance may not be more sustained than that. However, although cycling within a given episode may have only temporary prognostic significance, a recurrent tendency to polyphasic episodes appears to indicate an illness with greater long-term morbidity. In this naturalistic study, of course, treatment was uncontrolled. The authors noted that the tertiary-care centrers host more severe and chronic patients. Their conclusions were that the findings suggest the existence of a ″poor outcome, depression prone subtype of bipolar type disorder″ (dominance of depressive symptoms in each year of follow-up). The validity of such a subtype of bipolar type I [corresponding to the ″prevailingly depressed type″ of Angst (1978) and to the ″depression-prone″ characterized by Quitkin *et al.* (1986)] remains to be seen, and the type of antidepressive treatment to be assessed.

Turvey *et al.* (1999a,b), in this same CDS cohort, assessed a sample of 165 bipolar type I patients followed prospectively for up to 15 years (NIMH collaborative study of depression). Episodes beginning with major depression were significantly longer than those beginning with mania for the first three prospectively observed episodes when pooling all episode types (monophasic and polyphasic). Affective polarity at onset for the first prospectively observed episode was associated with polarity at onset for the remaining three episodes. Patients whose first prospectively observed episode began with depression had higher overall morbidity during the entire follow-up period.

Switching polarity within episodes was a strong indicator of poor prognosis. Most episodes among poor prognosis were polyphasic, while most episodes among the comparison group with a better prognosis were monophasic. There was no evidence of shortening of cycle length with increasing duration of follow-up for either the poor prognosis group or the entire sample. The relevance of these findings to the kindling model is discussed.

The Naples Study (Maj *et al.* 1989, 1995, Maj 1999)

The Naples Study included 375 patients, 165 males and 207 females (mean age 41 ± 10.1 years). They received lithium (mean plasma levels 0.5–1.0 mEq/L) and neuroleptics or benzodiazepines or antidepressants. Three hundred and thirty-seven of them were followed up for 5 years (1989–1992).

Two hundred and twenty-eight (67.6%) were still taking lithium after 5 years. One hundred and nine (32.4%) had interrupted this treatment for several reasons: side-effects ($n = 93$), inefficacy ($n = 35$), conviction of being cured ($n = 15$).

Comparing the lithium compliance group to the group having interrupted lithium, there were significantly more patients with psychotic features; 44.9% of patients having interrupted lithium had a recurrence within 5 months.

Maj *et al.* (1989) described the *"late non-response to lithium prophylaxis"*. Of the previous sample, 87 patients (51 male and 36 female, mean age 40.1 years) were followed up for 5 additional years. In total there was 10 years′ follow-up: (1) a first period of 5 years′ lithium compliance without affective episode; (2) a further 5 more years′ follow-up with clinical assessments with the SADS every 2 months. Eight patients were late non-responders (more than two affective episodes). They were compared to the group of 48 stable responders. In the group of late non-responders there were significantly more affective episodes before lithium (8.7 versus 5.7), more hospitalizations (5.5 versus 3.3) and the patients were older (46.5 years versus 39.4 years). Non-significant were the lithium serum level, life events, menopause, etc.

Maj (1999) reaches the following conclusion: regular lithium compliance and adequate dosage reduce morbidity: more than 85% reduction in more than 50% of patients. In malignant forms of bipolar disorders there is a relative inefficacy of treatment (high number of pre-lithium episodes and hospitalizations). Rapid cycling is a predictor of non-response; it is a severe variant of the disorder. There is poor acceptance of treatment by many patients: only 60% were compliant and still attending the clinic in Naples after 5 years.

Maj (1999) summed up the effect of lithium prophylaxis on the long-term course of bipolar disorder:

1. If regularly taken at adequate doses, it competes vigorously with the biological mechanism underlying the disorder and reduces morbidity (85% had a reduction >50%). Fewer than 40% were completely free of episode recurrences.
2. The more virulent the illness, the less effective was lithium. If there had been many pre-lithium episodes and hospitalizations, there was a very

low likelihood of complete suppression. "Rapid cycling may not be a qualitatively distinct subtype of the illness but simply a severe variant".
3. Interruption of lithium is accompanied by a high risk of recurrence.
4. There is a gap between efficacy and effectiveness.
5. The late non-response to lithium may be counteracted by the addition of another mood stabilizer.

The limited effect of lithium prophylaxis on the long-term course of bipolar disorder in ordinary clinical conditions is likely to be the product of at least three factors: poor acceptance of treatment, the virulence of the illness, and the association of treatment interruption with a high risk of relapse.

The Cologne Study (Marneros et al. 1991a)

The Cologne study is a naturalistic study involving 402 patients (published in a German monograph but with extensive English summary). The patients were followed up for, on average, 25 years after the onset of their illness. The diagnoses, made longitudinally, were as follows: schizophrenic disorders (148), schizoaffective disorders (101), affective disorders (106). A distinction was made between "episode" (cross-sectional diagnosis) and "illness" or "disorder" (longitudinal diagnosis). The "episodes" (cross-sectional diagnosis) were classified according to slightly modified DSM-III criteria into schizophrenic, affective (depressive, manic, manic-depressive mixed), schizoaffective (schizodepressive, schizomanic, schizomanic-depressive mixed) and non-characteristic episodes. The disorders were defined longitudinally.

The study distinguished between unipolar and bipolar affective and unipolar and bipolar schizoaffective disorders. With regard to the bipolar disorders, the following were found:

1. A dichotomy of schizoaffective disorders into unipolar and bipolar schizoaffective disorders, analogous to the dichotomy of unipolar and bipolar affective disorders, seems to be justified in that the differences between the former resemble those between the latter.
2. The most important differences between unipolar and bipolar schizoaffective disorders were found in gender, premorbid personality, occupation at onset, social class at onset, number and frequency of episodes and cycles, mean length of cycles, length of intervals and inactivity period.
3. Unipolar affective disorders differ from bipolar affective disorders in the following parameters: age at onset, occupation at onset, premorbid personality, stable heterosexual relationship, family members with schizophrenia, frequency of long-lasting pre-episodic alterations, number and frequency of episodes of illness, mean length of cycles and length of intervals.

4. The most important differences between the unipolar forms of the two disorders (affective and schizoaffective) were in age at first manifestation, which was lower in unipolar schizoaffective than in unipolar affective patients, and in outcome, more favourable in the unipolar affective than in the unipolar schizoaffective disorders.
5. Between the bipolar forms of the two disorders (affective and schizoaffective) only small differences were found, regarding some more favourable social aspects of outcome.
6. Building a voluminous group of bipolar disorders similarities and differences remain stable, as between the unipolar and bipolar forms of affective and schizoaffective disorders separately (Marneros *et al.* 1986–1998).

The Zurich Study of Angst and Preisig (1995a,b)

The Zurich Study of Angst and Preisig investigated the course and outcome of a clinical cohort of unipolar, bipolar and schizoaffective patients prospectively from 1959 to 1985. This paper reports the results of 27 years' prospective study of 186 unipolar depressives and 220 patients with bipolar disorders meeting DSM-III criteria for major depression or mania. Subjects were classified into four diagnostic subgroups, according to polarity and presence or absence of schizophrenic symptoms: unipolar depression, bipolar disorder, unipolar schizoaffective disorder and bipolar schizoaffective disorder. Course parameters were assessed for all samples. As the sequence of subtypes of affective and schizoaffective disorders progresses from unipolar depression, schizodepression, and pure affective bipolar disorder to schizobipolar disorder, a systematic decrease in age of onset and length of episode can be observed. Compared to unipolar disorders (unipolar depression and schizodepressive disorder), bipolar (bipolar and schizobipolar) disorders showed more periodicity, characterized by a greater number of total episodes, more episodes per year, but with shorter episodes and cycles. Despite the lower age of onset among schizoaffective subjects than for pure affective disorders, the only difference in course between the two groups was a greater frequency in episodes requiring hospitalization among schizoaffectives.

At the last follow-up in 1985, 53% of the patients had died. Eleven per cent of the sample (17% of all deaths) had committed suicide. The risk of suicide was associated with clinical severity and onset prior to the age of 60. However, there was no difference in suicide rates according to gender or diagnostic subgroup. Late onset of affective illness was associated with chronicity, which occurred in 10–19% of cases. Recovery was more frequent among unipolar than among bipolar patients. The 5-year remission rates (26% in unipolars, 16% in bipolars) were independent of the number of episodes.

The Chicago Follow-up study (Goldberg and Harrow 1995, 1999)

This is a prospective long-term assessment of adults hospitalized in the 1970s and 1980s for acute bipolar, unipolar depressive or psychotic episodes. Patients were followed up at 2-year intervals.

Seventy-three bipolars and 66 unipolars (RDC and DSM-III criteria) were re-evaluated 1.7 years after index hospitalization, and again 4.6 years and 8 years after they entered the research programme. Mean age at entry was 25.5 years. Psychosocial functioning was evaluated by LKP, an eight-point scale for global index of overall functioning.

During a 4.5-year period three major groupings of bipolar patients can be described:

1. Good overall functioning or complete remission (15–20%). Many appear stabilized on lithium in the first year.
2. Poor outcome at multiple follow-up assessments (10–15%): many recurrent affective episodes, frequent rehospitalizations, and very poor work performance.
3. Heterogeneous patient population with a variable outcome (50–60%): ″stable pattern of moderately impaired functioning″ or ″subsyndromal affective symptoms and occasional rehospitalization″.

Outcome appeared less favourable for bipolar manic patients than for unipolar patients. There was no gender difference. Eventually, over time, there developed a capacity for resilience or adaptability in coping. This reveals improved adaptation to the illness and a better coping mechanism.

Residual symptoms between episodes are common in many bipolar patients (Keller *et al.* 1992). Moreover, ″fewer than half of bipolar patients were able to maintain adequate role performance … fewer bipolar patients were able to work at least half of the time in the year preceding the first follow-up″. There is a strong association between affective relapse and poor overall outcome in the bipolar sample but not in the unipolar sample.

The UCLA Study (Gitlin, Hammen *et al.* 1995)

A cohort of 160 bipolar I (DSM-IV) patients were included during a 6-year period [mean follow-up 4.3 years; mean age 37 years; 18% married; 82% single or divorced; mean age at onset 24 years; mean number of past manic episodes 5.5 (SD = 4), of past depressive episodes 4.3 (SD = 3.7)]. The treatment was uncontrolled (mostly lithium; a small number of patients were treated with carbamazepine or valproate). Symptom assessment used a simple five-point scale from 0 to 4 (no symptoms, mild symptoms, moderate symptoms, marked symptoms, severe symptoms). Number of episodes and measure of cumulative symptoms (Average Mood Symptom Scale) were assessed, as was psychosocial status, on a four-point scale [from 4 (full,

stable employment, normal social functioning, supportive family relationship) to 1 (unemployment, complete social withdrawal, no family contact)].

The basic outcome in the 5th year of follow-up was as follows: 73% had had at least one full-blown manic-depressive episode (37% during the first year). The majority had had multiple episodes. The psychosocial ratings demonstrated considerable dysfunction. Occupational outcome was good for 28% and poor for 35%.

Average mood symptom scores were more highly correlated with poor psychosocial outcome than were numbers of episodes. "Cumulative psychopathology may more accurately represent the destructive process by which bipolar disorder leads to poor psychosocial function." Syndromal outcome predicts psychosocial dysfunction. Psychosocial functioning independently predicted syndromal relapse.

Life events and relapse

An interesting aspect of this study dealt with stress and life events (Hammen *et al.* 1997). Previously, Ellicott *et al.* (1990) had found high levels of life stress, with a risk of relapse 4.5 times higher than in patients without stress.

A group of patients having had more than 12 episodes showed a greater number of major events during the 6 months prior to relapse. Thus, even after 12 episodes, high stress conditions still predicted greater risk for relapse. In contrast to Kraepelin's emphasis on the independence of external factors, and in spite of Post's kindling (and sensitization) theory, severe stressors increased the risk for stress sensitivity, regardless of the number of episodes. There is a continuous circle: episodes lead to poor functioning, which in turn leads to further episodes. The greater association of stressors and relapse risk for patients with many prior episodes held true only for the effect of severe, not minor, stressors. Severe stressors are a significant risk factor for relapse in bipolar patients regardless of the number of episodes.

Some personality traits (e.g. cluster B traits) may increase the likelihood of particular types of psychosocial stressors. More than 60% of bipolar patients' stresses were partly or entirely the result of their own behaviours or characteristics (Hammen 1995). Personality variables predict both relapse and stress sensitivity. Bipolar individuals who are introverted and obsessional are more likely to relapse, with less access to the type of social network that might buffer the negative effect of stress.

Conclusions

1. Even in treated bipolars, relapses and/or subsyndromal symptoms are common.

2. Cumulative affective morbidity (length of episodes and nature of subsyndromal symptoms) predicts psychosocial outcome (importance of chronic low-level symptoms in predicting functional outcome), hence the importance of vigorously treating mild symptoms. More than half of the bipolar patients maintained on low serum lithium level (0.4–0.6 mEq/L) had subsyndromal affective symptoms and a four-fold risk of developing a full major affective relapse.
3. There is a complex relationship between psychosocial factors and syndromal outcome. One must combine pharmacological with psychosocial intervention to reduce symptoms and syndromes.
4. There are now several types of psychosocial interventions of proven efficacy: marital and family therapy, cognitive–behavioural therapy, interpersonal therapy (IPT), treatments to reduce highly expressed emotions, etc. Finally, it is essential for the patient to retain employment.

Other recent studies

Retrospective studies on outcome (Bordeaux, 1992)

Two retrospective studies of the first author's group (patients recruited from a primary and tertiary centre, Bordeaux) provide less pessimistic views.

1. A first group of 32 patients (mean age 46 years), who were hospitalized in our department in 1981 for a manic episode (retrospective diagnosis with DSM-III-R criteria), half of them with psychotic features, was reassessed 10 years later. Fifty per cent had been rehospitalized at least once and 31% more than three times; 54.8% were still receiving neuroleptics, 65.6% a mood stabilizer, etc.: 40.6% were unable to work. For 45%, social and occupational outcome was globally satisfactory. None of the factors examined (number of previous episodes, familial history, type of first episode, psychotic symptoms) was predictive.
2. In the second sample, 54 bipolar patients were admitted in 1986 to the same department with a manic episode (DSM-III-R retrospective diagnosis; 62% were psychotic). They were reassessed 6 years later (mean age 40.6 years). Seven subjects had died (one had committed suicide), and three had dropped out. Seventeen per cent had had no recurrence, 34% one to three recurrences, and 49% more than four recurrences; 74% were taking mood stabilizers, and 57% at least one neuroleptic; 57% were living with a partner and social and occupational outcomes were satisfactory in 54% of cases, characterized by less than three recurrences and no suicide attempt. The prognosis was better in the "monopolar manic type" (recurrence of only manic episodes).

   Finally, in the long term (more than 6–10 years), the illness could be stabilized and functional outcome improved.

Benazzi (1997) – Castiglione, Italy

Two hundred and three consecutive mood disorder outpatients (private practice) were observed during a follow-up of 3–6 months. Fifty-one per cent were unipolar, 45% were bipolar II and 4% were bipolar I patients. Compared to unipolar patients, bipolar II patients had a 3 times greater risk of switching: 17.3% versus 5.8%. Bipolar II patients had a lower age at onset and a higher frequency of atypical features than unipolar patients. Both unipolar and bipolar "switchers" had early age at onset and frequent atypical features, suggesting that these factors might increase the risk of switching in unipolar depression (in fact, some are bipolar disorders due to antidepressants, "bipolar type III").

Perugi et al. *(1998) – Pisa, Italy*

One hundred and fifty-five manic patients (DSM IIIR) were assessed. Thirty per cent had a chronic course arising from a hyperthymic temperament and recurrent mania, with a deteriorating pattern: constant euphoria, grandiose delusion, relatively low rates of sleep disturbance, psychomotor agitation, and hypersexuality. Deteriorative outcome was associated with gradual disappearance of acute mania with an increase in megalomanic delusions, alienation from loved ones, and decreased likelihood of medical and psychiatric care.

Amsterdam et al. *(1998) – Philadelphia*

As many as 45% of patients with major depression also meet DSM-IV criteria for bipolar II disorder. In a sample of 839 patients treated with fluoxetine (short- and long-term trials), 89 bipolar type II patients (mean age 41 ± 11 years) were compared to 89 age- and gender-matched unipolar patients and 661 unmatched unipolar patients (mean age 39 ± 11 years). The remitted patients were randomly assigned to double-blind treatment (five groups: fluoxetine 20 mg daily for different durations of treatment, after which fluoxetine was replaced by placebo). Antidepressant efficacy was similar for unipolars and bipolars in short-term therapy. Discontinuation for lack of efficacy was less frequent in bipolar type II (5%) than in unipolar (12%) patients (n.s.).

Conclusion: fluoxetine may be a safe and effective antidepressant monotherapy for the short-term treatment of bipolar type II depression and may also be effective in relapse prevention in patients with bipolar type II disorder.

Kessling et al. *(1999) – Copenhagen, Denmark*

This was a non-clinical study from a case register including all hospital admissions with primary affective disorder in Denmark during 1971–1993.

In all, 12 350 first-admission patients were discharged with a diagnosis of affective disorder, depressive or manic circular type. The rate of recurrence increased with the number of previous episodes, in both unipolar and bipolar disorders. Initially, the two types of disorders had different courses, but later the rate of recurrence was the same for both. The course of severe unipolar and bipolar disorder seems to be progressive in nature, despite the effect of treatment.

CONCLUSION

Bipolar type I and type II disorders have a worse long-term prognosis than does unipolar disorder. In spite of the better knowledge of this psychopathology and, above all, in spite of the many psychopharmacological agents now available, bipolar patients are still very much handicapped. Lithium remains the standard of care for this condition. Unfortunately, its prophylactic effects were, in the first controlled trials in the 1970s, estimated at more than 80%. This figure has been lowered to less than 50%. There is an exception for suicide prophylaxis; it has been clearly demonstrated in several studies that the risk of suicide, as well as premature mortality (mostly due to cardiovascular diseases), is reduced to the rate in the general population.

Goodwin (1999) in his foreword to Goldberg and Harrow's book (1999) proposes several explanations for this apparent decline in the prophylactic effect of lithium:

1. Differences between studies in the community and controlled studies in academic settings.
2. The diagnostic practices with a reduction in schizophrenia and an increase in bipolar disorders, including patients who would have previously received a diagnosis of schizophrenia, having certainly more psychotic features and being more disturbed.
3. The importance of co-morbidity, especially for drug and alcohol abuse, in particular among young patients.
4. The importance of personality disorder (axis II).
5. Cultural changes, with more mobility (divorce multiplied by 3, geographical instability multiplied by 2, stressful events, lack of support, etc.).
6. Prescription of antidepressants, which aggravate and complicate the clinical features and course.
7. Finally, a hypothetic cross-generational shift to more malignant forms of illness and a genetic mechanism of unstable DNA.

Nevertheless, long-term follow-up studies (running for more than a decade) could show a less pessimistic view. Furthermore, paradoxically, might we

not have used too many drugs, especially antidepressants, adding pharmacological instability to the patient's chaotic instability? Could it be that the length of hospital stay, which is now very short, due to increasingly stringent regulations, provides insufficient stabilization, with a revolving-door syndrome?

Many psychiatrists in private practice have the feeling that a good number of their patients are doing well. Are these patients ignored by research, and do they remain unknown at the academic centres? Should we reconsider more intensive psychotherapy and psychosocial measures especially designed for bipolar patients; 20–30 sessions after discharge are certainly not enough for very sick patients. Regular sessions for a much longer time would probably help to stabilize and reassure them and increase drug compliance.

Recently, Post (1998) pleaded for more research conducted with new pharmacological agents and drug associations:

"The problem of refractory bipolar illness deserves special recognition, since an increasing percentage of bipolar patients are now shown consistently to be less than adequately responsive to lithium carbonate – the only approved agent for the long-term prevention of the illness. Response-rate failures in many systematic and community samples are 70–80% over 2–3 years' follow-up, despite allowance of adjunctive antidepressant and antimanic augmentation strategies."

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Chapter twenty-one

The costs of treatment of bipolar disorder

Paul E. Keck, Susan L. McElroy, Lesley M. Arnold, Naakesh A. Dewan and Jerry A. Bennett

BIPOLAR DISORDER: A GLOBAL PUBLIC HEALTH PROBLEM

Bipolar disorder was the sixth leading cause of disability worldwide in 1990, accounting for 14.1 million total years of disability (Jenkins 1997). Unfortunately, according to projections from *The Global Burden of Disease* report (Jenkins 1997), the global burden of bipolar disorder and other major psychiatric disorders (schizophrenia, major depression, alcohol abuse and dependence, and obsessive–compulsive disorder) will increase by 10.5–15% over the next 20 years (Murray and Lopez 1997).

A number of factors contribute to the enormous costs of disability from bipolar disorder. First, bipolar disorder is common and, with an average early age of onset, is frequently a lifelong illness (Weissman *et al.* 1996, Kessler *et al.* 1994, Fogarty *et al.* 1994, Goodwin and Jamison 1990). For example, estimates from the Cross-National Collaborative Group epidemiological study indicated that the lifetime prevalence of bipolar disorder ranged from 0.3% (Taiwan) to 1.5% (New Zealand) (Weissman *et al.* 1996). The results of this study also replicated previous findings of an early age of onset of the illness (i.e. late adolescence and early 20s) and equal sex distribution (Kessler *et al.* 1994, Fogarty *et al.* 1994, Goodwin and Jamison 1990). In addition to being common, bipolar disorder is a recurrent illness; 80–90% of patients with an index manic episode will have subsequent affective episodes (Goodwin and Jamison 1990, Winokur *et al.* 1994). Untreated, the natural course of the illness is towards more frequent episodes with shorter intervals of mental health (Goodwin and Jamison 1990).

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 437–448.

A third factor contributing to high rates of disability is the lag of functional recovery from an affective episode behind symptomatic recovery. Many weeks and months may separate remission of symptoms and recovery of premorbid functional status (Dion *et al.* 1988, Keck *et al.* 1998a, Strakowski *et al.* 1998). In fact, many patients do not reach full functional recovery and recurrent affective episodes may lead to progressive deterioration in functioning between episodes (Coryell *et al.* 1993, Gillian *et al.* 1995, Prien and Gelenberg 1989, Solomon *et al.* 1995). Thus, disability from bipolar disorder is not simply limited to discrete affective episodes. For example, recent studies provided data regarding the impact of bipolar disorder on vocational functioning (Kessler and Frank 1997) and marital stability (Kessler *et al.* 1998). Drawing upon data from the United States National Comorbidity Survey (NCS), Kessler and Frank estimated that bipolar disorder (mania) accounted for 12 work loss days per month per 100 workers, and a 26% greater likelihood of work cut-back days compared with people without bipolar disorder (Kessler and Frank 1997). Data from the NCS also indicated that the risk of divorce was highest for bipolar disorder among all disorders analysed (major depression, dysthymia, anxiety, substance use and conduct disorders) (Kessler *et al.* 1998). Specifically, men with bipolar disorder were 3.3 times more likely than someone in the general population to have their marriage end in divorce, and women were 4.8 times as likely. Clearly, by these estimates, the personal, social and economic costs of bipolar disorder are staggering.

THE ECONOMIC COST OF BIPOLAR DISORDER

The cost of bipolar disorder in human suffering is incalculable. However, economic cost estimates at least provide a means of quantifying the impact of this illness and a means of demonstrating the benefits of effective treatment.

Recently, three studies have attempted to assess the economic impact of bipolar disorder in the US (Greenberg *et al.* 1993, Rice and Miller 1995, Wyatt and Henter 1995). In general, costs, in cost-of-illness studies, have typically been defined as core costs resulting directly from the illness and other related costs, including non-health costs of the illness (Rice 1994). Within the core and related cost categories there are direct costs (requiring expenditure of payments) and indirect costs (lost resources) (Rice 1994). Examples of direct costs include funds spent for hospital and nursing-home stays, physician and other professional services, medicines and equipment. Indirect costs include morbidity (e.g. disability) and mortality costs. Mortality costs include diminished and lost productivity.

In the first study to examine the economic cost of bipolar disorder, Greenberg *et al.* (1993) provided estimates of the morbidity costs of the

illness. In their analysis, patients with bipolar disorder in treatment were estimated to have lost approximately 152 million cumulative days from work, and untreated patients an additional 137 million days in 1990. Morbidity costs based on diminished productivity from affective symptoms from bipolar disorder or major depression were $6.5 billion for the male workforce and $9.0 billion for the female workforce.

In the second economic analysis, Rice and Miller calculated the economic burden of affective disorders as a whole in the US in 1985 and 1990 (Rice and Miller 1995). In 1985, affective disorders were estimated to cost the US economy $20.8 billion, rising to $30.4 billion in 1990 and accounting for approximately 21% of the costs of all psychiatric illnesses. Of the total cost in 1985, direct treatment costs comprised 58.4%, morbidity costs 8.1%, mortality costs 28.9%, and other related costs 4.6%. For patients with bipolar disorder specifically, impairment was highest in individuals aged 18–24 years. Morbidity costs (in 1985 dollars) were estimated at $137 million for people with bipolar disorder, 18–24 years old; $802 million 25–34 years old; $206 million 36–54 years old; and $18 million 55–64 years old. The authors concluded that "substantial potential cost savings to society could be gained by timely and appropriate treatment interventions to patients suffering from affective disorders" (p. 42).

In the third and most detailed analysis of the economic impact of bipolar disorder in particular, Wyatt and Henter (1995) estimated that the cost of this illness in the US in 1991 was $45 billion. Of the $45 billion total, $7 billion was expended on core costs which included the direct costs of inpatient and outpatient care and other related costs (see Table 1). Indirect costs of $38 billion were substantial, the greatest component of which was lost productivity of wage-earners and homemakers, together totalling $20 billion (Table 1). It is noteworthy that the cost of treatment totalled $6.6 billion, which represented just 14% of the total cost of illness. In contrast, morbidity and mortality costs of bipolar disorder were 5.7 times higher than treatment costs and accounted for 83% of the economic burden of this illness. Thus, the overall cost of treatment of bipolar disorder is only a small portion of its total economic cost and is greatly outweighed by the morbidity and mortality costs of the illness itself.

COST OF TREATMENT OF BIPOLAR DISORDER

Several recent studies have examined health service utilization and costs of care of patients with bipolar disorder in community and private settings (Perlick *et al.* 1999, McFarland *et al.* 1996, Johnson and McFarland 1996, Gabbard *et al.* 1997). Perlick *et al.* (1999) attempted to identify risk factors predictive of rehospitalization in 100 patients with bipolar I or II disorder or schizoaffective disorder, manic type diagnosed by Research Diagnostic

Table 1 Estimated economic cost of bipolar disorder in the United States in 1991

Core costs		*Amount ($million)*
Direct	Total inpatient care	2350
	Total outpatient care	300
	Total residential care	2980
	Medicines	130
	Substance abuse	720
	Shelters	80
		6560
Indirect	Lost productivity	
	Wage-earners	17570
Morbidity	Homemakers	3150
	Institutions	2860
	Family	6220
Mortality	Suicide	7840
		37640
	Total Cost	44200
Other related costs		
Direct	Total crime	2260
	Suicide	190
	Research training	50
	Transfer costs	−1300
		1200
	Total Illness	45400

*Adapted with permission from Wyatt and Henter 1995.

Criteria (RDC) (Spitzer *et al.* 1978) and followed for 15 months after index hospitalization. Patients were assessed using the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (SADS-L) (Endicott and Spitzer 1978) and an expanded version of the Brief Psychiatric Rating Scale (BPRS) (Lukoff *et al.* 1986). The results of a Cox regression analysis of time to rehospitalization revealed that older patients and those with a predominance of manic symptoms at index episode had a significantly greater probability of not being rehospitalized during the follow-up period. In contrast, the presence of neurovegetative symptoms of depression and a greater number of previous hospitalizations predicted rehospitalization. Overall, 44% of patients required rehospitalization over the subsequent 15 months after discharge. In this study it was unclear whether neurovegetative symptoms were associated diagnostically with bipolar depression, mixed mania or both. Since inpatient care contributes a substantial component to the cost of treatment of bipolar disorder, the predictive value of these factors

is potentially economically as well as clinically significant. These preliminary findings require further replication.

McFarland *et al.* (1996) examined the enrolment duration, health service use, and costs of care for patients with bipolar disorder and schizophrenia compared with an age- and sex-matched control group of patients with and without diabetes mellitus in a health maintenance organization (HMO). During a 4-year follow-up period there was no significant difference among the three groups in duration of HMO enrollment, suggesting that, at least in this HMO cohort, there was no evidence of early termination of HMO members with bipolar disorder or schizophrenia. However, psychiatric care of these patients also relied heavily upon the resources of community mental health services in addition to those provided by the HMO. Estimated (1990) treatment costs for the combined group of patients with schizophrenia and bipolar disorder were $380/month ($4560/year) compared with $149/month ($1788/year) for pharmacy controls. Costs for patients with bipolar disorder were not presented separately.

In a second study from the same HMO database, Johnson and McFarland (1996) examined the use and discontinuation (treatment adherence or compliance) of lithium among 1594 individuals who received prescriptions for this agent in a 6-year longitudinal cohort study. Not surprisingly, 75% of patients receiving lithium had a diagnosis of bipolar disorder. The administration of concurrent psychotropic agents in this group of patients was widespread: 54% received tricyclic antidepressants; 41% antipsychotics; 39% anxiolytics; 18% anticonvulsants; and 14% thyroid medications. The most striking findings of this survey concerned the adherence to lithium maintenance treatment. Among patients with bipolar disorder the median continuous use of lithium was only 65 days (95% CI, 46–128 days). This was in contrast to patients prescribed phenytoin for epilepsy whose median period of continuous use was 284 days (95% CI, 235–335 days). The predominant pattern of lithium use was of multiple periods of short continuous use rather than few periods of long continuous use. During periods of lithium use, patients had significantly more mental health visits per month but significantly less risk of psychiatric hospitalization compared with periods of non-use. Furthermore, patients with a pattern of interrupted multiple-period short continuous use had a relative risk of emergency psychiatric evaluation and of psychiatric hospitalization of 2.5 compared with patients with long continuous use. Since the costs of psychiatric hospitalization constitute the major component of treatment costs for bipolar disorder, the economic and clinical impact of lithium non-adherence in this study was likely to be substantial.

There are virtually no data regarding the economic impact of specific forms of psychotherapy on bipolar disorder. Nevertheless, Gabbard *et al.* (1997) suggested that psychotherapy should have a beneficial impact on a variety of costs associated with this illness. With the advent of operationa-

lized forms of psychtherapy (Basco and Rush 1996, Bauer and McBride 1996, Frank *et al.* 1997), this assumption can be tested in future research.

PHARMACOECONOMIC STUDIES IN BIPOLAR DISORDER

A number of studies have attempted to estimate the cost savings specifically associated with pharmacological treatments of bipolar disorder (Reifman and Wyatt 1980, McGreadie 1989, Peselow and Fieve 1987, Frye *et al.* 1996, Sajatovic *et al.* 1997, Keck *et al.* 1996a, Steffens and Krishnan 1997, Hirschfeld *et al.* 1999, Goldberg *et al.* 1998, Nelson 1987, Mather *et al.* 1999). Three studies estimated the cost savings attributable to the introduction of lithium for patients with bipolar disorder (Reifmann and Wyatt 1980, McCreadie 1989, Peselow and Fieve 1987). Reifman and Wyatt (1980) estimated the cost of care for patients with bipolar disorder during a single year (1965) before lithium was available in the US. They then compared these estimates with similar calculations during a single year (1969) after lithium became available. Finally, these cost savings were then extrapolated over the subsequent decade when lithium was the first-line pharmacological treatment for bipolar disorder. A number of assumptions and exclusions were incorporated in the calculations of cost savings from lithium. These assumptions included: that 40% of all patients with bipolar disorder would not respond to or tolerate lithium; that no patients with bipolar disorder received lithium before 1969; that the mean annual income of patients with bipolar disorder would not be significantly different from the mean annual income in the US; and that the same number of patients required treatment in 1969 as in 1965. Excluded from potential cost savings calculations were lithium's potential impact on public assistance costs; the value of productivity from homemakers; the cost of treatment in non-hospital settings, particularly private and community mental health outpatient service costs; and the potential gain in family productivity associated with improvement in subsyndromal symptoms from lithium. In total, these assumptions and exclusions yield a conservative estimate to the cost savings from lithium. With estimated gains in productivity from lithium treatment of $1.28 billion (1980 dollars) and cost savings of $2.88 billion, this study yielded an overall cost savings from lithium of approximately $4 billion in the 10 years following its introduction.

In the second study of the potential cost savings from lithium in bipolar disorder, McCreadie (1989) compared the average hospital length-of-stay for patients with bipolar disorder in southwest Scotland before and after the introduction of lithium. The average length-of-stay fell from 25 days/year before lithium to 11 days/year after. By assigning a bed day cost of £41.4 (1986), McCreadie calculated that the reduction in duration of hospitalization of 14 days/year per patient from lithium yielded a cost

Table 2 Studies of estimated cost savings per patient from pharmacological treatment of bipolar disorder

Study	*Medication*	*Cost savings* per patient per year*	*Treatment setting*
McCreadie (1989)	Lithium	$575	Inpatient
Peselow and Fieve (1987)	Lithium	$1735	Inpatient and outpatient
Frye *et al.* (1996)	Divalproex	$8540	Inpatient
	Lithium and carbamazepine	$6783	

*Calculations not adjusted for inflation over time.

savings of approximately £23 million (1986) for the 40 000 patients receiving the drug in the United Kingdom (Table 2).

Peselow and Fieve (1987) also estimated the cost savings from lithium by examining pre- and post-marketing data. For 32 patients with bipolar I disorder followed at their clinic, the number of affective episodes requiring hospitalizations in the 3-year period before lithium was 45, compared with 13 in the 3-year period after. Similarly, affective episodes requiring outpatient intervention dropped form 72 to 39. By assuming that the average length of stay for an affective episode averaged 20 days (*circa* early 1970s) at a cost of $250/day, the annual cost savings per patient from lithium was estimated as $1435 (1971 dollars) (Table 2).

Five studies have compared cost savings from treatment with different mood-stabilizing medications (i.e. lithium, valproate or carbamazepine) (Frye *et al.* 1996, Sajatovic *et al.* 1997, Keck *et al.* 1996a, Steffens and Krishnan 1997, Hirschfeld *et al.* 1999). The first comparative study, by Frye *et al.* (1996), was a survey of hospital length-of-stay of bipolar patients with manic or mixed episodes according to primary mood-stabilizing agent at their hospital. This was a naturalistic treatment study; thus, patients received antipsychotics and benzodiazepines in addition to a primary mood-stabilizer. The four mood-stabilizer treatment groups consisted of patients who received lithium, divalproex, carbamazepine, or combined lithium and carbamazepine. All mood-stabilizers were administered using gradual titration to therapeutic serum concentrations. The mean length-of-stay for patients treated with divalproex (10 ± 2 days) or combined lithium and carbamazepine (12 + 2 days) was approximately 40% shorter compared with patients treated with lithium (18 ± 3 days). The potential cost savings from divalproex were $8540/patient and were $6783/patient from the combination of lithium and carbamazepine, based on reductions in length of

stay (Keck *et al.* 1996b). As anticipated from other data regarding the component costs of treatment of bipolar disorder (Rice and Miller 1995, Wyatt and Henter 1995), the estimates of potential cost savings from divalproex and the combination of lithium and carbamazepine reflect the savings associated with shortened periods of hospitalization which are substantially higher than the costs of medications.

Sajatovic *et al.* (1997) also examined potential treatment cost differences among mood-stabilizers and their impact on hospital length-of-stay. Patients ($n = 96$) with a discharge diagnosis of bipolar disorder, mania were retrospectively divided into four treatment groups: lithium monotherapy, anticonvulsant (e.g. carbamazepine, valproate, clonazepam) monotherapy, combinations of mood-stabilizers, and no mood-stabilizers. Patients receiving multiple mood-stabilizers had significantly longer mean lengths-of-stay (30 ± 20 days) compared with patients receiving lithium (20 ± 14 days), an anticonvulsant (17 ± 9 days), or no mood-stabilizer (17 ± 14 days). As in the study of Frye *et al.* (1996), there were no significant differences among the four treatment groups in use and dose of concomitant antipsychotics and benzodiazepines. The significantly longer length-of-stay for patients on multiple mood-stabilizers may have been due to a greater degree of treatment-refractoriness in this group.

Two studies utilized decision analytic techniques to estimate the cost of treating patients with bipolar I disorder with different mood-stabilizing medications (Keck *et al.* 1996a, Steffens and Krishnan 1997). Keck *et al.* (1996a) estimated the cost of treatment with lithium or divalproex acutely and prophylactically for 1 year beginning with an index hospitalization for a manic or mixed episode or a recent course of rapid cycling. Decision analysis was chosen to estimate treatment costs because of a lack of health-economic data from patients prospectively treated with these agents over time (Basskin 1997). Data for the model were obtained from published studies, the University of Cincinnati Mania Project, (Keck *et al.* 1995, 1998a, Strakowski *et al.* 1998, McElroy *et al.* 1995) and a consensus panel of experts to estimate costs according to initial presentation (i.e. manic, mixed, or rapid cycling). Divalproex was initially administered via oral loading (20 mg/kg per day) (Keck *et al.* 1993) and this was reflected in the length-of-stay data from the University of Cincinnati Mania Project. Estimated overall costs of treatment according to this model are displayed in Table 2. These estimates suggested that, in the overall treatment of patients with bipolar I disorder, initial treatment with divalproex was associated with 9% lower costs than those with lithium. There were differences in cost savings according to clinical features, however. Cost savings were greatest for lithium in patients with classic mania ($1713/patient), and for divalproex in patients with mixed mania ($7184/patient) and rapid cycling ($6286/patient).

In the second decision analytic study, Steffens and Krishnan (1997) based their assumptions on factors influencing clinical decision-making (e.g. effectiveness, tolerability, and overall treatment cost) and broadened their consideration of medications to include lithium, valproate, carbamazepine, clonazepam, antipsychotics and electroconvulsive therapy (ECT). Based on estimates of how well each of these medications compared on the relevant factors influencing clinical decisions, three agents – lithium, valproate, and carbamazepine – emerged as the leading treatment options. Among these three, tolerability advantages led to choices of valproate over lithium and carbamazepine. For lithium to emerge as the leading choice, sensitivity analysis suggested that its efficacy should be better than with valproate, or its tolerability a less important consideration in clinical decision-making

Recently, data from the first prospective, randomized, naturalistic treatment study comparing clinical, quality-of-life, and medical cost outcomes in patients with bipolar I disorder were reported (Hirschfeld *et al.* 1999). In this study, 221 patients requiring hospitalization for an acute manic or mixed episode were randomly assigned to treatment with lithium or divalproex as the primary antimanic mood-stabilizer along with usual psychiatric care (including naturalistic use of antipsychotics and benzodiazepines). Of these 221 patients, 201 were followed for 1 year. Assessments were made at hospital discharge and after 1, 3, 6, 9 and 12 months and included ratings of manic and depressive symptom severity, quality of life and days disabled. In addition, health service utilization data were collected independently by monthly telephone interviews and medical record ascertainment.

At 12 months there were no statistically significant differences between the lithium- or divalproex-treated groups on clinical variables, quality-of-life outcomes or disability days. However, patients receiving divalproex were less likely to discontinue their mood-stabilizer for lack of efficacy or adverse events than patients receiving lithium. The average 1-year total treatment costs for patients receiving divalproex were $28911 compared with $30 666 for patients receiving lithium (difference $1755, CI – $505 to – 3004). As anticipated from earlier studies and modelling analyses, higher drug acquisition costs of divalproex were offset by lower inpatient cost compared with lithium. These findings are also consistent with those of Goldberg and colleagues who recently observed that costs associated with the length of hospitalization inversely correlated with the rate of titration of the antimanic mood-stabilizer (Goldberg *et al.* 1998).

Investigation of the economic impact of treatment with carbamazepine is limited to a single case reported (Nelson 1987). In this case study a patient with bipolar disorder unresponsive to previous trials of lithium, antipsychotics and several courses of ECT required 12 hospitalizations for a total of 227 days over a 13-year period. During the next 2 years during treatment with carbamazepine, this patient's affective symptoms remitted with no further hospitalizations. In the author's estimate, treatment cost savings

alone were 94%/month during treatment with carbamazepine compared with his prior course of illness.

The most recent innovation in calculating treatment costs for patients with bipolar disorder employed a computer simulation model (Mather *et al.* 1999). In this model, treatment duration, cohort size and initial clinical state can be varied. Clinical outcomes and economic consequences of using one or more mood-stabilizers to treat various phases of the illness can be generated using this simulation.

CONCLUSION

From the studies reviewed above, a number of aspects regarding the economic impact of bipolar disorder are clear. First, the cost of this illness in disability and human suffering is profound. Second, the economic cost of the illness far outweighs the costs of treatment. Third, cost savings may differ among the available mood-stabilizing medications, depending on clinical and pharmacological variables. Fourth, the costs of hospitalization contribute the single greatest share of treatment costs, greatly outweighing the costs of drug acquisition. Thus, decisions regarding the inclusion of medications for patients with bipolar disorder on formularies require consideration of the impact of successful treatment on preventing morbidity and mortality, enhancing productivity and preventing hospitalization (Keck *et al.* 1998b).

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Chapter twenty-two

Bipolar disorder and schizophrenia: Unifying the concept of psychosis through brain morphology

Lynn E. DeLisi

INTRODUCTION

Kraepelin formulated the concept of two aetiologically distinct categories of psychosis, one that was a slow continually deteriorating illness, and the other with a chronic, but remitting cyclic course (1896). It was, however, towards the end of his career that he noted the distinction between the two was not always clear and may not be as he originally wrote. In the preface to Barclay's English translation of Kraepelin's *Dementia Praecox and Paraphrenia* (1919) George Robertson wrote that "He is not satisfied with his delimitation of its boundaries, nor with all the sub-divisions he has created." Nevertheless, it is his first descriptions that influenced the development of a psychiatric nosology, despite the lack of clear direct evidence to substantiate it.

As early as the late 18th century Haslam (1796) published descriptions of clearly psychotic individuals who at autopsy were frequently found to have "ventricles that were much enlarged and contained a considerable amount of water". During the 19th century large ventricular space, or cerebral atrophy was described by others to be present in patients who had a chronic psychotic illness (Hecker 1871, Meynert 1884), and Alzheimer reported neuronal loss post-mortem (1897). Kraepelin was also clear, by the

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 449–459.

beginning of the 20th century, that dementia praecox was a brain disease. In fact he reviewed several post-mortem investigations finding a variety of microscopic changes in the brains of patients diagnosed as dementia praecox, illustrating what he called "sclerotic nerve-cells" characteristic of the disease (Kraepelin 1919, p. 217). Despite concluding that "nothing certain" could be reported about the "morbid anatomy" of "manic-depressive insanity" (Kraepelin 1921, p. 164), he suggested that the crucial element determined by the presence of "brain disease" is a deteriorating clinical course, further admitting that cases of manic depression with deteriorating course exist, as well as dementia praecox with cyclic occurrence. However, subsequent to the popular views of Freud and his followers, from the early 1900s through the 1960s little attention was given to brain structural pathology in the psychoses, despite several pneumoencephalographic studies showing enlargement of the cerebral ventricles in patients with chronic schizophrenia (Lemke 1935, Haug 1962) and in manic-depressive psychosis (Nagy 1963).

It was not until the late 1970s that these findings were brought to the forefront of psychiatric research with the publication of computerized tomography studies showing ventricular enlargement and cerebral atrophy in patients with schizophrenia (Johnstone *et al.* 1976, Weinberger *et al.* 1979a,b). Studies of affective disorder soon followed (Jacoby and Levy 1980, Pearlson and Veroff 1981, Nasrallah *et al.* 1982). In the subsequent two decades of research numerous studies have replicated these findings and several meta-analyses and extensive reviews of the data have been produced for schizophrenia (Raz and Raz 1990, Van Horn and McManus 1992), bipolar disorder (Soures and Mann 1997, Videbech 1997, Steffens and Krishnan 1998), or comparing both together (Elkis *et al.* 1995). The association of ventricular enlargement with psychosis is one of the most replicated biological findings in psychiatry. While patients with heterogeneous mood disorder, as a group, tend to have less ventricular enlargement than patients with schizophrenia (Elkis *et al.* 1995), when only affective disorders (bipolar or recurrent major depression) with psychosis are evaluated this may not be the case (e.g. Jacoby and Levy 1980, Jacoby *et al.* 1983, Targum *et al.* 1983).

Since the mid-1980s magnetic resonance imaging (MRI) has been applied to studies of psychiatric patients and, with its expanding capabilities and resolution, data have accumulated on volumetric measurements of several cortical and subcortical structures in patients with schizophrenia (reviewed by McCarley *et al.* 1999) and affective disorders (Soures and Mann 1997, Okazaki 1998).

Post-mortem studies, while only able to obtain most material from patients at the end stage of illness, have added a dimension of validity to several analyses that are limited to present-day image technological problems. Some of these have had both schizophrenia and bipolar cohorts in the same analyses, but most have been neurochemical. Morphological post-mortem studies have focused on schizophrenia, although a recent report of

cell loss in the frontal cortex of patients with depression warrants further investigations in parallel with the schizophrenia literature (Rajkowska *et al.* 1999). The debate still exists as to whether there is excessive cell loss in schizophrenia, or just reduction in the size of the neuropile (Harrison 1999, Arnold and Trojanowski 1996, Benes *et al.* 1991, Selemon *et al.* 1995).

THE MORPHOLOGICAL FINDINGS

An anomaly in the development of cerebral asymmetries has been hypothesized as the crucial variable that determined all other observed structural brain variations in schizophrenia and primary to the development of the disorder (Crow *et al.* 1989). A continuum of psychosis from affective disorder to schizophrenia has also been considered at the same time (Crow 1986). Documentation of cerebral asymmetries and anomalies of their development is also present in several publications (reviewed in DeLisi *et al.* 1997, Lohr and Caligiuri 1997, Crow *et al.* 1989). Schizophrenic patients overall appear to have reductions of reversals of normal cerebral asymmetries of the anterior and posterior brain shape, sylvian fissure, planum temporale and other structures, although considerable normal variation exists. Left hemisphere dysfunction is considered characteristic of schizophrenia. On the other hand, asymmetry studies of bipolar disorder are less clear, and as summarized in Lohr and Calgiuri, either suggest right hemisphere dysfunction or no deviance from normal. It is interesting also that the latter may change with fluctuations of depression to mania (Pettigrew and Miller 1998). Structural studies of asymmetries have been very limited in bipolar subjects who have tended to be controls for comparisons with schizophrenic patients (Brown *et al.* 1986, Tsai *et al.* 1983).

Studies of total brain size in schizophrenia were reviewed by Ward *et al.* (1996), concluding that a small, but significant, reduction was present in brain size, but not extracranial size, in schizophrenia. Few similar studies of bipolar disorder have appeared in the literature. It is likely that smaller brain size is associated with a more severe form of psychosis (poor prognosis) regardless of the diagnosis.

Table 1 summarizes the author's overall view of the extensive literature on the major morphological anomalies reported and their specificity. Clearly, the most consistent finding is that lateral ventricular enlargement is present in both schizophrenia and affective disorder, as mentioned above. Regional cortical volume reductions have been less well studied, although frontal lobe volume is reduced in schizophrenia in some studies (reviewed in McCarley *et al.* 1999) and one recent post-mortem study (Rajkowska *et al.* 1999) is reported of neuronal loss and pathology in frontal lobes of patients with major depression. Temporal lobes, and separately the superior temporal gyrus, have been measured and both found in several studies to be

Table 1 Structural anomalies found in schizophrenia and/or affective disorder with confirmation in several studies and suggested by meta-analyses; ? = controversial or not certain (some studies may show it, some do not, or more studies needed to be certain)

Brain structure	*Present in schizophrenia*	*Present in affective disorder*	*Method for identification*
Cerebral asymmetries	Reduced or reversed	Normal	CT, MRI, post-mortem
Corpus callosium changes	?	?	MRI, post-mortem, schizophrenia only
Lateral ventricles	Enlarged	Enlarged	Pneumoencephalograms, CT, MRI, post-mortem
Brain size	Small decrease	?	CT, MRI, post-mortem
Frontal lobe	? Reduced	?	MRI, post-mortem
Total temporal lobe volume	Reduced	? Reduced	MRI
Superior temporal gyrus	Reduced on left	Normal	MRI
Hippocampus	?	?	Reduced in MRI, but not post-mortem
Parahippocampal gyrus	Reduced on left	?	MRI, post-mortem
Amygdala	?	Enlarged	MRI
Caudate	Enlarged (medication effect)	Enlarged	MRI
Signal intensities	?	Increased (vascular?)	MRI

reduced in schizophrenia, usually greater on the left than right (McCarley *et al.* 1999). Much less has been studied in affective disorder, but some studies indicate whole temporal lobe volume loss (Roy *et al.* 1998), while normal superior temporal gyrus volume has been found (Hirayasu *et al.* 1998, Schlaepfer *et al.* 1994). Data on the hippocampal volume reductions appear inconsistent in both schizophrenia and affective disorder. While the majority of MRI studies appear to find reduced volume of these structures (reviewed in Razi *et al.* 1999), post-mortem studies fail to find evidence of this (reviewed in Dwork 1997). We have proposed that the seemingly reduced measurements of medial temporal lobe structures on MRI scans could result from enlargement of the temporal horns of the lateral ventricles and their masking of the boundaries of adjacent tissue on scans (Razi *et al.* 1999). A few curious studies find amygdala enlargement on MRI in affective disorder (e.g. Strakowski *et al.* 1999, Altshuler *et al.* 1998); these need to be more extensively pursued. Several MRI studies of caudate nucleus show enlargement in both schizophrenia and bipolar disorder, but this has been shown to be a direct result of neuroleptic treatment (Chako *et al.* 1994). Finally, increased signal intensities of unknown significance and origin have been observed in MRI scans of patients with both bipolar disorder and major depression, and is related to the degree of cognitive impairment (Videbech 1997). Only one study appears with similar findings in schizophrenia (Persaud *et al.* 1997).

THE TIME-COURSE OF BRAIN STRUCTURAL CHANGE IN PSYCHOSIS

Both schizophrenia and bipolar psychosis are lifetime disorders that peak in severity and thus detection of psychotic symptoms during early adulthood. The age of onset of schizophrenia is in mid-20s. with males tending to earlier onset than females by approximately 2 years (reviewed in DeLisi 1992). Bipolar disorder, on the other hand, has a peak age of onset that ranges from late adolescence to the mid-20s, depending on the method for determining onset, but no difference in age of onset between males and females has been reported (Goodwin and Jamison 1990). The sex differences in schizophrenia are related to the severity of illness, males generally more severe than females, while sex differences in affective disorder are mainly with prevalence; that is, a greater prevalence of major depression among females than males, but equal prevalence of bipolar disorders.

The course of illness, at the extreme ends of the spectrum of schizophrenia to bipolar disorder, is characterized by a chronic active deteriorating psychosis of many years duration, in the case of poor prognosis schizophrenia, to episodic psychosis with complete recovery between episodes in classical bipolar disorder. However, frequently the course of schizophrenia is par-

tially episodic, positive psychotic symptoms resolve for periods of time and, on the other hand, bipolar disorder may frequently not have complete recovery from episodes, or have them increase in frequency to the point where the individual does not return to normal functioning between these episodes. At the centre is schizoaffective disorder, in which both affective and psychotic symptoms overlap and often are subjectively described as either schizophrenia, bipolar disorder, or major depression with psychosis, by independent diagnosticians. It seems possible that these clinical variations in illness course represent an underlying variable course of brain growth and brain structural change throughout the life-span of each individual.

Several studies have recently been reported of continual brain structural change in follow-up scans of patients with schizophrenia. These are non-localized changes (reviewed in DeLisi 1999). There are fewer studies of patients with bipolar disorder. Woods *et al.* (1990), while finding progressive ventricular enlargement in some patients with schizophrenia, found less in patients with bipolar disorder by comparison. On the other hand, an early study by Sachetti and colleagues (1990; Vita *et al.* 1988) found bipolar patients to have ventricular change over time, but not patients with schizophrenia.

CONCLUSIONS

One can thus conclude, from the heterogeneous literature on both schizophrenia and affective disorders, that it is not brain anomalies that are associated with a specific diagnosis *per se,* but that underlying deviant brain growth, organization and ageing are likely to determine the lifetime course of psychopathology. Both schizophrenia and the affective disorders have symptoms in common during the course of illness, but how and when they develop over time is the key question.

Both disorders are genetically determined, but not with a specific Mendelian pattern, and frequently symptoms of affective disorder overlap with schizophrenic psychoses within families (e.g. Henn *et al.* 1995). Both disorders have been the topic of high-risk studies of children, and subtle abnormalities have been found in children who eventually develop schizophrenia as well as those who develop bipolar disorder, although they differ in specific behaviours. In one study (Done *et al.* 1994, Crow *et al.* 1995) over-reactive deviant social behaviour (including hostility towards adults and peers) and poor concentration were present in pre-schizophrenic children at ages 7 and 11, but relatively minor deviant behaviour was detected in pre-affective disorder children. In another study (Cannon *et al.* 1997), both pre-bipolar and pre-schizophrenic children had poorer pre-morbid social adjustment than controls, but it occurred earlier in childhood in pre-schizo-

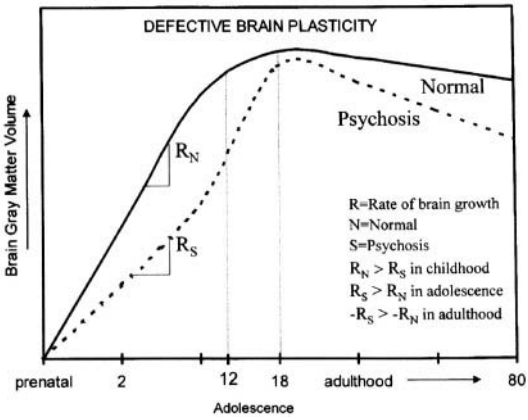

Figure 1 Hypothesis for defective brain plasticity in the psychoses.

phrenic individuals and later and to a lesser degree in pre-bipolar children. Walker *et al.* (1996) found that deviant externalized behavioural problems of childhood are associated with smaller brain volume and ventricular enlargement in adult patients with schizophrenia.

It is possible that the key factor underlying the detected brain abnormalities and resultant behavioural pathology is the control over the rate of brain growth (Figure 1), how this rate determines regional structural volumes at any point in one's life course, and it how it differentially controls the separate development of both sides of the brain. If genetic variation is present in factors that control aspects of brain development, growth of the brain will vary among individuals during childhood, during adolescence when new connections between neurons are said to be reorganized, and during adulthood when the brain is ageing. A decreased rate of development of some portions of the brain in childhood, aberrant connectivity forming in adolescence and an accelerated rate of regional neuronal ageing, and variations of these, could explain the brain anomalies of both schizophrenia and affective disorder; their similarities as well as their differences. Vulnerability for psychosis could be produced by extremes in this variation in differential brain growth. It is thus hypothesized (Figure 1) that brain growth may be slower in some parts of the brain relative to others in schizophrenia during childhood; that during adolescence, while it may catch up, the connectivity introduced may be diffuse in critical regions; and that during adulthood the same rate-controlling factors may be operant in determining the degree and amount of cortical loss during ageing and neuronal repair during stress. Based on some of the studies of pre-morbid social adjustment and degree of cerebral asymmetry, bipolar disorder may be associated with less brain growth deviance during childhood, although during adolescence it is possible that connectivity may be more diffuse than

normal. Perhaps slower growth in childhood leads to permanent vulnerability towards a chronic unremitting illness, while with a normal rate of childhood brain development, episodes of malfunctioning have the critical structure needed to recover more easily. Variants between these two extremes would then develop a lifetime illness course somewhere mid-way between a poor-prognosis non-reversible state and clearly spaced episodes with complete recovery and functioning.

At present there are several issues that remain unresolved. Among these are: (a) whether there are structural changes that are specific to schizophrenia, bipolar disorder, or major depression or some common to both disorders; (b) defining the time-course to these structural changes and whether they vary in relation to illness course; (c) determining what underlies the structural changes and whether they are interrelated. The time has come to consider psychiatric diagnoses in terms of lifelong brain disease, rather than DSM categories of morbidity.

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Chapter twenty-three

On entities and continuities of bipolar disorders

Andreas Marneros

THE ADJUSTABLE HOMEOSTASIS

It can be said with certainty that, 2400 years after Hippocrates, almost 2000 years after Aretaeus of Cappadocia, approximately 150 years after Jean-Pierre Falret and Jules Baillarger, 100 years after Kraepelin's "Manisch-Depressives Irresein" and 33 years after Jules Angst's monograph and the publication of Carlo Perris, we have learned a lot about bipolar disorder. However, much remains to be learned. In the past 2400 years we have become able to answer some questions, but many are still open. The findings and theories presented in this book are those advanced over the past 150 years that have drawn a line between unipolar and bipolar disorders. Nevertheless, one can assume that the dichotomy unipolar versus bipolar is not complete. It is incomplete insofar as the dichotomous development into unipolar–bipolar has a common basis, namely the affectivity or mood. The common basis renders the whole not "dicho-tom" but "a-tom", i.e. not separable.

In unipolar and bipolar diseases something morbid forces the mood or affectivity to run off the rails. This "something" – sometimes autonomic, such as a biological factor or a biological force, but sometimes the impact of a psychological event – disturbs the normal homeostasis of affectivity. I have described this homeostasis (Marneros 1999a) as "adjustable". With the term "adjustable homeostasis of affectivity" I mean that human beings do not have a stable level of affectivity, even under normal psycho-biological conditions. It normally moves, like a liquid in an unstable vessel, between two poles of healthy affectivity. Changes between happiness and sadness,

A. Marneros and J. Angst (eds), Bipolar Disorders: 100 years after manic-depressive insanity, 461–464.

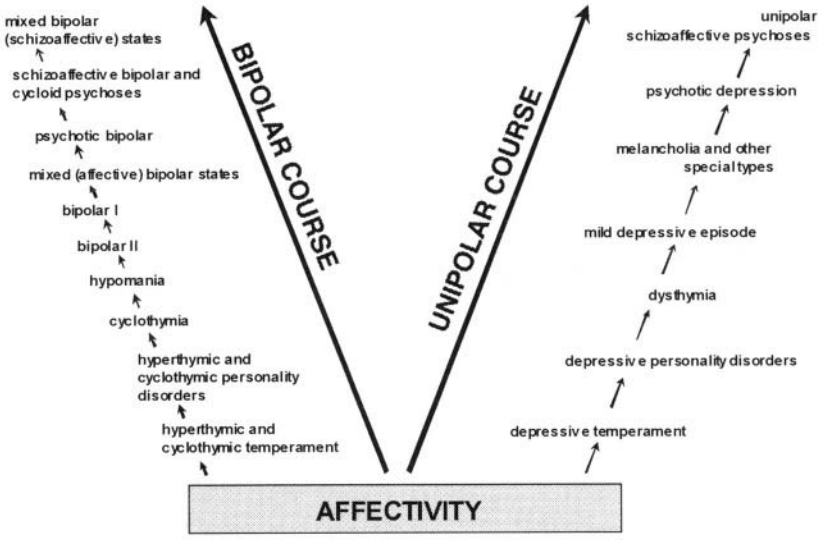

Figure 1 Bipolar and unipolar continuum (Marneros 1999a).

between a low and a high level of activity and drive, between low and high self-confidence, between laughing and crying, are the normality. The changes may occur over a period of a few minutes, a few hours or a few days. The vessel is unstable. Yet the liquid – under normal conditions – does not leak out. The polarity of mood is a normal condition. Perhaps this is something that makes human beings human, makes them "anthropos". But perhaps more than this. Perhaps the polarity of functions is something that defines life.

Under normal conditions the fluctuations and movements do not go beyond their psychologically, sociologically and biologically acceptable limits. Usually no liquid is shaken out of the unstable vessel. But when this unstable normality is disturbed, mood leaks out of the vessel into two possible streams. Within these streams flow other functions: volition, thinking, drive, perception and so on. The direction of one stream is the direction of "restriction", what the German psychopathologist Werner Janzarik (1959) termed "dynamic restriction". All mental functions flowing in this "stream of restriction" are diminished. This is the stream of depression, the stream of the unipolar affective disorders.

The other stream is characterized – again using Janzarik's terms – by "dynamic expansion" or "dynamic instability". It shows changes between "restriction", "expansion" and "instability". This is the stream of the bipolar disorders (Figure 1).

THE CONTINUITY OF A DICHOTOMY

We can assume that different pathophysiological and pathopsychological mechanisms determine the direction of the stream of disturbed affectivity. But perhaps there is not a gap between unipolar and bipolar disorders, but rather a common basis, a bridge. And indeed a bridge really exists. The common basis of both unipolar and bipolar disorders is namely affectivity and its disturbances. This fact is compatible with the idea of a psychotic continuum. It can be considered that the derailed affectivity, now in its dichotomous direction, increases in complexity and severity as a river broadens and deepens. Near its origin a river is a thin trickle of water, sometimes almost imperceptible, but later it can develop into a strong, destructive torrent. Perhaps the beginning of the unipolar direction is only the depressive temperament. Perhaps there is a borderline between the adjustable homeostasis of affectivity and a depressive temperament which is sometimes invisible or difficult to draw. But depressive personality disorder is something more than depressive temperament and perhaps something less than dysthymia. Dysthymia is sometimes, at least phenomenologically, indistinguishable from a mild, long-lasting depressive episode. The concept of double depression shows how transparent are the boundaries between dysthymia and major depression. Melancholia and some other forms of major depression can be viewed as an increase of the disturbance of affectivity. More severe is psychotic depression, and at the very mouth of the river is the unipolar schizodepressive episode.

Very similar is the development of the direction characterized by ″dynamic expansion″ and by ″dynamic instability″ or by changes between dynamic restriction, expansion and instability. The boundaries between hyperthymic or cyclothymic temperament and normal affectivity are also sometimes imperceptible. However, going downstream, an increase in the disturbance leads successively to hyperthymic or cyclothymic personality disorders, cyclothymia or hypomania, bipolar II disorders, bipolar I disorders, the mixed affective disorders, a more severe type of affective disorders, then to psychotic bipolar disorders and, further on, the schizoaffective bipolar disorder, and finally – at the mouth of the river – the schizomanic depressive episode, the mixed schizoaffective state, which in my opinion is the most severe form of bipolar disturbance. Within this dichotomous direction of deranged affectivity some other subgroups of unipolar and bipolar disorders can be defined, such as the seasonal affective disorders and rapid cycling.

Perhaps future research will provide answers to the remaining questions concerning whether unipolar and bipolar are separate entities or points on a psychotic continuum. Nevertheless we can agree with what Aretaeus of Cappadocia wrote 2000 years ago:

"τρόποι εἴδεσί μεν μύριοι,
γένει δέ μοῦνο εἶς ...",

namely, "There are many different phenomenological types of these illnesses, but they all belong to one and the same family."

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