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THE TREATMENT OF BIPOLAR DISORDER

Integrative Clinical Strategies & Future Directions

EDITED BY
ANDRÉ F. CARVALHO
AND EDUARD VIETA

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Foreword

This excellent new book on bipolar disorder is written by leading international experts who have advanced our understanding of the field in recent decades. It starts with modern diagnostic classification, reviews comprehensively and critically the complex field of available treatment methods, and concludes with highlights of current research and discussion of future developments.

Bipolar disorder is a common mental illness, affecting approximately 2.4% of the general population worldwide, although this is arguably a significant underestimation of its true prevalence. One particular feature of the disorder, namely the subjective experience of hypomania as simple well-being or as a return to health after severe depression, leads to substantial under-reporting and under-diagnosis.

On the fundamental issue of classification, the contributors trace the extension of the simple dichotomy of unipolar depression vs bipolar disorder into several subtypes including diverse sub-threshold bipolar and mixed syndromes and discuss the relative merits and appropriateness of categorical and dimensional approaches to the illness. But for treatment decisions a refined categorical classification remains indispensable and should not neglect the patient's comorbid psychiatric and somatic syndromes and diagnoses.

The course of bipolar disorder is characterised by an early onset (often in childhood or adolescence), multiple recurrences of episodes, frequently incomplete interepisode remission, and substantial consequences in terms of social and cognitive impairment and reduced quality of life. It is furthermore associated with significant morbidity and elevated mortality rates due to comorbidities and suicide.

The volume's main focus is treatment. It provides a masterly description of the evidence-based, effective treatments available for the integrative management of the different stages of this complex and debilitating disorder. These range from early interventions, where a staging model can be helpful, to the numerous acute and long-term maintenance prophylactic therapies, pharmacological and psychotherapeutic. There is ample evidence that specific psychological and psychotherapeutic interventions are valuable adjuncts to pharmacological treatment. A key role is played by psychoeducation (illness awareness, adherence, habits, identification of warning signs) and the involvement of the family (especially in children, adolescents and the elderly). ECT still proves useful in treating some patients, and cognitive dysfunction in bipolar disorder is a new target for evidence-based psychological treatment. But, the authors point out that despite decades of investigation there is still a shortage of clinical trials on bipolar mixed states, rapid cycling bipolar disorder and cyclothymic disorder.

Special chapters deal with differentiated treatments for children/adolescents, the elderly, and women with bipolar disorder.

This volume is an invaluable source of current expertise, a concise guide to the integrative management of bipolar disorder. It provides sound evidence that an appropriate combination of treatments can profoundly improve patients' lives.

Jules Angst

Contents

Abbreviations

ω-3FAs	omega-3 fatty acids
A	amperes
AA	arachidonic acid
ACC	anterior cingulate cortex
ACE	angiotensin-converting enzyme
ADHD	attention deficit hyperactivity disorder
ADRs	adverse drug reactions
AEDs	antiepileptic drugs
AIM	antidepressant-induced mania
AIWG	antipsychotic-induced weight gain
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazoleproprionic acid
AN	anorexia nervosa
APA	American Psychiatric Association
ATP	adenosine triphosphate
BAD	bipolar affective disorder
BAP	British Association for Psychopharmacology
BAR	bipolar at-risk
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
BED	binge eating disorder
BF	bi-frontal
BLT	bright light therapy
BMI	body mass index
BN	bulimia nervosa
BPRS	Brief Psychiatric Rating Scale
BT	bi-temporal
C	coulombs
CAM	complementary and alternative medicine
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBT	cognitive behaviour therapy
CBT-R	CBT-Regulation
CCT	controlled clinical trial
CD	conduct disorder
CGI	Clinical Global Impression
CIA	clozapine-induced agranulocytosis
CNR1	cannabinoid receptor 1
CNS	central nervous system
COBRA	Cognitive Complaints in Bipolar Disorder Rating Assessment
ConLiGen	Consortium on Lithium Genetics
CONSORT	Consolidated Standards for Reporting Trials
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CPS1	carbamoyl phosphate synthase 1
CR	cognitive remediation
CRF	corticotropin releasing factor
CS	case series
DALY	disability-adjusted life years
DASS	Depression, Anxiety, and Stress Scale
DBS	deep brain stimulation
DHA	docosahexaenoic acid
DHEA	dehydroepiandrosterone
DLPFC	dorsolateral prefrontal cortex
DPP	depressive predominant polarity

DRD1	dopamine receptor D1
DRD2	dopamine receptor 2
DRD3	dopamine 3 receptor
DRESS	drug-related rash with eosinophilia and systemic symptoms
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders* (5th edition)
DSPD	delayed sleep phase disorder
DTI	diffusion tensor imaging
dTMS	deep repetitive transcranial magnetic stimulation
ECG	electrocardiograph
ECT	electroconvulsive therapy
EDs	eating disorders
EEG	electroencephalography
ELRs	excellent lithium responders
EM	extensive metabolizer
EMBLEM	European Mania in Bipolar Longitudinal Evaluation of Medication
EMDR	eye movement desensitization and reprocessing
EMP +	EM Power Plus
EMRs	electronic medical records
EPA	ethyl-eicosapentanoate/eicosapentaenoic acid
EPO	erythropoietin
EPS	extrapyramidal side effects
ER	extended release/endoplasmic reticulum
ES	effect size
FAAH	fatty acid amide hydrolase
FAST	Functioning Assessment Short Test
FDA	Food and Drug Administration
FEWP	Free and Easy Wanderer Plus
FFT	family focused treatment/therapy
FGAs	first-generation antipsychotics
FGF2	fibroblast growth factor
FR	functional remediation
FTD	frontotemporal dementia
GABA	central gamma-aminobutyric acid
GAF	global activity
GI	gastrointestinal
GP	general practitioner
GSK-3	glycogen synthase kinase-3
GSK3B	glycogen synthase kinase 3 beta
GWAS	genome-wide association studies
HAM-D	Hamilton Rating Scale for Depression
HCV	hepatitis C virus
HDRS	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPA	hypothalamic pituitary adrenal
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
Hz	hertz
ICD-10	*International Classification of Diseases* (10th revision)
IGF-1	insulin-growth factor 1
IGF-1-R alpha	insulin-like growth factor 1 receptor alpha subunit
IGFBP5	IGF-binding protein 5
IL	interleukin
IMs	intermediate metabolizers

IPF1	insulin promoter factor 1
IPSRT	interpersonal and social rhythm therapy
ISBD	International Society for Bipolar Disorders
ITT	intention to treat
lDLPFC	left dorsal lateral prefrontal cortex
KA	kainate
KMAP-BP	Korean Medication Algorithm Project for Bipolar Disorder
LCLs	lymphoblastoid cell lines
LD	linkage disequilibrium
LDX	lisdexamphetamine
LOCF	last observation carried forward
LTD	long-term depression
LTP	long-term potentiation
MADRS	Montgomery-Åsberg Depression Rating Scale
MAO	monoamine oxidase
MAS	Mania Assessment Scale
MBCBT	mindfulness-based CBT
mC	millicoulombs
MC4R	melanocortin receptor 4
MCCB	MATRICS Consensus Cognitive Battery
MDD	major depressive disorder
MDQ	mood disorders questionnaire
mECT	maintenance ECT
MetS	Metabolic Syndrome
MF-PEP	multi-family psychoeducational psychotherapy
Mg	magnesium
mGluRs	metabotropic glutamate receptors
MHC	major histocompatibility complex
MMP16	matrix metalloproteinase 16
MPH	methylphenidate
MPP	manic predominant polarity
MRI	magnetic resonance imaging
MRS	Mania Rating Scale/ magnetic resonance spectroscopy
ms	milliseconds
MS	mood stabilizer
MST	magnetic seizure therapy
MT	motor threshold
NAC	N-acetyl cysteine
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NICE	National Institute for Health and Care Excellence
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartate
NNH	numbers needed to harm
NNT	number(s) needed to treat
NOS	not otherwise specified
NTRK2	neurotrophic tyrosine kinase receptor type 2
OABD	older-age bipolar disorder
OCD	obsessive–compulsive disorder
OCPs	oral contraceptives
OFC	olanzapine/fluoxetine combination
PCr	phosphocreatine
PED	psychoeducation
PET	positron emission tomography
PI	polarity index/phosphatidyl inositol
PLP1	proteolipid protein 1
PM	poor metabolizer
PMDD	premenstrual dysphoric disorder
POS	polycystic ovarian syndrome
PP	predominant polarity
PTSD	post-traumatic stress disorder

QoL	quality of life
RCT	randomized controlled trial
RDC	research diagnostic criteria
rDLPFC	right dorsal lateral prefrontal cortex
RDoC	Research Domain Criteria
RfCBT	rumination-focused CBT
RLAI	risperidone long-acting injectable
rTMS	repetitive transcranial magnetic stimulation
RUL	right unilateral
SAD	seasonal affective disorder
SCIP	Screen for Cognitive Impairment in Psychiatry
SCN	suprachiasmatic nucleus/nuclei
SGAs	second-generation antipsychotics
SIADH	secretion of antidiuretic hormone
SJS	Stevens–Johnson syndrome
SJW	St John's Wort
sl-MFB	superolateral medial forebrain bundle
SMR	standardized mortality ratio
SNPs	single nucleotide polymorphisms
SNRIs	serotonin-noradrenaline reuptake inhibitors
SPECT	single-photon emission computed tomography
SSC	specialist supportive care
SSRIs	selective serotonin reuptake inhibitors
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
sTNFRSF1A	tumour necrosis factor receptor superfamily, member 1A
SUD	substance use disorder
SZA	schizoaffective disorder
TAU	treatment as usual
TCAs	tricyclic antidepressants
TD	tardive dyskinesia
tDCS	transcranial direct current stimulation
TEAS	treatment-emerging affective switches
TEMPS-A	Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire
TEN	toxic epidermal necrolysis
TIMA	Texas Implementation of Medication Algorithms
TMAP	Texas Medication Algorithm Project
TMS	transcranial magnetic stimulation
TNF	tumour necrosis factor
TSD	total sleep deprivation
UD	unipolar disorder
UK	United Kingdom
UM	ultrarapid metabolizer
US	United States
VNS	vagus nerve stimulation
VNTR	variable number of tandem repeats
WBT	well-being therapy
WHO	World Health Organization
WFSBP	World Federation of Societies of Biological Psychiatry
XBP1	X-box binding protein 1
XR	extended release
YMRS	Young Mania Rating Scale
ZFPM2	zinc finger protein multitype 2

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Chapter 1

The current classification of bipolar disorders

Gin S. Malhi and Yulisha Byrow

The classification of bipolar disorders in DSM-5 and ICD-10/11

Emotions define humans perhaps even more so than the ability to reason, and drive all forms of experiences—namely, art, music, and literature. This is possible because of the sheer variety and range of emotions that we are able to experience, and this complexity has meant that defining emotional normality and separating aberrations has proven difficult.

In psychiatry, bipolar and related disorders refer to affective disorders that typically consist of fluctuations in mood ranging from depression to mania in varying degrees. Clinically, the first and most pressing problem facing clinicians is the diagnosis of bipolar disorder and its accurate identification and classification. Research findings suggest that approximately 1.25% of patients with major depressive disorder transmute to a diagnosis of bipolar disorder per year.[1] Ruggero and colleagues,[2] who periodically assessed individuals with a bipolar diagnosis, found that the misdiagnosis of bipolar disorder is remarkably common and that 49.7% of individuals were assigned an incorrect non-bipolar diagnosis over a ten-year follow-up period. Part of the complexity of bipolar disorder stems from its natural course, because the illness usually first manifests with depression but bipolar disorder cannot be diagnosed until the occurrence of a manic episode. Consequently, patients experiencing depression, who have never had a manic episode, are understandably and quite appropriately diagnosed with major depressive disorder (MDD), and treated with antidepressants. This is problematic for those patients that have an underlying bipolar illness because antidepressants alone are often ineffective and instead may precipitate mood instability and even a manic episode.[3] This is a major concern because in clinical practice diagnosis determines treatment and provides the necessary shorthand for communication between doctors, health professionals, and patients.

A lack of diagnostic specificity is also a critical issue for research. In order to advance the treatment and prevention of bipolar disorder, findings from clinical research trials need to be satisfactorily mapped onto clinical practice. But the translation of research into practice remains difficult, in both psychiatry and

psychology, because of the variable definition of bipolar disorder within extant psychiatric classificatory systems.

Therefore, in this chapter we first describe the diagnosis of bipolar disorders in relation to the most widely used taxonomies; namely, the *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) (DSM-5) and the *International Classification of Diseases* (10th revision) (ICD-10).[4,5] We then compare and contrast the framework and approach used by these classification systems alongside the yet to be released ICD-11, and critically discuss the clinical and research implications of important discrepancies.

Historical perspective

When considering the history of the classification of psychiatric illness it is important to remember that the present-day bipolar disorder nosology is the cumulative product of a wide range of early philosophers and physicians. In this section we selectively describe contributions made by a few influential physicians in the nineteenth and twentieth centuries.

During a time when psychiatry was still taking shape and clinical symptoms were thought to represent different stages of one universal type of insanity, Karl Kahlbaum and his associate Ewald Hecker introduced the complicated concept of *time* into psychiatric nosology. Essentially, they recognized that symptoms and behaviours of patients differ in relation to the age of onset of an illness and accordingly change with time, thus underscoring the clinical significance of the course of an illness.[6] Furthermore, they described and defined psychiatric illnesses such as dysthymia, cyclothymia, and paranoia—terms that remarkably remain relevant and in use today.

Following on from Kahlbaum and Hecker's seminal work, Emil Kraepelin coined the fitting and descriptive term manic-depressive illness, which eventually spawned the modern-day term—bipolar disorder. Kraepelin's model of 'manic depression' was derived purely from clinical observations and thus still applies and influences our modern-day understanding of bipolar disorder. His key achievement in this regard was to separate manic-depression from schizophrenia (dementia praecox) and position mania and depression at opposite poles of a continuum.[7] Following Kraeplin's work, Karl Leonhard in 1957 added to the definition of manic-depressive illness incorporating both unipolarity and bipolarity as separate entities. Notably, he maintained Kraepelin's emphasis on the *cyclical* and *recurrent* nature of these disorders.[8]

Current classification systems

The length of time that has lapsed since the last revision of both DSM and ICD is quite extraordinary. DSM-5 was published 19 years after DSM-IV, and ICD-11, the long-awaited successor to ICD-10 (1992), is yet to be published, with a proposed date of 2018. One of the principal reasons for this delay was the expectation that research would provide a neurobiological basis to psychiatric disorders and that the taxonomy of neuropsychiatric disorders would finally be based on an understanding of aetiology and pathogenesis. But despite valiant efforts no

meaningful biomarkers for psychiatric disorders have emerged. Consequently, DSM-5 remains a largely descriptive and phenomenology-based classificatory system that clusters symptoms into syndromes and defines disorders categorically. DSM was developed primarily by American psychiatrists, psychologists, and other health professionals and is therefore widely used in the United States (US). Clinically, it is used to code psychiatric disorders and for investigative purposes and clinical studies. DSM is also utilized by the American legal system to determine medical healthcare rebates governed by insurance schemes. However, outside the US, DSM-5 is principally used for research purposes.

The major alternative classification system is the International Classification of Diseases developed by the World Health Organization (WHO), which published its 10th revision in 1992. It is widely used internationally in health systems including, for example, the United Kingdom (UK) and Australia. The 11th revision of ICD (ICD-11) is underway and is due to be released in 2018. The current chapter, therefore, discusses some of the proposed diagnostic criteria for bipolar disorder set out in the currently available beta version.*

ICD-10 was developed in consultation with many health professionals from different countries and it encompasses all health-related illness and disease in addition to mental disorders. In terms of classifying mental health disorders there are two versions of ICD-10—one that adopts a more clinical focus and the other more oriented towards research. However, in practice, ICD is mostly utilized by medical professionals, particularly in European countries, to measure the use of services.

Importance of diagnosis relevant to research and clinical practice

Given the resources spent developing and implementing classification systems it is imperative to consider why diagnosis is an important concept, and more specifically the usefulness of diagnoses in different contexts. From a research perspective, diagnosis is typically used to select samples for investigative purposes such as aetiology and treatment. The use of a common language facilitates communication between researchers and research groups, and while a categorical approach ensures diagnostic reliability, it often compromises diagnostic validity—a long-standing concern. Robins and Guze were among the first to recognize the importance of developing a structured framework to clarify psychiatric disorders with a view to underpinning diagnosis with neurobiological substrates.[9] Contemporaneously, an influential body of work by Spitzer et al. established the Research Diagnostic Criteria,[10] a classification system using definitive criteria to describe psychiatric illness with the aim of improving the diagnostic reliability of mental illnesses. Today, with the release of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC), the importance of biologically derived evidence in diagnosing mental illness is once again in the limelight, with emphasis returning to evidence that draws on neurobiology, as well as the aetiology of mental illnesses.

* It is important to note that there are likely to be changes made in the final version of ICD-11.

Importantly, research examining treatment outcomes uses categorical classificatory systems to recruit clinical samples and therefore clinical treatment strategies are based on these findings. There are inherent disadvantages in this approach, because in clinical drug trials patients with comorbidities or particularly complex presentations are routinely excluded and samples that undergo testing tend to be 'over-selected'. For example, many clinical drug trials recruiting a depressed population exclude patients with active suicidal ideation, a common clinical symptom that has key significance for immediate and longer-term management. Therefore, it is unclear whether the samples recruited in such trials are truly representative of the clinical population that they are thought to reflect. Thus, an inevitable tension emerges between competing demands—because it is best to categorize individuals into homogenous samples in order to determine treatment effects for specific populations, but by using a categorical approach and limiting complexity that occurs in the clinical context, the translation of research into practice is invariably constrained.

When adopting a clinical perspective clinicians use diagnoses such as bipolar disorder as a guide for case formulation and to facilitate communication between patients and clinicians, as well as between mental health professionals. While diagnoses offer a significant input into the treatment plan developed for patients with bipolar disorder it is important to remember that bipolar symptoms occur within the context of a broader set of experiences. Thus, it is important to consider aspects of an individual's life that may have contributed to the development of the disorder, such as, adverse life events, dysfunctional personality style, lifestyle issues (eg, smoking and substance misuse), and genetic vulnerability, along with other contextual factors that may facilitate resilience in patients, such as, positive emotions, secure attachment styles, and a supportive social environment, to formulate a comprehensive and individualized treatment plan.[3,11] These contextual factors are not captured by existing diagnostic classification systems.

Limitations of current taxonomy

Successive iterations of DSM culminating in DSM-5 have gradually shifted the classification of bipolar disorders away from Kraepelinian concepts, by placing greater emphasis on polarity than the longitudinal pattern of mood disorders (cyclicity and recurrence). But in reality, the nature of bipolar disorder is only evident when its course is mapped longitudinally and, over time, initial depressive symptoms gradually give way to (hypo)manic episodes. The cross-sectional approach of current classification systems fails to capture the evolution of bipolar disorder and instead views the diagnosis as a 'state' rather than a 'trait'. This is at odds with the true nature of bipolar disorder, which is a relapsing and remitting illness that evolves over the lifetime of an individual.

Another inherent limitation of both DSM and ICD classification systems is the 'equal' weighting of all bipolar disorder symptoms. For example, equal significance is attached to recurrent thoughts of suicide, guilt, and fatigue when determining a diagnosis of a major depressive episode. However, clinically, suicidal thoughts and guilt confer different connotations and are arguably more important and possibly

more characteristic of severe presentations of depression than fatigue. Thus, grouping individuals meeting criteria for a broad diagnostic category such as a 'depressive episode' is likely to generate heterogeneous groups with significant variation in illness severity and clinical symptomology.

Brief overview of DSM-5 bipolar and related disorder sections

In DSM-5, bipolar and related disorders are situated between schizophrenia spectrum and other disorders and depressive disorders. For an overview of all the diagnostic categories see Figure 1.1 and for a summary of diagnostic criteria see Table 1.1.

Bipolar I disorder is the modern derivative of manic-depressive illness, and while there is no requirement to have experienced a major depressive episode or psychosis to fulfil criteria, most individuals with this disorder will experience a major depressive episode at some point during their lifetime. The defining feature of bipolar I disorder is mania and the classic features of a manic episode include persistent elevated and expansive, or irritable, mood, and persistently increased activity or energy lasting a period of at least one week. These symptoms must also cause marked impairment in functioning and/or require hospitalization.

Bipolar II disorder requires an individual to have experienced at least one hypomanic and depressive episode with a clinical course defined by recurring mood episodes. Hypomania is similar to mania with elevated mood or euphoria, but these symptoms typically do not cause marked impairment in functioning even though they last at least four consecutive days.

Individuals with *cyclothymic disorder* typically experience chronic fluctuations in mood from hypomania-like symptoms to depressive symptoms for at least two years. However, the changes in mood symptoms would not meet criteria for a hypomanic or depressive episode as they are, by definition, less severe and of shorter duration.

Brief overview of ICD-10 bipolar disorder section

In ICD-10, single manic episodes are distinguished from recurrent manic and/or depressive episodes. For an overview of all the diagnostic categories see Figure 1.2 and for a summary of diagnostic criteria see Table 1.2. Individuals experiencing a single manic episode can potentially receive a diagnosis, ranging in increasing severity, from hypomania to mania with psychotic symptoms. However, note that a single mixed affective episode is considered separately and classed under 'Other single mood disorder'.

Recurrent manic and depressive episodes are classified under 'Bipolar affective disorder' (BAD) (see Figure 1.2). The severity of manic episodes is judged based on the presence of psychotic symptoms and the severity of depressive episodes is captured as mild, moderate, or severe with or without psychosis. The characteristic feature for all BAD diagnoses is the presence of *at least one other affective episode* (from the opposite pole of the mood spectrum) or remission of symptoms.

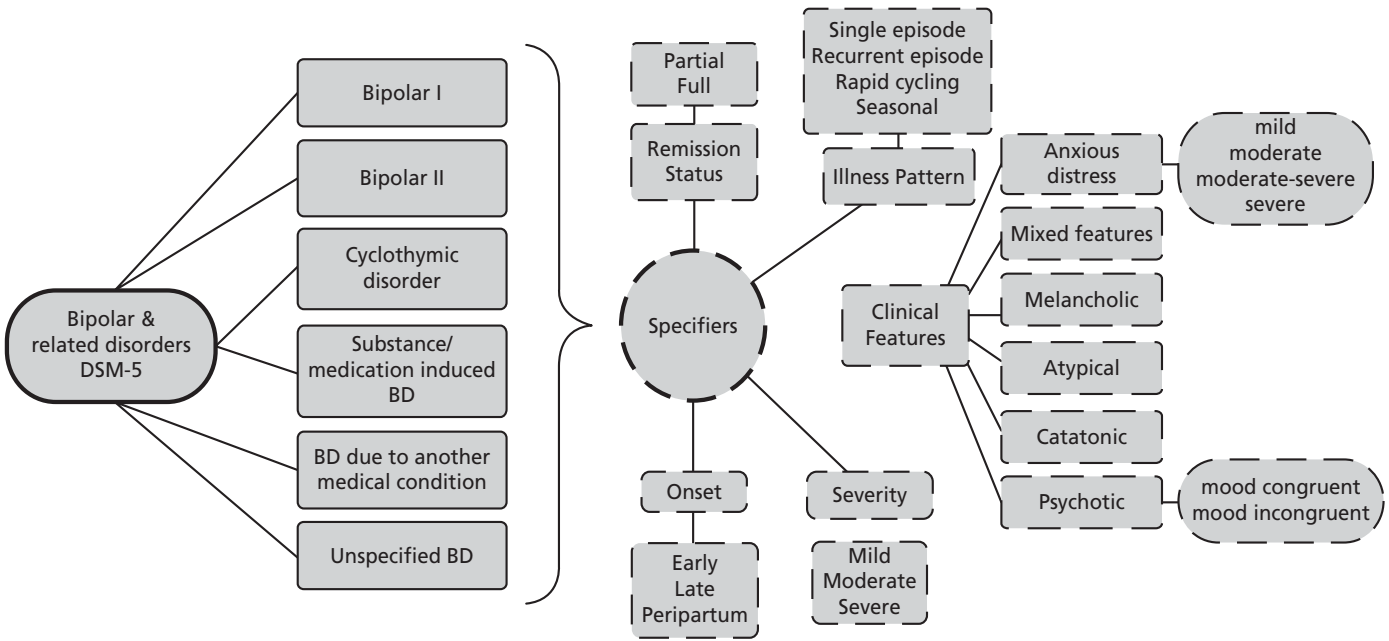

Figure 1.1 Classification of bipolar and related disorders. All bipolar and related disorders are subsumed within an independent section in DSM-5. For each of these diagnoses (solid border) any number of specifiers (dashed border) can be applied.
Data from *Diagnostic and statistical manual of mental disorder*, 5th ed., 2013, American Psychiatric Association.

Table 1.1 Summary of DSM-5 diagnostic criteria for bipolar and related disorders

DSM-5			
	BD I	**BD II**	**Cyclothymia**
Main Symptom Criteria (Mania)			
Elevated or irritable mood	+	+ (Often irritable)	+
Increased activity or energy	+ (goal directed)	+	+
Increased self-esteem	+	+	+
Decreased need for sleep	+	+	+
Pressured speech	+	+	+
Distractibility	+	+	+
Increased risk taking	+	+	+
Increased sociability/ over-familiarity			
Increased sexual energy			
Delusions/ hallucinations			
Main symptom criteria for major depressive episode (same as MDD)		+	
Severity and duration of episodes			
	Mania	**Hypomania**	**Sub-threshold mania**
Number of symptoms	≥ 3/≥ 4 if the mood is irritable	≥ 3/≥ 4 if the mood is irritable	≤ 3 symptoms
Duration of episode	≥ 7 days (or any duration if hospitalized)	≥ 4 days	–
Impact on functioning	Disrupts social & occupational functioning or hospitalization or psychotic features	Not severe enough to disrupt functioning or result in hospitalization	Hypomania/depression symptoms cause significant distress or impairment in functioning
Depression			
Number of symptoms		≥ 5 symptoms	< 5 symptoms
Duration		2 weeks	< 2 weeks
Frequency of episodes		≥ 1 hypomanic + ≥ 1 depressive episode	Fluctuating between hypomanic and depressive symptoms for ≥ 2 years (1 year for children/ adolescents). Never been without symptoms for > 2 months at a time.

Data from *Diagnostic and statistical manual of mental disorder*, 5th ed., 2013, American Psychiatric Association.

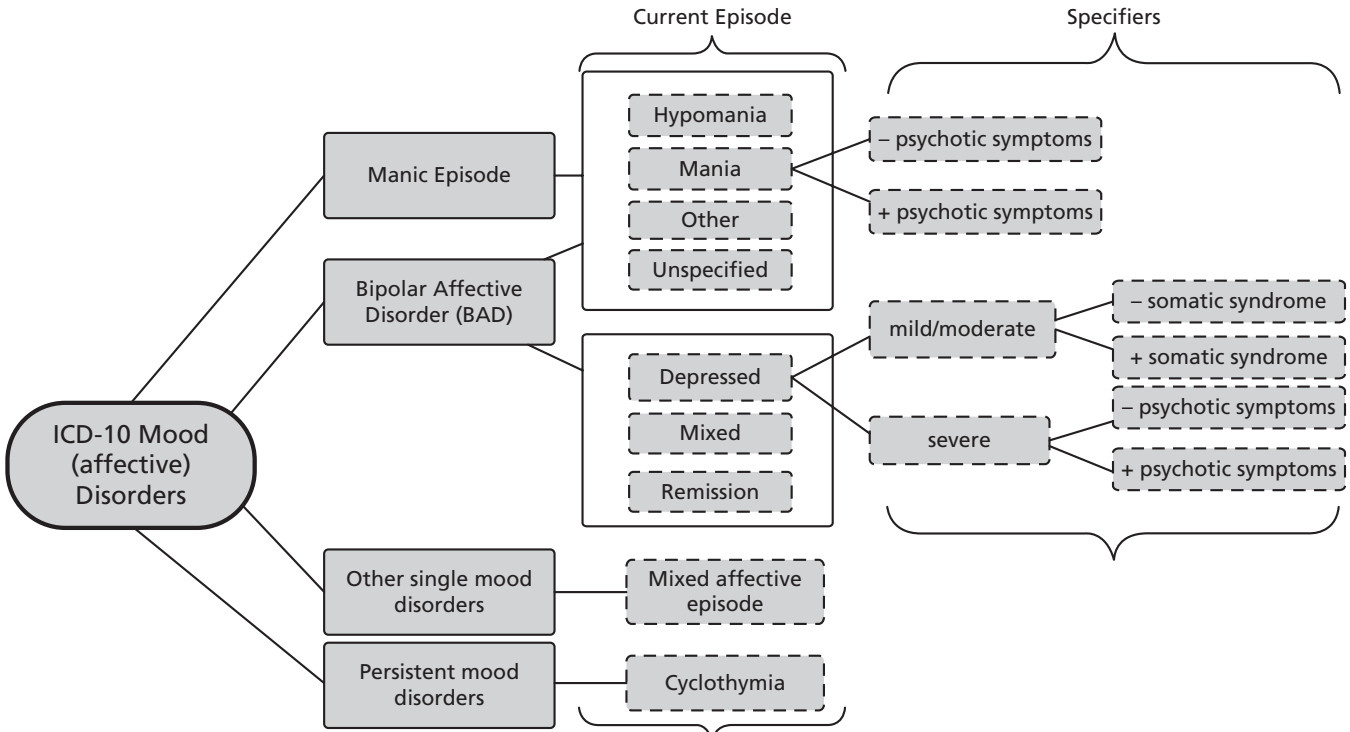

Figure 1.2 The ICD-10 classification system. A parsimonious approach to diagnosis using ICD-10 is to first consider whether the affective episodes are single or multiple present (solid border): a period of mania/hypomania falls under 'manic episode' whereas a single mixed episode falls under 'other single mood disorders'. At least two episodes are necessary to qualify for bipolar affective disorder (BAD). The specifiers are relevant to clinical features and severity of manic and depressive episodes.

Data from *International Classification of Diseases (ICD)*, version 10. Copyright (1992) World Health Organization.

Table 1.2 Summary of ICD-10 diagnostic criteria for bipolar and related disorders

ICD-10				
		Mania		
Main symptom criteria	**Hypomania**	**Mania w/ out psychotic symptoms**	**Mania with psychotic symptoms**	**Cyclothymia**
Elevated or irritable mood	+	+	+	
Increased activity or energy	+	+	+	+
Increased self-esteem	+	+	+	+
Decreased need for sleep	+	+	+	+
Pressured speech	+	+	+	
Distractibility	+	+	+	
Increased risk taking	+	+	+	
Increased sociability/ over-familiarity	+	+ (loss of normal social inhibitions)	+ (loss of normal social inhibitions)	+ (gregariousness)
Increased sexual energy	+	+ (sexual indiscretions)	+ (sexual indiscretions)	+
Delusions/ hallucinations			+ [a]	
Sharpened or atypically creative thinking				+
Increased talkativeness				+
Over-optimism				+
Severity and duration of episodes				
			Mania	
	Hypomania		**Mania**	**Cyclothymia**
Number of symptoms	≥ 3 symptoms		≥ 3/≥ 4 irritable mood only	≥ 3 depressive & ≥ 3 elevated mood symptoms
Duration of episode	≥ 4 days (several days)		≥ 7 days (or any duration if hospitalized)	≥ 2 years of mood instability

(continued)

Table 1.2 Continued

ICD-10			
	Depression		
	Mild	**Moderate**	**Severe**
Number of symptoms	≥ 4 symptoms in total	≥ 6 symptoms in total	≥ 8 symptoms in total
Duration of episode	≥ 2 weeks	≥ 2 weeks	≥ 2 weeks

[a] Cannot be culturally inappropriate, impossible, third person, or running commentary

Data from *International Classification of Diseases (ICD)*, version 10. Copyright (1992) World Health Organization.

Cyclothymia is classified under 'Persistent mood disorders' and is defined as a persistent course of fluctuating mild depression and mild elation. These 'episodes' are not severe enough to meet criteria for BAD or recurrent depressive disorder.

Summary of major differences in ICD-10, ICD-11, and DSM-5 and their implications

A future aim for both the American Psychiatric Association and World Health Organization has been to harmonize the diagnostic criteria outlined by both DSM-5 and ICD-11, so as to create complementary classification systems. This has not yet been achieved and so this section provides a succinct overview of the more fundamental differences between DSM-5, ICD-10, and the beta version of ICD-11. For a summary of the differences and similarities between these classification systems see Table 1.3.

Structural differences

Perhaps the most conspicuous difference between DSM-5 and ICD-10 is that, in the former, bipolar disorders are placed in a separate section between schizophrenia (and other related disorders) and depressive disorders. This shift reflects the emerging neurobiological links between these disorders, especially in terms of genetics. However, given that phenomenologically bipolar disorder consists of both mania and depression with predominance in fact of the latter, separating depressive and bipolar disorders as distinct entities lacks face validity and may not be meaningful. In contrast, ICD-10 captures both depressive and bipolar disorders within a single mood disorders section. ICD-11 beta version maintains this grouping, which is then divided into depressive and bipolar sections.[12]

Mania

Another key distinction is the diagnosis of bipolar II disorder in DSM-5, which is absent from ICD-10. A second equally significant point of difference is that ICD-10 does not recognize the occurrence of a 'single manic episode' as a criterion sufficient for diagnosing bipolar I disorder whereas DSM-5 does and predicates the diagnosis wholly on mania. Furthermore, DSM-5 distinguishes between mania and more

Table 1.3 Differences and emerging similarities between DSM-5, ICD-10, and ICD-11

	DSM-5	ICD-10	ICD-11 (beta version)
Differences			
Structural grouping	BD and related disorders and depressive disorders defined in two separate but adjacent sections.	BAD and MDD included in mood disorders section.	As ICD-10.
Cyclothymia	Will not satisfy criteria if mood is stabilized for more than 2 months at a time.	Allows for stability of mood for months at a time.	Mood symptoms present more often than not over a 2-year period.
Mixed episodes	Included as a specifier for depressive, manic, & hypomanic episodes in both bipolar disorder and MDD.	Mixed episodes are a separate diagnosis within the BAD section. A separate diagnosis is given for a single mixed episode.	Remains a potentially separate diagnosis (a diagnostic subtype for BD I with equivalence to mania). Can be a single or multiple episode
Points of potential convergence			
Bipolar II disorder	Includes BD I disorder (relevant to manic episodes) and BD II disorder (relevant to hypomanic episodes).	No BD II diagnosis. Hypomanic, manic, and mixed episodes subsumed under BAD diagnosis.	Includes BD I disorder (relevant to manic episodes) and BD II disorder (relevant to hypomanic episodes).
Bipolar I disorder, single manic episode	Requires at least one manic episode to meet criteria for BD I.	Cannot meet criteria for BAD with a single manic episode.	Requires at least one manic episode to meet criteria for BD I.
Increased activity or energy	Included as one of the two key essential criteria for a (hypo) manic episode (criterion A). Thus, is specifically required to meet diagnostic criteria for a (hypo) manic episode and BD I and II.	Not specifically required to meet diagnostic criteria for a (hypo)manic episode; however, included in criterion B.	Included as essential for meeting BD criteria.

Data from *Diagnostic and statistical manual of mental disorder*, 5th ed., 2013, American Psychiatric Association; data from International Classification of Diseases (ICD), version 10. Copyright (1992) World Health Organization.

modest presentations such as hypomania, which in conjunction with depressive episodes define bipolar disorder I and II respectively. In comparison, ICD-10 is less granular and simply subsumes recurrent hypomanic, manic, or mixed episodes within the broader diagnosis of BAD. These fundamental differences in classification can lead to significant discrepancies in clinical, research, and epidemiological data. Fortunately, the soon-to-be-released ICD-11 is likely to partly rectify these problems. The beta version suggests that ICD-11 will distinguish bipolar disorder I and II, as well as redefine bipolar I disorder criteria to include 'one or more manic or mixed episodes'.

Increased activity or energy in mania

An important development in DSM-5 is the addition of 'abnormally and persistently increased goal-directed activity or energy' in combination with the mood elevation (or irritability) criterion. This is specifically required to meet diagnostic criteria for a (hypo)manic episode and bipolar I/II disorder. This refinement better reflects real-world presentations and improves the specificity of diagnosis but there is a risk that it broadens the category and compromises sensitivity. While ICD-10 does include increased energy and activity as a symptom in bipolar disorder, it attracts less emphasis than in DSM-5 (eg, a diagnosis of (hypo)mania does not necessitate an increase in energy or activity). However, the beta version of ICD-11 follows the example of DSM-5 and includes 'increased energy and activity' as an essential criterion for the diagnosis of bipolar disorder.

Another significant development in DSM-5 is that mania persisting beyond the effect of an antidepressant or electroconvulsive therapy is now regarded as equivalent to a manic episode and, in an attempt to recognize variants of mania such as those triggered by treatment, ICD-11 alludes to shortening of the duration criteria in relation to treatment for mania.

Cyclothymia

In DSM-5, cyclothymic disorder essentially describes an individual with abnormal but subsyndromal vicissitudes of mood present for at least half the time during a two-year period. It is relatively unchanged since the time of Kahlbaum and Hecker.[13] Specifically, it stipulates that the individual cannot be without hypomanic or depressive symptoms for longer than two months at a time whereas, interestingly, ICD-10 allows for stability of mood for months at a time. This requirement by DSM-5 for mood stability to last no more than two months at a time has been criticized for being somewhat arbitrary because there is no evidence supporting this particular duration (or indeed any length of time) between episodes. Furthermore, it detracts from the core features of cyclothymia; namely, the persistence of subsyndromal symptoms over a period of years.[14] Thus, the ICD-11 (beta version) definition of cyclothymic disorder does not include this caveat and instead specifies that symptoms should be present for 'more of the time than not' during a period of at least two years.

Mixed episodes

In a dramatic change, DSM-5 has eliminated DSM-IV mixed episodes, effectively negating their status as a separate diagnosis. Instead, mixed presentations are

now captured through specifiers attached to either depressive or (hypo)manic episodes and this can be applied to both bipolar disorder and unipolar depression. The 'mixed features' specifier requires that at least three symptoms from the opposite affective pole are present. This relaxation of the previously more stringent requirements in DSM-IV—namely, fulfilment of complete criteria for both a manic and depressive episode for one week—means that mixed presentations will be diagnosed more widely. This reflects reality because, in practice, patients with mixed or subsyndromal features are relatively common but were not coded or captured by DSM-IV criteria.[15,16,17] Thus, including mixed features as a specifier in DSM-5 affords the opportunity to describe patients with greater accuracy and specificity. However, apart from simply increasing the number of individuals who will receive a diagnosis of bipolar disorder, the mixed features specifier, as currently defined, will also generate new problems because of its exclusion of those features that are common to both depression and mania.[18,17] The selection of some features over others has been criticized because exclusion of psychomotor agitation, irritability, and distractibility removes the core features of mixed states. Based on clinical experience and research evidence, mixed presentations often feature distractibility, irritable mood, and psychomotor agitation.[3,19,20,21] Currently, ICD-10 accommodates mixed episodes within BADs, and the diagnosis requires at least two affective episodes that are both prominent for the greater part of the current episode of illness, lasting for at least two weeks. For a single mixed episode, an entirely separate diagnosis exists within the 'other mood disorders' section, which stipulates an affective episode lasting for at least two weeks characterized by either a mixture or rapid alternation (usually within a few hours) of hypomanic, manic, and depressive symptoms. In line with proposals from some researchers, the current beta version of ICD-11 retains mixed features as a separate diagnosis subsumed within bipolar I disorder only.[22] The inclusion of mixed features as a specifier relevant to any bipolar or related disorder diagnosis, as in DSM-5, emulates more of a dimensional rather than categorical approach to defining clinical features, as in ICD-10/11. However, there may be disadvantages associated with including mixed episodes as a specifier rather than a separate diagnosis; for example, it may decrease the specific research focus on mixed states and could potentially lead to ineffective treatment of mixed states with antidepressant monotherapy.[18,21,22]

Conclusion

This chapter has described the nature of the diagnostic classification of bipolar disorders in DSM-5, and ICD-10 and -11. In doing so, it is apparent that while both the American Psychiatric Association and WHO are attempting to harmonize the diagnostic criteria in both DSM-5 and ICD-11, many subtle differences remain. These are important because they will impact both clinicians and researchers and generate differing epidemiological data.

Current psychiatric nosology remains dependent on phenomenology and cannot advance significantly until reliable neurobiological markers are discovered. Therefore, clinicians need to rely on careful clinical assessment, ideally longitudinally, to arrive

at diagnoses and this is especially important for an illness such as bipolar disorder—a chronic recurrent illness that remains challenging to define and treat.

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Chapter 2

Should the bipolar disorders be modelled dimensionally or categorically?

Gordon Parker and Amelia Paterson

Introduction

The modelling of psychiatric illness underpins the way we think about disorders, plan treatment approaches, and educate others about these conditions. As such, the modelling of psychiatric conditions may be deceptively important. Psychiatric disorders are either modelled categorically or dimensionally, with diagnostic manuals usually imposing a categorical model as they seek to classify 'cases'. While the modelling of psychiatric illness is of concern to modern psychiatrists, dimensional versus categorical approaches to modelling have been considered and compared since ancient Greek times. As detailed by Goldberg,[1] Plato championed the categorical approach to classification while Aristotle favoured the dimensional approach and, as such, they are often referred to as the Platonic and Aristotelian approaches, respectively.

Goldberg noted several ascriptions to the categorical 'Platonic' approach,[1] later associated with Kraepelin. Firstly, it assumes that conditions are independent. Second, that individuals can be classified as 'cases' or 'non-cases' in relation to a condition. Goldberg suggested that the contrasting Aristotelian dimensional approach is most closely associated with the work of Adolf Meyer—who effectively proposed a model of 'reaction types', with conditions being defined simply by severity. Meyer judged that it was more important to pay attention to the patient's experience than to their clinical features and diagnosis, especially since, as psychotherapy was the treatment of choice for all conditions, diagnosis was considered of little importance. Goldberg observed that 'diagnoses according to the Aristotelians, are man-made abstractions, liable to be discarded or modified according to their usefulness'.

Returning to the issue of 'caseness', Goldberg observed that the strict Platonic view positions illnesses as akin to the concept of pregnancy—in that you either have the condition or you do not. In essence, you cannot sensibly be a 'little pregnant any more than you can be intensely pregnant'. He noted that this approach creates difficulties for those who have symptoms at the sub-threshold level and that the case/non-case model would simply view them as having a *low probability* of having the

condition (rather than a *less severe* condition). Goldberg noted that, in contrast, the Aristotelians have no problem with sub-threshold cases as their model is dimensional and they are able to assimilate the concept of severity within their model.

Goldberg's summary position was that 'categorical and dimensional models are merely alternative ways of looking at the same data; it is not that one is right and the other wrong'. We argue an alternate 'and/or' view—that there are some psychiatric conditions (eg melancholia, bipolar disorder) that are quintessentially categorical and some (eg personality disorders) that are dimensional. The task of psychiatric classification is therefore to determine which is *the* valid model for the particular condition rather than adopt a Procrustean approach of imposing a single umbrella model across all conditions as if it has universal application. A reasonable aspiration but, in light of the lack of validating measures, difficult, if not impossible, to resolve for most conditions.

Theoretically, we might also assume that 'diseases' have categorical status (ie you either have the disease or you do not) whereas 'non-diseases' are more likely to reflect extensions of normal states (eg anxiety, personality style) and are therefore intrinsically dimensional. Such a model, therefore, obliges us to define disease and non-disease states. Taylor provided one model in suggesting three levels of categorization—diseases, illnesses, and predicaments.[2] Predictably, the three levels vary by the putative relevance of biological, social, and cultural factors.

The disease category was conceptualized by him as being a physical reality, based on changes in the structure of tissues but does not necessarily include any physical suffering or 'illness' (ie one can have a disease but not be ill) and with schizophrenia being an example. The illness category weights the subjective experience of the patient and incorporates the social role of being ill, and with anxiety states providing an example. In contrast to the disease category, illness is based on the description of its perceived phenomena rather than any alteration in bodily tissues. Finally, the predicaments category was conceptualized as capturing 'problems of living' conditions (eg dependence on illicit drugs) and is both diverse and changeable, being based on the person's experience of environmental phenomena as well as on social and cultural expectations.

Any aversion to categorical models in psychiatry is not mirrored in clinical practice. Clinical psychiatrists who operate to a categorical model generally seek to diagnose with some precision for two principal reasons—firstly, for communication to the patient and to colleagues, and secondly, because they assume that differing conditions require quite differing therapeutic approaches. In contrast, psychiatrists who operate to a dimensional model will have less interest in diagnosis, and weight dimensional constructs like severity as they judge such constructs to shape the patient's level of distress and help-seeking behaviour, and often the treatment to be provided (eg electroconvulsive therapy (ECT) for severe depression, antidepressant drugs for moderate depression, and psychotherapy for mild depression).

Categorical psychiatric models can be readily challenged for their failure to demonstrate clinical features that define the condition at the 'necessary and sufficient' level and are also specific to that condition (ie are not possessed by any other condition), as well as for failure to demonstrate distinct biological determinants and/or to

have a benchmark diagnostic test. Such criteria have not been met for any psychiatric condition, a reality that has led to nihilism about any attempt to delineate psychiatric diseases—and the suggestion that psychiatry is unable to 'carve nature at its joints'.

Such a problem is, however, not unique to psychiatry and is handled in varying ways in other fields. For example, anthropologists use the construct of 'thick description' in allowing definition by 'patterns' and accepting that the patterns (not dimensions) are imprecise. In medicine, however, only a minority of conditions have specific clinical features and/or a confirmatory laboratory test. Neurologists nevertheless position Parkinson's disease as a 'categorical' disease—in that it is either present or absent—although it has variable rather than absolutely specific clinical features. Respecting its prototypic expressions, they make a probabilistic estimate as to whether Parkinson's disease is present or absent on the basis of a number of the variable clinical features. In essence, they assume a categorical model and seek to differentiate Parkinson's disease from other causes of parkinsonism rather than adopt a primary dimensional model which might simply weight severity of the condition or of its components such as gait disturbance or tremor.

The use of such a categorical model has advantages (subject to the condition being quintessentially 'categorical') in being more likely to identify those with or without the condition and in heuristically advancing research into its causes and optimal treatment. Thus, there are many advantages to psychiatry seeking to identify those conditions which are categorical. A dimensional model is appropriate for those states that are truly dimensional and may be appropriate as a default option for conditions whose status remains indeterminate. Such an approach—of allowing both models—assumes that the underlying structure of the condition is respected and categorical or dimensional status is accorded on the basis of supportive validity data rather than simply opinion. Building on criteria proposed by Robins and Guze,[3] we can argue that, if a condition is truly intrinsically categorical, it might be reasonably assumed to have prototypic clinical features, to have a relatively specific primary cause (be it biological, psychological, or social), to have its own intrinsic natural history and to have a preferential response to treatment. In considering the bipolar disorders, we will argue the greater relevance of a categorical rather than a dimensional model by reviewing such criteria.

It is important to note that it is possible to dimensionalize everything and, conversely, to create categories or pseudo-categories from intrinsically dimensional constructs. For instance, most people asked to distinguish between a building and a car would effectively differentiate them as independent categorical entities. However, those holding a dimensional view might simply differentiate them as one being big, the other small, both lying along a dimension of 'size'. Which is likely to be the more valid model? Which the most informative? Conversely, entities may be 'dimensionalized'. For example, in a study by Krueger et al. on dimensionalizing psychiatric conditions,[4] factor analyses of DSM-III-R clinical features for ten disorders (major depression, dysthymia, generalized anxiety, agoraphobia, social phobia, simple phobia, obsessive compulsive disorder, conduct disorders, marijuana dependency, and alcohol dependency) were imposed. The authors concluded that their two-factor solution was the best, being able to simply refine the clinical features into two contrasting

'internalizing' and 'externalizing' dimensions. In essence, quite disparate psychiatric conditions were 'dimensionalized' along internalizing and externalizing domains. The model was empirically derived but how intrinsically valid is it and, more importantly, how useful is it in clinical practice?

Psychiatry's classificatory manuals weight or impute diagnostic 'categories' and, commonly, impose categories on underlying dimensions. Recent *Diagnostic and Statistical Manual of Mental Disorders* (DSM) manuals classify personality disorders in this way, by assigning a diagnosis when a set number of criteria are met. The *International Classification of Diseases* (10th revision) (ICD-10) likewise distinguishes between 'severe', 'moderate', and 'mild' depression, albeit with qualitative descriptions differentiating the three 'categories'. The problem with the imposition of any cut-off score is that it will, of necessity, assign some false positives and some false negatives. There is an additional problem that has emerged from the dimensional approach. The DSM-III criteria for obsessive–compulsive disorder were set at a lower cut-off than previous 'case' definitions and resulted in a substantive increase in the prevalence of the condition. DSM-III introduced a diagnosis of major depression and a set of minor depressive categories. Subsequently, the depressive dimension was extended by many theorists to include sub-clinical or sub-syndromal depression. In the 1950s, clinical depression was thought to have a lifetime risk of less than 5%. Now if such depressive extensions are included, it is a ubiquitous experience. Extending 'caseness' to such a low level rightly risks judgements about psychiatry 'pathologizing' sadness and misery in relation to mood disorders, and similar concerns about several other listed conditions.

In considering the bipolar disorders we can examine the data at several levels. Firstly, do the bipolar disorders differ categorically or dimensionally from the unipolar disorders? Secondly, do constituent bipolar disorders differ categorically or dimensionally from each other?

Distinguishing bipolar disorder from unipolar depression

The bipolar disorders were once effectively viewed as belonging with the unipolar depressive disorders. As detailed by Goodwin and Jamison,[5] 'the French 'alienists', Falret and Baillarger, independently and almost simultaneously formulated the concept that mania and depression could represent different manifestations of a single illness. Griesinger viewed mania as the end stage of a progressively worsening melancholic depression and viewed both as reflecting different stages of a unitary condition.[6] While Kraeplin made the distinctive contribution of separating dementia praecox and manic-depressive insanity, he positioned all of the major affective disorders (including mania) into a single category and, as observed by Goodwin and Jamison, doubted that melancholic depression and the bipolar disorders were really separate illnesses.

It was not until 1957 that Leonhard introduced a bipolar-unipolar distinction, following his observation that, for those who had recurrent affective illnesses, some experienced both depression and mania, while others experienced depressive

episodes only. He further noted that those patients with a history of mania had a higher rate of mania in their families compared to those with recurrent depressive episodes only.

The categorical bipolar-unipolar distinction was not introduced into formal classificatory systems until 1980 when it was incorporated into the DSM-III and subsequently into the ICD-10 manuals. Thus, prior to Leonhard's classification, the bipolar disorders were positioned together with the unipolar depressive disorders and, at times, positioned together with schizophrenia. Bleuler,[7] in particular, viewed the relationship between manic-depressive illness and schizophrenia as a continuum without a sharp line of demarcation.[5] However, modern psychiatric manuals now unequivocally position the bipolar disorders as categorically different to the unipolar disorders.

Bipolar II disorder similarly developed gradually from what was previously an undifferentiated domain largely neglected by psychiatry. The concept of hypomania was first defined by Mendel in 1881 in his work '*Die Manie. Eine Monographie*' (which translates to 'The Mania. A Monograph'), in terms strikingly similar to the modern definition of hypomania. The symptoms were primarily elevated mood, pressured speech, and increased motor activity consistent with the typical clinical picture of mania but to a lesser degree.[8] The term cyclothymia was then used by Kahlbaum in 1882 to describe alterations between elation without psychosis and melancholia which did not progress to dementia.[9]

During the early twentieth century, personality-based mood fluctuations—cyclothymia and hypomania—were lumped together as 'the milder forms of the manic depressive psychosis'[10] and among a subset of practitioners, concern as to how to diagnose and treat such conditions was evident. However, from the 1930s to 1970s, the concept of hypomania or 'milder forms' of bipolar disorder seems to all but have disappeared from the literature. It was not until 1969, when Dunner began work at the National Institute of Mental Health, that research on anything resembling a bipolar II category began. His seminal work looked at a category of bipolar I participants, a category of unipolar participants and a category he describes as 'in between'—who experienced hypomania but not mania (Dunner, personal communication). He reported that the bipolar II participants had manic symptoms similar to the bipolar I sample but to a less severe degree. He also found that the bipolar II group were similar to a bipolar I group in the likelihood of having relatives with bipolar disorder and that the bipolar II group was at higher risk of suicide compared with both bipolar I and unipolar groups.[11]

With the 1980 release of the DSM-III, the concept of hypomania was for the first time officially defined as 'a clinical syndrome that is similar to, but not as severe as, that described by the term "mania" or "manic episode" '. However, bipolar II disorder was still considered an 'atypical bipolar disorder' and considered only briefly in that edition of the manual, without any formal diagnostic guidelines provided. This meant that, although bipolar II began to be used as a category in research studies, without formal diagnostic criteria it was left to each independent research to decide what 'similar to, but not as severe as' mania might mean. Consequently, research studies varied in their classifications and terminology with some referring to 'bipolar

other', 'unclassified', or 'UP+' when referring to what we would now consider bipolar II disorder (Dunner, personal communication). Rifkin (a member of the DSM-III Work Group) is quoted as saying that 'a diagnostic scheme must do a lot of lumping, and I doubt if it's worth making a separate category for an episode of hypomania'.[12] Dunner noted that as mania was uncommonly diagnosed in America at the time, supporting both a unipolar/bipolar distinction and bipolar I/bipolar II distinction was an unpopular position (personal communication).

Dunner and Tay[13] eventually established that bipolar II (with a hypomanic episode of three or more days) could be reliably diagnosed by experienced clinicians, a finding which was largely responsible for the inclusion of a bipolar II disorder in the DSM-IV in 1994. However, the ICD-10 had meanwhile defined hypomania as being four or more days and, as a consequence, a minimum period of four or more days was imposed as a DSM-IV criterion for hypomania in order to maintain consistency.[14]

Dimensional modelling of the bipolar disorders

While there are some theorists who position the bipolar disorders (bipolar I and bipolar II) as lying along a dimension that ranges through to the unipolar disorders, dimensional models tend to focus on the extent to which there may be a continuum within the bipolar conditions. The most accepted bipolar disorders are bipolar I and bipolar II and they define the territory for consideration of the extent of which these two conditions are best differentiated. Some consideration should also be given to bipolar III states (which are generally viewed as states of mania or hypomania induced in response to the initiation of an antidepressant or its rapid increase in dose). However, the bipolar dimension has been extended beyond this by many theorists.

Akiskal has been a strong proponent of a 'spectrum' or dimensional model for the bipolar disorders. His bipolar spectrum theory arose from findings that there are some patients lacking documented highs but who have a hyperthymic temperament (a personality style marked by being consistently happier than the average). These hyperthymic unipolar patients are similar to bipolar patients in terms of a family history of bipolar disorder and the percentage of male cases.[15] In one paper,[16] bipolar I is positioned as quintessential manic depression, bipolar II captures those with depressive and hypomanic mood swings, bipolar III is hypomania associated with antidepressant medication, bipolar IV is depression superimposed on a 'hyperthymic temperament', and bipolar V is 'cyclic mixed depressions'.[17,18] In another paper, Akiskal further developed the spectrum model to include both a bipolar VI category defined by cognitive decline and mood instability with an onset in older age[18] and a bipolar II ½ category defined by cyclothymia with depression.[19] Akiskal has further argued[20] for a set of behavioural signs that identify bipolar II disorders being declared in behavioural ways rather than by mood disturbances (a 'soft spectrum'). Such behaviours or traits include polyglotism (the ability to master many languages), eminence, creative achievement, professional instability, multiple marriages, a broad repertoire of sexual behaviour, impulse control problems, as well as ornamentation and flamboyance (principally involving red and other bright colours). Akiskal has

proposed the 'rule of three' hinting at soft bipolarity. Exemplars include three failed marriages, three failed antidepressants, three simultaneous jobs, proficiency in three languages, flamboyance expressed in a triad of bright colours, three impulse control behaviours, and simultaneous dating of three individuals.

Such a model is quintessentially dimensional in assuming a gradation of severity. It is—as for diagnostic manuals—categorical in that grades (one to six) are assigned as if diagnostic differentiation can be accorded at each level.

Angst et al.[21] also proposed a categorical broadening of the bipolar disorder domain by use of a bipolar specifier. Their bipolar specifier was designed for use with a DSM-IV-TR diagnosis of a Major Depressive Episode in those with some symptoms of bipolarity. The bipolar specifier broadens bipolar diagnosis to those who are excluded from DSM diagnoses by including those with only three symptoms of bipolar disorder when irritable, those who only experience highs when taking an antidepressant, and those who only experience highs shorter than four days. Use of the bipolar specifier compared to DSM-IV-TR criteria increased the likelihood of bipolar diagnosis in a depressed sample by almost three times. They suggest this indicates that a large number of patients diagnosed with a unipolar condition could be more meaningfully be conceptualized as sub-threshold bipolar disorder.

A strong proponent of a dimensional model is Phelps whose detailed argument[22] will now be summarized. He argues that patients with mood disorders occupy a 'continuum between major depression and bipolar disorder (as extremes) but without any natural dividing points to separate the two', allowing that varying degrees of bipolarity are possible. He is not alone in such an opinion, with the diagnostic guidelines for bipolar disorder issued by the International Society for Bipolar Disorders suggesting that bipolar II disorder is best characterized as part of a spectrum of bipolar illness.[23] Phelps then argued against the categorical model on the basis that if two illnesses present similarly but are truly independent conditions then there should be 'zones of rarity' between them, or points on a continuum where no patients can be placed. Thus, between unipolar and bipolar depression all patients with the unipolar expression should be on one side of the gap and all patients with bipolar disorder on the other side. Phelps refers to two studies which compared the number of hypo/manic symptoms experienced by those with depression and those with bipolar disorder. If a zone of rarity exists then the depressed participants should have few hypo/manic symptoms while the bipolar participants should have many and there should be nobody in between. Such a zone of rarity was not found.[24,25]

Next he reviewed a study by Ghaemi et al.[26] which identified a number of bipolar 'soft signs'. Such features include repeated episodes of major depression, early age of onset of major depression, a first-degree relative with a bipolar disorder, a hyperthymic personality, atypical symptoms when depressed, brief episodes of major depression, a psychotic episode of depression, post-partum depression, hypo/mania while taking an antidepressant medication, loss of response to an antidepressant medication, and seasonal mood shifts. In essence, those authors argued for bipolar status being able to be predicted on the basis of such soft signs rather than on the basis

of formal hypo/manic features. The logical problem here is that it risks allocating a bipolar diagnosis to an individual who has never had any hypo/manic symptoms.

Phelps advocated consideration of both soft signs and individual bipolar symptoms when considering where a person may lie on the bipolar spectrum and utilizing a Bipolar Spectrum Diagnostic Scale to examine all of the necessary components in a structured manner. He proposed that using the scale allows the clinician to establish whether the patient shows *any* indication of bipolarity and from there recommends a collaborative approach where the patient is encouraged to investigate their own symptoms. He indicates that a collaborative approach allows the patient to be the expert in their own condition and will so produce a more ecologically valid model of their experiences on which to base treatment.

However, the consideration is then, as conceded by Phelps, how much bipolarity is enough to change a unipolar treatment strategy for a bipolar treatment strategy? Phelps does not provide a pristine answer, instead raising issues important for consideration. Treatment risk is the primary concern, with risks coming in many forms. The risk of treating a patient with underlying bipolarity (who does not meet criteria for bipolar disorder) with an antidepressant has not been established. Phelps extrapolates from the bipolar literature to assume that, as antidepressant treatments have risks in bipolar disorder (in causing switching, mixed states, or a worse illness course), it may be reasonable to assume a level of risk in sub-threshold bipolarity. Inversely treating those with a truly unipolar condition with a mood stabilizer invokes the risk of side effects associated with those medications, which may be greater than the side effects associated with antidepressants. The issue here is how much the patient requires antimanic efficacy in their medication compared to how much they require antidepressant efficacy. Where there is a question of 'how much' bipolarity a patient has, Phelps raises the possibility of an antidepressant treatment which is not an antidepressant and details nine treatments with known antidepressant efficacy which are not antidepressants. These include exercise, psychotherapy, light therapy, lithium, omega 3, thyroid hormones, lamotrigine, quetiapine, and olanzapine. If the patient is aware of their own condition and an active participant in investigating their own symptomatology, then a discussion of the risks and benefits of such treatments may be the most robust solution.

Rather than adopt a spectrum approach entirely, Phelps advocates the use of a spectrum model alongside the traditional categorical model. For example, for a patient with a clear-cut bipolar I condition the inclusion of a spectrum model in psychoeducation may only be confusing. However, when there is some question of bipolarity, a spectrum approach may be an informative conceptualization for both the patient and clinician.

Categorical modelling of the bipolar disorders

Recent DSM manuals (including DSM-5) define mania and hypomania (and thus bipolar I and bipolar II disorders) categorically but, paradoxically, with very similar criteria sets. In essence, DSM symptoms are identical for both mania and hypomania—as is the cut-off score for their presence—so that the two conditions are

essentially only differentiated across duration, severity, and hospitalization parameters. Each is limited in application. Duration is problematic as the DSM imposition of four days for hypomania and seven days for mania were generated by expert opinion and consensus rather than empiricism. In one of our studies,[27] the imposition of those minimum duration criteria would have denied a bipolar I diagnosis in 46% of the relevant patients and some 60% of the bipolar II subjects. 'Severity' is extremely difficult to judge, and especially the simple DSM-5 barrier of mania and hypomania being associated with and without 'marked impairment' respectively, and when those in hypomanic states may actually have improved functioning. Hospitalization is theoretically problematic, in that there is no medical condition defined by hospitalization, a criterion which also assumes such an option as being available to all those with the condition.

Categorical models have essentially been developed theoretically rather than from any primary empirical approach. We now overview two empirical studies that we undertook. Firstly, in essence, after examining for differences between bipolar I and bipolar II participants[27] an 'isomer' model for distinguishing between the two groups was proposed. The study used an extension of the DSM-IV diagnosis for mania, where bipolar I participants were required to experience either (i) distinct impairment, (ii) psychotic features at any time, or (iii) hospitalization during a high but were not required to be manic for any particular duration. A bipolar II diagnosis was assigned to those who met DSM-IV criteria for hypomania (again ignoring any duration criterion) but did not experience any of the three noted specific bipolar I features. Of the 157 participants recruited, 49 were assigned to a bipolar I group and 52 to a bipolar II group. Psychotic features were relatively common in the bipolar I group (being experienced by two-thirds) while one-third had required hospitalization. Importantly, 41% of the bipolar I participants had experienced psychotic features when *depressed* compared with 0% of the bipolar II participants. Further, there were no significant differences between the bipolar I and II groups in the severity of manic or hypomanic symptoms, suggesting the 'core' mood and energy constructs to bipolar disorder was not likely to differentiate between the conditions.

A follow-up study was conducted in a larger sample to examine the validity of such a model.[28] Using a clinically diagnosed sample of 632 bipolar participants, those with psychotic symptoms when high were assigned to a bipolar I category while those without such symptoms were assigned to a bipolar II category. Comparable with the previous research, a large number of the bipolar I participants also experienced psychotic symptoms when depressed (57.4%) while only a small number of bipolar II participants experienced psychotic depression (8.1%). The psychosis-weighted diagnostic model also provided greater differentiation between bipolar I and II groups (compared with DSM diagnosis) on employment status, family history of bipolar disorder, and (contrary to expectation) (hypo)manic symptom scores. The differential between bipolar I and bipolar II groups when diagnosed according to this model suggests it is truly separating groups at an intrinsic 'joint' in their natural presentation.

We therefore argue for a categorical 'isomer' or 'mirror image' model. The isomer model posits a core mood and energy component for both mania/hypomania and depression, which is dimensionally but not categorically more severe in bipolar

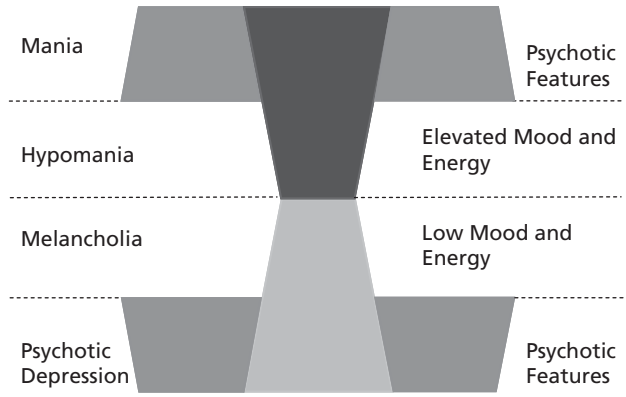

Figure 2.1 The core and mantle model

I than in bipolar II. The model then includes a psychotic 'mantle' where, during elevated mood and energy phases the bipolar I patients have experienced categorical psychotic features at some stage of their life during manic episodes (and often during depressive episodes) while the bipolar II patients have never experienced psychotic features when 'high' or when depressed. Thus, the model contains both dimensional and categorical components. The core mood and energy construct is dimensional (and not incisive in differentiating bipolar I and II states) while the presence or absence of psychotic features when high is categorical and provides the point of differentiation between bipolar I and II states (see Figure 2.1).

Less categorical but of some clinical importance is that our findings also indicated that bipolar I depression is likely to be psychotic depression or melancholic depression in its nature, while bipolar II depression is virtually never psychotic in nature but likely to be melancholic in its type.

More recently, in a second study, we[29] conducted a mixture analysis on 1,081 clinically diagnosed bipolar I and II outpatients using scores on hypomanic severity to determine whether there was evidence of bimodality. Our results suggested the presence of a two sub-population solution (thus, indicating bimodality), arguing for a categorical distinction of the bipolar disorders and with the presence/absence of psychotic features when 'high' as the most substantive feature in determining subtype differentiation.

In conclusion, while there are many different ways to conceptualize the bipolar disorders, the choice of a categorical or a dimensional model is based on multiple factors. First and foremost, the model has to respect the underlying nature of the disorders and therefore be a valid reflection of natural conditions. While both dimensional and categorical models have some support from empirical studies, neither is irrefutable and as such it is, as yet, up to the individual clinician to determine which model reflects the clinical population. Secondly, from a utility perspective, it is important to consider which model allows for useful treatment decisions to benefit the patient. While a categorical model allows for simplified treatment decisions and psychoeducation, a spectrum model allows for more variability in presentation which may be

of benefit to some patients. It is the opinion of the authors that considering both the underlying nature of the bipolar disorders and the utility of the models in clinical practice, a categorical model would be most appropriate. In particular, hypomanic and manic features show specificity to bipolar I and II disorders respectively, while those conditions appear to show differential response to differing mood-stabilizer medications, with lithium appearing more appropriate for bipolar I and lamotrigine for bipolar II disorder.[30] Additionally, the respective presence or absence of psychotic features distinguishes bipolar I disorder from bipolar II disorder. Thus, a categorical model appears the more appropriate model for conceptualizing differences between the bipolar I and II states.

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Chapter 3

The treatment of bipolar disorder in its early stages: current techniques, challenges, and future outlook

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Introduction

In recent years in psychiatry, a renewed focus on prevention and early intervention across various illness domains has arisen.[1] This is in part related to the simple logic that if a condition can be prevented or illness trajectory optimized, improved prognosis and reduced burden of disease (for the individual and society) may follow. More recently, the increasingly unsustainable costs of healthcare have led to prevention and early intervention becoming even higher health policy and research priorities.[1] For these important reasons, prevention and early intervention are of central importance in the optimal management of bipolar disorders.[1]

Bipolar disorder tends to begin with symptoms of depression rather than mania, which is what is required for diagnosis, and the prodrome of the disorder is even more non-specific, with symptoms of anxiety, sleep disturbance, attention and behavioural symptoms common, as is substance abuse. There is also a lack of robust (sensitive and specific) clinical and biomarker predictors of onset of bipolar disorders.[1] This has made the task of prevention and early intervention more challenging. Nonetheless, given the clear importance of this pursuit, renewed efforts at biomarker discovery have included emphasis on prevention. 'P4 medicine', characterized by predictive, preventative, personalized, and participatory approaches,[2] has become the framework for novel technologies such as genomics and digital healthcare. It is important for clinicians at the frontline of care to remember that new medical technologies need to be housed within the public health wisdom of this P4 model of healthcare.

Early intervention (also known as secondary prevention) has been pioneered in psychiatry over the past two decades, with novel early intervention for psychosis programs gaining global traction since emerging in the mid-1990s in Australia. While the literature and clinical services for early intervention in bipolar disorders

are considerably less developed than those for schizophrenia and psychosis, early intervention in bipolar disorders has also been an emergent focus of research over the past decade in particular.[1] This chapter seeks to provide readers with an overview of the current state of the art in early intervention in bipolar, challenges in the field, and promising areas of research which may translate to enhanced clinical care in years to come. Indeed, for early intervention in bipolar disorders there may be even greater opportunity to retard neuroprogression, the progressive damage occurring to the brain with subsequent episodes of illness, than in schizophreniform psychosis, given there seems be less structural brain changes at incident episodes than for schizophreniform psychotic illnesses.[3] The emergence of nutraceutical and lifestyle-based therapeutics acting on inflammatory and neuroprotective pathways offers an interesting opportunity for low-hazard therapeutic trials in the non-specific prodrome of illness.[1] Should the body of evidence for such reach a tipping point, it is plausible that one day there will be active neuroprotective interventions suitable for those in prodrome.[1] As initial studies in this frontier move to larger comparative cohort studies, the utility of this latter approach may eventually be established, but at this stage this area remains an important research front.

Illness staging and minimizing the impact of neuroprogression

Staging bipolar disorder

In several sub-disciplines of medicine, the concept of stage of illness is employed to better tailor care and optimize outcomes. Oncology with its 'Tumour Node Metastasis' system, and cardiology with its American Heart Association 'Classes of Heart Failure' system are prime examples. For most psychiatric conditions—bipolar disorders included—there is a lack of clarity of the underling pathophysiology. This clearly makes application of the staging approach used elsewhere in medicine more difficult. Nonetheless, there do appear to be multiple threads of both clinical and biological empirical data suggesting that a staging model may have real-world utility in bipolar disorders.[1,4]

Historically, in psychiatry many conditions have presented late—after many years of symptoms and untreated illness. With reduced levels of stigma and better community awareness of mental illness, along with generally greater access to psychiatric services, there is much opportunity in the modern era to both engage patients early in their course of bipolar disorder and study differential outcomes based on earlier interventions.[1] These important social factors have enabled greater study of, and care for, those in the early phases of their illness during the past two decades.[1]

Staging models have been proposed (see for reviews[1,4] and see Table 3.1 for an overview of a recent proposal). The earliest stage is stage 0—this stage reflecting individuals who have risk factors, but as yet have not manifested any clinical features of illness. Risk factors include genetic diathesis, perinatal complications, adverse lifestyle risks, childhood maltreatment, psychological stressors, and substance abuse. The non-specific nature of these risk factors makes specific indicated preventative

Table 3.1 A potential clinical staging model for bipolar disorder

Clinical stage	Definition	Potential interventions
0	Increased risk of severe mood disorder (eg, family history, abuse, substance use) No specific current symptoms	Mental health literacy Self-help
1a	Mild or non-specific symptoms of mood disorder	Formal mental health literacy Family psychoeducation Substance abuse reduction Cognitive behavioural therapy, supportive counselling
1b	Prodromal features: ultra-high risk	*1a* plus therapy for episode: phase specific or mood stabilizer
2	First episode threshold mood disorder	*1b* and case management, vocational rehabilitation, specific psychotherapy
3a	Recurrence of sub-threshold mood symptoms	*2* and emphasis on maintenance medication and psychosocial strategies for full remission
3b	First threshold relapse	*2a* and relapse prevention strategies
3c	Multiple relapses	*3b* and combination mood stabilizers
4	Persistent unremitting illness	*3c* and clozapine and other tertiary therapies, social participation despite disability

Data from Bipolar Disorder, 9.7, 2007, Berk M et al, 'Setting the stage: from prodrome to treatment resistance in bipolar disorder', pp. 671–8; data from *Journal of Affective Disorders*, 100.1, 2007, Berk M et al, 'The potential utility of a staging model as a course specifier: a bipolar disorder perspective', pp. 279-81.

interventions problematic due to a large false positive rate—only a fraction of those with risk factors converting to illness over time. But notwithstanding this, among those with generic and non-disorder specific at-risk profiles, there is value in reinforcing general health steps including healthy lifestyles, self-help strategies, psychological counselling, safer use of substances, and mental health literacy. This is salient as risk factors for mental health disorders overlap with those for other common non-communicable disorders.

In particular, greater awareness of the symptoms of bipolar disorders and when to seek help for them is an important element of mental health literacy—something increasingly accessible in the digital age (see, for example, http://www.bipolarcaregivers.org). Stage 1 describes the prodromal stage—a stage where there remains a paucity of evidence to predict the course of illness. For this reason only general measures as outlined earlier are appropriate, with a particular emphasis on awareness of illness symptoms, when to seek help, and where possible serial review by a clinician to monitor at-risk mental state. Developing a therapeutic alliance, engagement, and trust with a clinician early on can be key determinates of subsequent success in care should illness manifest. There is insufficient evidence to argue for specific treatments of the prodrome at present, but fostering a culture of

psychoeducation and awareness of how to access services should symptoms emerge is a sensible approach.

Stage 2 is defined as the first episode of illness and since mania is mandatory for a *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) (DSM-5) and *International Classification of Diseases* (10th revision) (ICD-10) diagnosis of bipolar I—stage 2 in bipolar I is the first episode of mania, and in bipolar II disorder the first hypomania. It is at this stage that opportunities for early intervention in bipolar arise. This creates some problems with optimal early interventions, as for many cases the first pole to manifest of the illness is the depressive one, but given the need for elevated states to confirm the diagnosis there is no alternative—early intervention approaches to depression notwithstanding. For some cases, their index mood episodes will be an elevated state without any previous depressive episodes; this group potentially having opportunity for earliest possible intervention in their illness, and potentially best prognosis.

Stage 3 of bipolar is recurrence of mood episodes, and is the stage where most research into bipolar disorder has traditionally been conducted. By stage 4, there is by definition a persistent unremitting nature of the illness. It is hoped that early intervention in stage 2 will improve long-term prognosis, but empirical evidence to establish this has not yet been confirmed. Nonetheless, as with early intervention in psychosis (as in cancer and cardiovascular disease), there is a strong argument that engaging people early in their illness course will be linked to better treatment outcomes, help foster adherence with care, and hopefully translate to better long-term outcomes. This is the basic premise behind early intervention in bipolar disorder. Long-term differential outcomes studies stratified by early intervention versus no early intervention are lacking, leading to a need for some caution in the area. This is particularly important at a policy level where if heath resources are diverted from later-stage sufferers to early stage sufferers of bipolar, there is need to be mindful of the empirical limitations of the evidence. Beyond the psychosocial and putative compliance benefits for early engagement, the early intervention model is also predicated on the importance of neuroprotection as a key goal of treatment.[5] Neuroprotection mitigating against volume change in key brain regions, pathways that promote neuronal growth, proliferation, or survival, and protect against neuronal or glial insults forms a putative biological theoretical underpinning for early stage treatment to improved prognosis.[5] Both neuroimaging and neuropsychological studies suggest the neuroprogression model of bipolar has validity, and in turn helps validate the notion of prioritizing early intervention in the illness.[1,5]

Neuroimaging in the neuroprogression of bipolar disorder

Neuroimaging and cognitive evidence suggest that there may be a neuroprogressive aspect to bipolar disorder.[1] Various brain regions have been implicated, including the anterior cingulate cortex, amygdala, hippocampus, basal-ganglia, dorsolateral-prefrontal cortex, and orbitofrontal cortex.[6,7] Importantly, the volumetric abnormalities appear to be dependent on stage of illness—consistent with the neuroprogression hypothesis.[5] But only a handful of studies have examined patients early

in their course of illness. Adler and colleagues[8] identified increased grey matter volumes in a caudal region of the anterior cingulate cortex (ACC). It also appears the pituitary is increased in size in young adults with bipolar disorder,[9] as well as previously published data regarding volumetric increases in the amygdala and pituitary occurring prior to, and shortly after, a first episode of affective psychosis.[3] Collectively, these findings—mindful that there are negative studies—suggest hypertrophy of brain regions involved with elevated stress response around the time of illness onset, ultimately leading to volumetric loss in later stages. Early intervention might be beneficial to inhibit the deleterious downstream biochemical changes associated with bipolar disorder, especially oxidative stress and inflammation, while also exerting neuroprotective effects.[5] These effects may help to mitigate broader neuroprogressive structural changes. For example, the postulated neuroprotective role of lithium is supported in the literature[10] and neuroimaging studies suggest adolescents with bipolar disorder on mood stabilizers—like lithium—may be protected from volumetric brain loss.[11] Additionally, atypical antipsychotics used clinically as mood stabilizers may have neurotrophic or neuroprotective effects,[12] although this literature is inconsistent, and there have been suggestions in preclinical studies that the converse may be true.

Neuropsychology in the neuroprogression of bipolar disorder

Data from neuropsychological studies also helps support the neuroprogressive hypothesis of bipolar disorder, and further underpins the rationale for early intervention. Early studies of cognitive impairments in children at risk of bipolar (due to one or both parents being diagnosed) shows a trend to slowed reaction times on visual tasks,[13] and significant differences between visual and performance IQ.[14] El-Badri and colleagues[15] demonstrated that a greater number of affective episodes were associated with poorer executive functioning and visual task performance in euthymic young adults with varying numbers of previous mood episodes. This finding was supported by a review[16] of 11 studies conducted on the impact of increasing numbers of episodes on neurocognition, concluding there were increasing deficits over increasing numbers of episodes in some papers, while other papers included in the review found no relationship. If the number of previous affective episodes is associated with cognitive impairment, it follows that prophylaxis against affective episodes could slow neuroprogression and improve the prognosis of bipolar disorder in the long term.[1] The literature here is lacking; however, one study found that delay to first treatment was associated with more frequent and more severe episodes of depression and more time spent in rapid cycling states.[17]

Clinical factors in the neuroprogression of bipolar disorder

There is also some evidence that age and illness progression may influence response to treatment. A meta-analysis of 12 double-blinded randomized controlled trials investigating olanzapine (an atypical antipsychotic) use in bipolar disorder found that fewer previous manic episodes was associated with significantly higher response rates to treatment for both mania and depression, and also a lower chance to relapse

into manic or depressive episodes.[18] Another study examined 4,714 Danish bipolar disorder sufferers who were prescribed lithium and found that early prophylactic use of lithium was also associated with significantly improved response to treatment.[19] Furthermore, lithium has been found to be effective in adolescents where it is proposed to be more effective in preventing affective episodes than in adults.[20] It has also been suggested that young adults with bipolar disorder may benefit more from group psychoeducation than older adults.[21] However, another study following 764 bipolar disorder patients found that bipolar disorder morbidity during lithium treatment was unrelated to numbers of previous episodes.[22]

Collectively, both neuroimaging and neuropsychological studies suggest that bipolar disorders may have a staged nature, which could be ameliorated by early intervention, but results have been mixed. It may be the case that certain subgroups of patients are more prone to neuroprogression. Delineating a neuroprotective genetic profile and inflammatory load stratification of diathesis to such neuroprogression may be a useful future strategy.[23] It is also possible that some people are predisposed to go on to 'malignant' or 'benign' courses from the outset, and that the scope for intervention may be smaller than conceptualized. In the interim, the progressive nature of bipolar (in at least some sufferers) helps support the case for early intervention being a priority, with potential to improve the long-term prognosis of the condition. Indeed, on average there is a large delay between the onset of bipolar disorder symptoms and correct diagnosis and treatment which represents a large opportunity for improved care.

Influence of neuroprotective pharmacological therapies in bipolar disorder

Mood-stabilizing agents appear to have neuroprotective effects. Their potential to be disease modifying, to alter the course of illness, is a function of their ability to prevent or impede the cascade of cellular loss underpinning the structural, cognitive and clinical changes in bipolar disorder.[5] The putative mechanisms of action of the mood stabilizers, principally lithium and valproate, but increasingly atypical antipsychotics, include actions that reduce apoptosis and oxidative stress.[5] Treatment with either lithium or valproate increases levels of bcl-2 (an anti-apoptotic protein) in animal studies.[24,25] and atypical antipsychotics also appear to increase bcl-2 levels.[26] Glycogen synthase kinase-3 (GSK-3), is another protein involved in regulating apoptosis and cellular resilience, and has cytoprotective effects.[27] It appears to be inhibited by lithium, and this mechanism may be a key element of lithium's mechanism of action.[28] Lithium also appears to help protect cells from excitotoxic apoptosis, a process that contributes to hippocampal atrophy, and has been shown to increase N-acetyl aspartate—a marker of neuronal viability[29] and to increase grey matter in bipolar patients.[30] Markers of oxidative stress appear to be elevated in bipolar disorder, and both lithium and valproate appear to reduce oxidative stress in preclinical models.[31] Neurotrophic factors such as BDNF (brain-derived neurotrophic factor) have also been implicated in the underlying pathophysiology of bipolar disorder, and again both lithium and valproate, as well as some atypical antipsychotics such as quetiapine, appear to increase BDNF in animal models.[32]

Taken collectively, the neuroimaging and neuropsychological evidence for neuroprogression in bipolar, along with putative neuroprotective mechanisms of mood stabilizers used in bipolar, help to support the case for prioritizing early intervention; the simple aim being to minimize neuroprogression and optimize prognosis for sufferers.

Developmental stage and psychosocial impact minimization

Beyond the case for early intervention to potentially attenuate the neuroprogressive aspects of bipolar and enhance long-term prognosis, there is a pressing argument for the value of early intervention to limit the psychosocial developmental impacts of the condition. Bipolar disorders typically have onset during late adolescence and early adulthood. These are key phases of maturation into adulthood, with establishment of both work and personal life foundations for later adulthood.[1] Developmental impacts during these stages of life stand to disproportionally produce psychosocial adjustment handicaps compared with illness that has onset in later life when many developmental milestones have been attained. Furthermore, the total life burden of disease from a health economic perspective stands to be greater for conditions with onset in early adulthood. For these reasons there is a strong case to optimize early treatments in hopes of minimizing impediment or derailment of normal development in early adulthood.[33,34] Tohen and colleagues[34] noted that when functional recovery from bipolar is not achieved early in the course of illness, it is rarely attained later. The early stages of the disorder provide an opportunity to support normal adolescent development and prevent the development of secondary morbidities, such as financial difficulties, employment difficulties, and poor self-esteem, which may accumulate with multiple affective episodes over time. Conus and McGorry[35] also highlighted the protective impact of interventions assisting young bipolar adults to develop and secure their social networks. Such considerations make a compelling case for early intervention in bipolar disorder.

Engagement and adherence

Early intervention in bipolar is an opportunity to optimize both engagement with care and adherence to treatments. Engagement and adherence with treatment are key factors for long-term prognosis, and mould expectations of treatment and long-term attitudes to treatment. Despite the importance of engagement and adherence, there is relatively little empirical data to guide practice. This may in part reflect difficulties in recruiting at times poorly adherent/motivated subjects into longitudinal studies. Nonetheless, there is merit in considering aspects of engagement and adherence in early stage bipolar.

Several factors have been associated with medication and treatment adherence.[36] Psychological factors include: an external locus of control, cognitive dysfunction, fear of side effects, and negative attitudes towards treatment—which can be exacerbated by depressive-phase cognitions. Lack of social support, stigma and family