

The bipolar spectrum: Conceptions and misconceptions

S Nassir Ghaemi and Shannon Dalley

Aust N Z J Psychiatry published online 7 March 2014

DOI: 10.1177/0004867413504830

The online version of this article can be found at:

<http://anp.sagepub.com/content/early/2014/03/07/0004867413504830>

Published by:



<http://www.sagepublications.com>

On behalf of:



The Royal
Australian &
New Zealand
College of
Psychiatrists

[The Royal Australian and New Zealand College of Psychiatrists](http://www.ranzcp.org)

Additional services and information for *Australian and New Zealand Journal of Psychiatry* can be found at:

Email Alerts: <http://anp.sagepub.com/cgi/alerts>

Subscriptions: <http://anp.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

>> [OnlineFirst Version of Record](#) - Mar 7, 2014

[What is This?](#)

The bipolar spectrum: Conceptions and misconceptions

S Nassir Ghaemi¹ and Shannon Dalley²

Australian & New Zealand Journal of Psychiatry
00(0) 1–11
DOI: 10.1177/0004867413504830

© The Royal Australian and
New Zealand College of Psychiatrists 2014
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
anp.sagepub.com



Abstract

Objective: This review aims to address concerns about the potential overinclusiveness and vagueness of bipolar spectrum concepts, and also, concerns about the overlap between bipolar illness and borderline personality.

Method: Narrative review based on historical and empirical studies.

Results: Bipolar disorder (BD) and major depressive disorder (MDD) came to be separate entities with the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM III), in contrast to the Kraepelinian manic-depressive insanity (MDI) concept, which included both. The bipolar spectrum concept is a return to this earlier Kraepelinian perspective. Further, very different features differentiate the *disease* of bipolar illness (family history of bipolar illness, severe recurrent mood episodes with psychomotor activation) from the *clinical picture* of borderline personality (dissociative symptoms, sexual trauma, parasuicidal self-harm). The term ‘disorder’ obfuscates an ontological difference between diseases, such as manic-depressive illness, and clinical pictures, such as hysteria/post-traumatic stress disorder/dissociation/borderline personality.

Conclusions: Bipolar spectrum concepts are historically rooted in Kraepelin’s manic-depressive illness concept, are scientifically testable, and can be clearly formulated. Further, they differ in kind from traumatic/dissociative conditions in ways that can be both historically and scientifically established.

Keywords

Akiskal, bipolar spectrum, borderline personality, DSM-5, Koukopoulos, Kraepelin, Leonhard, mixed, temperaments

The meaning and validity of bipolar spectrum concepts are commonly questioned (Kuiper et al., 2012). These concerns often reflect misconceptions about the bipolar spectrum concept, and about the history of psychiatric nosology. In this review, we provide a perspective that seeks to clearly describe bipolar spectrum concepts, and address misconceptions that abound about it.

Bipolar disorder is not manic-depressive illness

The first misconception to clear up is that bipolar disorder is not the same thing as manic-depressive illness. Many colleagues think about psychiatry as if nothing existed before Ronald Reagan was president of the United States. In other words, they have no awareness of psychiatric nosology, in any scientific detail, before the radical revision of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III) in 1980.

Some say that the DSM may have many faults, but it is a good first step into discussing psychiatric nosology. Not if the first step takes one off a cliff.

In the case of mood illness, one has to stop before the first step to examine the question of whether the basic bipolar/major depressive disorder nosology is valid in the first place. In other words, to be able to even begin to assess the validity of the bipolar spectrum concept, one has to first assess the validity of the bipolar disorder concept. Many use the presumed validity of the latter to question the validity of the former. The opposite may be the case.

¹Mood Disorders Program, Tufts Medical Center, Tufts University School of Medicine, Boston, USA

²Mood Disorders Program, Tufts Medical Center, Boston, USA

Corresponding author:

Nassir Ghaemi, Tufts Medical Center, Department of Psychiatry, 800 Washington St, Boston, MA 02111, USA.

Email: nghaemi@tuftsmedicalcenter.org

The best introduction to the concept of a bipolar spectrum is to go a step back before the bipolar concept itself, back to the earlier concept of manic-depressive insanity (MDI), usually associated with psychotic features. Introduced by Kraepelin (1921), and slightly rephrased as manic-depressive illness (to include the majority of subjects without psychotic features), the MDI concept was divided officially in 1980 in the DSM-III into bipolar disorder and major depressive disorder (MDD) (Goodwin and Jamison, 2007). This division is in turn a variation on the original division made in the 1950s by Karl Leonhard of MDI into bipolar and unipolar recurrent psychoses (Leonhard, 1957), which, if broadened to include non-psychotic mood presentations, was rephrased in the 1960s and 1970s by American researchers (headed at the Washington University of St Louis) as bipolar illness and unipolar depressive illness (Woodruff et al., 1974). This American revision of Leonhard's idea was the basis for the Research Diagnostic Criteria (RDC) of the 1970s (Spitzer et al., 1978), which was transformed into the DSM-III (American Psychiatric Association, 1980). In that last transition, from the RDC to DSM-III, the American Psychiatric Association became involved, and decisions were no longer primarily based on research considerations, but on the political preferences of the profession (Shorter, 2009). Since most American psychiatrists were psychoanalytic, they tended to use the DSM-II diagnosis of 'neurotic depression' frequently. Yet that term was excluded from the Washington University concept; unipolar depression consisted of severe recurrent depressive episodes. Neurotic depression was not severe (it was mild to moderate), not recurrent (it was chronic), not just depressive (anxious symptoms were prominent), and not episodic (it was constant) (Roth and Kerr, 1994). Yet to pass DSM-III, the RDC criteria were altered to include all those features – being non-recurrent, chronic, and anxious – as also part of the unipolar depressive syndrome (Shorter, 2009); this hybrid condition was renamed 'major depressive disorder'. The word 'disorder' was tagged onto every DSM-III diagnosis to avoid making any etiological judgments (Ghaemi, 2012); thus, the term 'illness', which implied a medical disease, was dropped, producing bipolar 'disorder' and MDD.

One can see, after all these distortions, that the bipolar disorder concept is *very different* from manic-depressive illness. Also, one sees that MDD was broadened to include many types of depressive symptom presentations that were not seen as part of the disease of recurrent depression. In the classic studies on unipolar depression that led to DSM-III, the diagnosis was made only if there were three or more depressive episodes (Perris, 1966); recurrence was seen as essential to the disease of unipolar depression, which was an 'endogenous' (Leonhard, 1957) (i.e. biologically based) disease (even limited by Leonhard only to those with concurrent psychotic features).

In sum, the broad MDI concept as a medical disease was replaced by a rump concept of bipolar 'disorder', and a large concept of depressive symptom-complexes (MDD).

The very narrow bipolar disorder concept differs from the old MDI concept considerably. Not only is it much narrower, but its core feature is different. For bipolar disorder, the condition is defined by polarity: presence or absence of a manic episode (Leonhard, 1957). For MDI, the condition is defined by episodicity: recurrent mood episodes define the illness, irrespective of polarity (Kraepelin, 1921). Ten depressive episodes mean MDI. Ten manic episodes mean MDI. The fact that the episodes are depressive or manic is irrelevant. The number '10' is relevant: recurrence defines the illness (Goodwin and Jamison, 2007).

MDI means recurrent manic *or* depressive episodes. Bipolar disorder means recurrent manic *and* depressive episodes. These are quite different concepts.

Put otherwise, MDI is basically bipolar disorder *plus* much of what we call MDD. MDI is much broader than bipolar disorder.

Often it is said that DSM-III was neo-Kraepelinian (Klerman, 1986). It was not: for mood illnesses, it was, and is, *neo-Leonhardian* (Ghaemi, 2013). By accepting the bipolar concept, DSM-III turned away from Kraepelin and toward Leonhard, and this process has now been taken for granted with DSM-IV and now DSM-5. Psychiatry has moved away from the Kraepelinian MDI concept to such an extent that many assume that the bipolar/MDD dichotomy is obviously true.

The bipolar spectrum concept is a way of trying to go back to the Kraepelinian MDI concept, or at least to reopen the scientific discussion such that we can revisit whether it was correct to make the decision in 1980 to divide MDI into a small bipolar and large MDD concept.

Validators of diagnosis

DSM-III divided MDI into bipolar disorder and MDD based on the accepted validators of psychiatric diagnosis, which were introduced in 1970 by the Washington University researchers (Robins and Guze, 1970) as five-fold: symptoms, family history, course, treatment response, and biological markers. It was claimed that bipolar disorder and MDD differed in all forms:

1. Symptoms: in both conditions, depression is present, but in only one condition is mania present (Leonhard, 1957).
2. Family history: early genetic studies indicated that if mania is present in a patient, it is also present in family members; but if only depression is present in a patient, mania is not present in family members (Angst, 1966; Perris, 1966).
3. Course: recurrent depression was seen to have fewer and longer episodes than recurrent mania plus

depression, where episodes were shorter and more frequent. Age of onset was later in recurrent depression (around age 30) and earlier in recurrent mania plus depression (around age 20) (Angst, 1966; Perris, 1966).

4. Treatment response: recurrent depression responded to tricyclic antidepressants; recurrent mania plus depression responded to lithium (Shorter, 2009).
5. Biological markers: recurrent depression was seen as involving abnormalities in norepinephrine and possibly serotonin function; recurrent mania was seen as involving abnormalities with dopamine function (Schildkraut, 1965).

Two classic studies, both published in the late 1960s in Europe, were seen as central to confirming Leonhard's work. One large study was headed by Carlo Perris (Perris, 1966) and a different one by Jules Angst (Angst, 1966). As Dr Angst frequently says, when he presented his results to his mentors, he was told that he couldn't be correct, since his results contradicted Kraepelin. Angst's work was based on his Zurich cohort, a prospective study since the late 1950s. About 10 years of prospective data were used by him to support the Leonhardian nosology.

After DSM-III

For about two decades, the neo-Leonhardian consensus of DSM-III held. The only objections came from a few experienced clinical researchers: in the US, Hagop Akiskal (Akiskal, 1983), and in Europe, Athanasios Koukopoulos (Koukopoulos et al., 1980). Akiskal began studies in the 1970s in the first specialized mood clinic in the US, and he identified many patients who seemed to fall in between the bipolar and unipolar categories of the Washington University school (Akiskal, 1983). He thus proposed maintaining the bipolar/unipolar distinction, but broadening the bipolar category to include a 'bipolar spectrum' (Akiskal, 1983). In this spectrum, he included atypical depressive presentations and mood temperaments. In Rome, Koukopoulos found that he could not confirm some of the claims made in favor of the unipolar/bipolar dichotomy. In particular, he cast doubt on the treatment response criterion: many unipolar patients did not respond to antidepressants; they seemed to have other features of bipolarity, such as a highly recurrent course and early age of onset (Koukopoulos et al., 1980). Even the symptom distinction was debatable: Koukopoulos found that many depressed patients had manic symptoms, and many manic patients had depressive symptoms. In other words, mixed states were much more frequent than pure mania or pure depression (Koukopoulos and Tundo, 1992), and thus the attempt to distinguish the two was difficult, and perhaps unnecessary. Both Akiskal and Koukopoulos returned to Kraepelin's work and found

confirmation of their findings in the observations of Kraepelin.

An important third critic was Frederick Goodwin, director of the National Institute of Mental Health (NIMH) in the US in the late 1980s and early 1990s when he published his classic textbook *Manic-Depressive Illness* (Goodwin and Jamison, 2007). Goodwin, with his co-author Kay Jamison, reviewed the scientific literature, and found evidence contradicting the 1960s and 1970s literature that had led to the DSM-III neo-Leonhardian dichotomy. The genetic literature could be interpreted as supporting Kraepelin or Leonhard: mania did seem to run in families, but there was as much depression (or more) in families of manic probands as in families of depressive probands (Gershon et al., 1982). In other words, depression did not run in families separate from mania. Further, Goodwin noted that lithium was effective in recurrent depression, not just bipolar disorder (Prien et al., 1974). As biological research grew in the 1990s and 2000s, it also became clear that neurotransmitter theories about catecholamines had been very simplistic in the 1970s (Hyman and Nestler, 1996). Second messengers and long-term neuroplastic changes in the brain were seen in mood illnesses (Manji, 1992), and there were often similarities between unipolar and bipolar disorder definitions in those biological mechanisms (Manji et al., 2000).

In the 1990s and 2000s, the new class of atypical neuroleptics was developed, which showed clear efficacy in acute mania, but also, in many cases, efficacy for depressive episodes, not limited to bipolar disorder but even in MDD with some agents (Nelson and Papakostas, 2009). Some anticonvulsants, such as lamotrigine, were much more effective in preventing depression rather than mania (Goodwin et al., 2004), and the presumed strong efficacy of antidepressants in MDD was thrown into doubt with the discovery of a large number of negative unpublished studies (Turner et al., 2008). In sum, the simplistic treatment response distinction between antidepressants for MDD and mood stabilizers/neuroleptics for bipolar disorder was greatly weakened.

Mood lability is not diagnostic of bipolar illness

A second common misconception of the bipolar spectrum concept is that its core feature is mood lability. Some argue that since mood lability is a diagnostic criterion for borderline personality, this approach leads to a 'bipolarization' of personality disorders (Kuiper et al., 2012). In fact, this concern is based on not appreciating a scientific approach to nosology. All of DSM suffers from this unscientific bent. Suppose one wants to define a diagnosis by certain symptoms; which symptoms should one pick? The most common? The most different from other conditions? If you wish to describe pneumonia clinically, without any

biological features, which symptoms would you pick? Fever? Or cough with productive sputum? Fever is a common and severe symptom of pneumonia, but it is nonspecific. Cough with productive sputum is less common, and less bothersome or *dysfunctional*, but it reflects the underlying disease process. Here is a key difference between the non-Kraepelinian nosology of post-DSM-III psychiatry, and Kraepelin's insight. Kraepelin directly rejected basing a nosology on symptoms. He wanted to base it on whatever clinical features reflected the underlying disease process (if a disease is present; an important point to be discussed later) (Kraepelin, 1907). DSM uses the term 'disorder' as an agnostic, atheoretical appellation for all psychiatric constructs, and, to the extent this vague concept is defined, it is meant to reflect 'harmful dysfunction' (Wakefield, 1992, 2007). Fever is quite a harmful dysfunction in pneumonia, but it doesn't help us pick out that condition from others, nor does it help to get any progress in understanding its cause or cure.

Mood lability, along with anxiety, is the fever of psychiatry. It happens with many conditions, but it does not necessarily reflect underlying disease processes when present. Kraepelin felt that course of illness reflected the underlying disease process of manic-depressive insanity, and so he thought that other symptom presentations – such as depression versus mania, such as mood lability versus not – were not diagnostically important (Kraepelin, 1921). Contrary to the linguistic assumption behind the title 'mood' disorders, 'mood' may not be central either to the diagnosis or pathophysiology of 'mood disorders'. Rather, there is strong evidence that psychomotor activation is far more central to manic-depressive illness (Cassano et al., 2012), not mood per se, and this can include rapid thinking, feeling and movement, which sometimes can be related to impulsivity, but often is not. In contrast, as we will see below, the core clinical features that represent the etiology and pathogenesis of borderline personality may also have nothing to do with mood lability, but rather dissociation.

The need for conceptual precision

In addition to the misconceptions addressed above, there is a need to address concerns regarding the precision with which bipolar spectrum concepts are defined. It has been argued that bipolar spectrum concepts '*involve vague and overinclusive language*' (Kuiper et al., 2012). Besides the fact that borderline personality concepts clearly do as well (are 'rejection sensitivity' and 'unstable interpersonal relationships' specific to borderline personality only in life?), this is a valid concern. Here we will describe three different approaches to bipolar spectrum concepts, describing their historical origins and claims. It will be seen that they are not the same, but that they can all be precisely described, and scientifically tested.

Akiskal's subtype approach and temperaments

As mentioned previously, in the early 1980s, Hagop Akiskal presented an approach to a broadening of the very narrow DSM-III bipolar type I concept that emphasized subtyping (Akiskal and Pinto, 1999): Type II would become accepted officially a decade later in DSM-IV in 1994, allowing for mild manic episodes called hypomania, if they occurred with recurrent depression. Akiskal also proposed adding type III, antidepressant-induced hypomania, and other subtypes including depression with a family history of bipolar disorder, and mood temperaments, in particular hyperthymia, meaning constant hypomania as part of one's personality (not episodes as in type II bipolar illness).

The notion that hypomania also occurs and is reflective of bipolar illness should not have been controversial at all, since it was present in the manic-depression scientific literature for a century (Kraepelin, 1921). The idea that antidepressant-induced mania should be included also should have been uncontroversial since there was zero evidence for the exclusion criterion in 1994 whereby mania associated with antidepressants could not 'count' as diagnostic for bipolar disorder. That exclusion was instituted by the DSM-IV leadership, as they have stated explicitly (Frances, 2010), solely to discourage the diagnosis of bipolar illness, since they were broadening the definition otherwise by allowing for hypomania. This type of decision based on clinical beliefs about what diagnoses are good or bad to diagnose, rather than based strictly on the scientific evidence, is the kind of 'pragmatic' approach that has made DSM revisions less scientific, rather than more, with successive revisions (Ghaemi, 2012). DSM-5 has made an exception, which proves this rule, by bowing to the overwhelming evidence that antidepressant-associated mania is 200-fold more common in bipolar disorder (about 10–20% depending on clinical population and drug) (Goldberg and Truman, 2003) than in MDD (less than 1%) (Ghaemi, 2008; Perlis et al., 2011; Tondo et al., 2010, 2013).

The most original aspect of Akiskal's approach is the emphasis on mood temperaments, such as hyperthymia and cyclothymia, as an important part of the bipolar spectrum. This is where the differential diagnosis with personality disorders becomes an issue (Akiskal, 2004). Since those conditions are chronic, not episodic, the course distinction of severe episodic recurrence is not helpful in distinguishing those mood temperaments from borderline personality. These mood temperaments had also been defined by Kraepelin (1921) and others, such as Kretschmer (1921 [1970]), and were always seen as mild variants of their corresponding diseases: dysthymia (depression), cyclothymia (manic-depressive cycling), hyperthymia (mania), and 'schizothymia' (schizophrenia) (Kretschmer, 1921 [1970]). Half a century later, DSM-III kept some (dysthymia, cyclothymia), excluded hyperthymia, and renamed another

(schizotypal personality disorder), moving most to 'axis I', implying an illness, as opposed to seeing them, as they always had been seen, as personality states (hence needing to be on axis II, as with schizotypal personality). These temperaments seem to be genetically (Evans et al., 2005; Kelsoe, 1997) related to bipolar illness or severe unipolar depression; they occur in about one-half of persons with bipolar illness (Vöhringer et al., 2012), which is much more frequent than in the general population (Akiskal et al., 1998). They are highly validated psychometrically (Akiskal and Akiskal, 2005; Akiskal et al., 1998, 2005, 2006) and well-operationalized (Vöhringer et al., 2012). In sum, a case can be made that they are at least as well scientifically validated, if not more so, than borderline personality (see below). The lack of attention to these mood temperaments reflects in part the error of placing them as competing 'disorders' to the mood illnesses of which they are variations: one can have 'bipolar disorder' with severe recurrent manic or depressive episodes, and cyclothymia as a mood temperament in between mood episodes. But since the DSM system sets them as competing, few clinicians make this observation. The almost complete clinical inattention to hyperthymic temperament in post-Reagan nosology is a notable example of scientific amnesia, yet to be corrected in clinical practice.

Koukopoulos' mixed states

Also in the early 1980s, as noted above, Koukopoulos took a somewhat different approach. Instead of subtyping and focusing on temperaments, he emphasized analysis of the mood episodes themselves, and concluded that the DSM-III bipolar/MDD dichotomy failed because polarity failed. Most mood episodes were not purely depressive or manic, but mixed, and hence one could not create a stable and valid nosology on what was uncommon or even may not exist at all (Koukopoulos et al., 2005).

Koukopoulos defined 'mixed depression' as depression occurring with excitation, meaning manic symptoms (such as flight of ideas or talkativeness), but also agitation, irritability and rage, marked anxiety, and suicidal impulsivity (Koukopoulos et al., 2007). Koukopoulos saw this highly agitated and tense depressive state as the opposite of melancholia, which is markedly psychomotor retarded and not irritable or rageful. He thought that mixed depression gets much worse with antidepressants and responds to neuroleptics, while melancholia responds best to electroconvulsive therapy (ECT) and sometimes to antidepressants, but is best prevented with mood stabilizers such as lithium.

Other researchers, such as Franco Benazzi in particular, studied mixed depression in detail and reported high rates in bipolar illness, but also notable rates in MDD (Benazzi, 2000, 2001, 2002, 2005, 2007). Working with Akiskal, Benazzi replicated his Italian findings in other settings (Benazzi and Akiskal, 2001).

Angst, whose work had been so central to the move away from Kraepelin's MDI, continued his Zurich study and found many intermediate forms of mood conditions between the original bipolar and unipolar ideal types (Angst, 1998, 2007). He also described the presence of mixed states as very common in all depressive conditions. Defined as three or more manic symptoms occurring for any duration (not limited to 4 days or longer as in DSM-IV), Angst and his colleagues have reported that about one-half of all depressive episodes, even in MDD, involve mixed states with the presence of manic symptoms (Angst et al., 2011). Thus, Angst has become supportive of the bipolar spectrum concept (Angst, 2007; Angst et al., 2012).

If Koukopoulos and Angst are correct, it is a category mistake to claim that broadening the definition of mixed states will 'further obscure the boundary between major depression and bipolar disorder' (Malhi, 2013). The whole point is that such a statement assumes that the concept of 'major depression' is scientifically valid, which is questionable, and that there is a clear boundary to be drawn between 'major depression' and bipolar disorder. As Koukopoulos and Angst have reported, and Kraepelin clearly observed as well, if it is true that most mood episodes are mixed, then there is no clear boundary to be found between depression and mania. This is a major reason why the polarity distinction should not be, on this view, the deciding factor in the nosology of mood. If the pure poles are uncommon, they should not be how we diagnose. If most cases are mixed, we should admit that fact, and base our nosology on something else (such as recurrence). It is not a matter of 'further blurring boundaries', but rather of seeing clearly what boundaries exist and do not exist.

'Bipolar spectrum illness': An operationalized definition

We have proposed an approach to the spectrum concept that focuses on how to distinguish it from unipolar depression (Ghaemi et al., 2002). Taking into account all of the above work, instead of subtyping further, we suggested having a general definition for those patients who fall in the middle of the mood spectrum between the classic unipolar and type I bipolar extremes. This 'bipolar spectrum disorder' (which we would rename 'bipolar spectrum illness' since we do not want to use the term 'disorder' anymore) would represent recurrent severe depression (as in Leonhard's unipolar depression), but with a family history of bipolar disorder or antidepressant-induced mania or a number of other features of bipolarity to depressive symptoms, course, or treatment response (mixed or melancholic features, early age of onset, many episodes, poor antidepressant response or tolerance). The presence of hyperthymic or cyclothymic mood temperaments was also suggested to be part of this bipolar spectrum concept

(Ghaemi et al., 2002). Defined this way, about one-third of MDD could be seen as meeting the operationalized bipolar spectrum illness definition (Rybakowski et al., 2007; Smith et al., 2005).

Most important for the critique made by some colleagues (Kuiper et al., 2012), this operationalized definition of bipolar spectrum illness is as precise and testable as any DSM-based diagnosis.

Personality ‘disorders’

When operationalized as above, our approach was limited to the Kraepelinian and Leonhardian concepts, in both of which the presumption was that patients experienced severe depressive episodes. Thus, the bipolar spectrum illness definition we gave presumed that patients had severe recurrent depressive episodes. In our view, this inclusion criterion automatically distinguished the bipolar spectrum illness definition from borderline personality. But, as some colleagues have noted (Kuiper et al., 2012), the relationship between bipolar spectrum definitions and borderline personality is important and needs to be clarified.

In our minds, this clarification must include a more scientific understanding of what we mean by not only using the bipolar spectrum terminology, but also what we mean by the term ‘borderline’, and, more broadly, by the concept of ‘personality disorders’.

We use all these quotation marks because we are not certain that there is any scientific validity to the concept of personality disorders in general, much less borderline personality. Or, if there is such validity, it is of a quite different nature than the scientific validity of manic-depressive illness.

The first step, in our view, is to recognize that bipolar illness and borderline personality are *ontologically* different. They are different types of things. Their similarities are superficial, their differences profound. The perception of similarity comes from using the term bipolar ‘disorder’ versus borderline personality ‘disorder’. The disorder term produces a linguistic equality which is not scientifically present. By using the term ‘disorder’, proponents of DSM categories have equalized all diagnoses (Ghaemi, 2012). This is a major conceptual error, an ontological mistake, which means a mistake in understanding the basic nature of different things. Red skies differ from red apples; they are very different things; they are similar only superficially by being red in color. Similarly, manic-depressive illness is a disease of the body and brain, with many well-known biological abnormalities that are well replicated; it has been defined more or less as it is at least for a century or more; its definition is squarely in the medical model, requiring no beliefs beyond the acceptance of standard medical concepts such as signs, symptoms, syndromes, course, genetics, and biology. Borderline personality, in contrast, is, in our view, our culture’s interpretation of what used to be called

‘hysteria’. It is a Freudian interpretation of dissociative symptoms that happen in persons who experience trauma, usually sexual, early in life, in such a way that their personality development is derailed (Gunderson, 1984). It requires the ideological commitment to a host of psychoanalytic speculations, such as transference, countertransference, projection, denial, and so on (Gunderson, 1984). Its biology is poorly understood, and it is much less genetic than manic-depressive illness (Bienvenu et al., 2011; Kendler and Prescott, 2006). The concept, as now used, was invented relatively recently, about 40 years ago (Kernberg, 1967, 1968).

These two clinical constructs are entirely different in their histories and key characteristics. All they share in common is mood lability and impulsivity. Many other psychiatric pictures include impulsivity (gambling addiction, substance abuse) or mood lability (frontal lobe syndrome, agitation of multiple causes). These superficial symptoms are like the redness of skies versus apples. They are not core features of these conditions, which differ so markedly in other ways.

It is well to give up the term ‘disorder’ and remind ourselves that superficial similarities are few, and major differences are many, when examining these conditions. Kraepelin distinguished between ‘disease-processes’ (*Krankheitsprozessen*), such as MDI, and ‘clinical pictures’ (*Zustandsbildern*) (Beumont, 1992; Decker, 2004) such as the whole range of anxious, mood, and dissociative symptom presentations that are seen in hysteria. The bipolar spectrum is a disease-process; borderline personality is a clinical picture, but not a disease. They differ in kind, although they have superficial symptom similarities. Neither is part of the other, nor should be confused with the other (Bassett et al., 2012).

Red skies are not red apples.

Differentiating the bipolar spectrum versus borderline personality

As noted previously, a major error leading to concerns about confusing the bipolar spectrum with borderline personality has to do with overemphasis on mood lability, which is not central to bipolar illness. Psychomotor activation is the key feature of bipolar illness that probably best reflects the disease process, along with the recurrent course. Similarly, mood lability can be seen as a superficial non-specific symptom of borderline personality. Assuming borderline personality is a scientifically valid clinical construct, what clinical features represent its underlying pathogenic process?

To answer this question, it may be useful to ask a historical question beforehand: What did we used to call these patients before we began to call them borderline in the late 1960s (Kernberg, 1967, 1968)? Pseudoneurotic schizophrenia immediately preceded the borderline term: these were patients who were usually neurotic, but then became

psychotic when psychoanalyzed (Hoch and Cattell, 1959; Hoch and Polatin, 1949). They were on the *border* (hence the later borderline term) between neurosis and psychosis, in the psychoanalytic metaphysics. Before pseudoneurotic schizophrenia, they tended to be called hysteria (Micale, 1995), especially when their psychological symptoms were mixed with physical problems (such as paralysis) (Shorter, 2006). Some were labeled as neurasthenia in the late 19th century. What did all these conditions have in common? At least in the Freudian tradition, from which the borderline concept derives, the etiology of these conditions was seen as the emotional effects of sexual trauma (real or imagined) (Micale, 1995). The symptom presentations that were characteristic (as opposed to nonspecific; i.e. mood lability and anxiety) were generally seen as dissociative, with flashbacks, nightmares, and emotional numbing (Micale, 1995; van der Hart and Dorahy, 2006). Dissociative symptoms are common in borderline personality and rare in manic-depressive illness (Benazzi, 2006; Gunderson, 1984). Further, sexual trauma occurs in 50–70% of persons with borderline personality (Fossati et al., 1999; Soloff et al., 1994; Wiederman et al., 1998; Zanarini, 2000) versus 10–20% of the general population (Briere and Elliott, 2003; Molnar et al., 2001) and 20–30% of bipolar samples (Conus et al., 2010; Maniglio, 2013). Self-cutting and parasuicidal behavior happens consistently in 60–70% of persons with borderline personality (Joyce et al., 2010) and as little as 0.9% of persons with bipolar illness (in over 5000 subjects examined in the National Comorbidity Survey) (Nock and Kessler, 2006). Higher rates are found in clinical samples of bipolar illness (Haw et al., 2001), and some report even higher rates in clinical bipolar samples than in borderline personality (Joyce et al., 2010). Yet those conflicting reports are not replicated by other investigators (Large et al., 2010), and do not outweigh data from the general population (Nock and Kessler, 2006), which are more valid for the illness as a whole. They also do not outweigh the best quality evidence, available prospective studies, which indicate a clear relationship between sexual abuse, not bipolar illness, and parasuicidal behavior (Fliege et al., 2009).

In sum, sexual abuse and parasuicidal behavior are many times more common in borderline personality than bipolar illness. If we take the historical and scientific literature seriously on mood temperaments, as we should, it seems scientifically indefensible to diagnose borderline personality in persons with family histories of bipolar illness, who meet diagnostic definitions of hyperthymia or cyclothymia, and who have no sexual abuse or self-cutting behavior. Yet, by slavishly following DSM criteria for borderline personality, such persons are commonly misdiagnosed as having that condition based on diagnostically non-specific features of mood instability, interpersonal conflicts, rejection sensitivity, sexual impulsivity, and anger. This kind of extremely broad definition of borderline personality, in contrast to the bipolar spectrum

concepts described above, would appear to deserve the criticism of being vague and overinclusive. The epithet of bipolar ‘imperialism’, somewhat inappropriately made by some Western psychiatrists (Paris, 2004), could more correctly be changed to *borderline imperialism*: the clinical policy whereby any angry impulsive patient receives that label, often applied in a way that patients experience as pejorative (Nehls, 1999), while all the other many causes for anger and impulsivity, including bipolar illness, are ignored or dismissed.

Biopsychosocial errors

A common mistaken claim is that there are biological aspects to borderline personality, and thus it is not a mainly psychosocial condition. Further, it can be claimed that there are important psychosocial contributions to the development of bipolar illness, and thus it is not mainly a biological condition. These claims ignore the distinction between etiology and pathogenesis. Bipolar illness is almost completely genetic in its etiology, with over 80% genetic heritability based on twin studies; psychosocial factors hardly contribute at all to its etiology, based on the best summary of many genetic studies (Bienvenu et al., 2011). It is false to claim that heritability is similar between bipolar illness and borderline personality: personality traits are only half as genetic as bipolar illness, not exceeding 50% when summarizing multiple studies (Bienvenu et al., 2011). If the genetic predisposition to borderline personality is limited, as noted, the psychosocial contribution has been proven to be major. Thus, the two conditions are quite distinct in etiology.

The overlap claimed for biological and psychosocial factors for both conditions applies to pathogenesis, not etiology. Psychosocial factors can affect the course of bipolar illness (Miklowitz, 2010), and the triggering of episodes (Goodwin and Jamison, 2007), but not the inherent underlying etiological susceptibility to the illness itself (Bienvenu et al., 2011).

Similarly, brain neurochemistry is affected by life experiences (Kandel, 1999), thus sexual traumatic experience will have neurobiological effects. This can influence the course of borderline personality, but the presence of such neurobiological abnormality does not indicate a biological etiology for the condition. It is a consequence, not a cause.

Thus, studies which find similarities in neurobiology between bipolar illness and borderline personality (Coulston et al., 2012) do not provide nosological evidence that the two conditions are the same, or that they overlap, unless such biological data can be shown to be etiologic, which is not the case.

The above misconceptions often reflect a strong attachment to the assumptions of the biopsychosocial model, which as we have shown elsewhere (Ghaemi, 2009), is simply eclecticism, the combining of all perspectives for all conditions, producing the type of vague nosology that

allows for the easy conflation of bipolar illness and borderline personality.

The failed DSM approach to restricting diagnostic thresholds: Spectrum-phobia

Much of the concern about spectra has to do with fear of overdiagnosis, or the false-positives problem. DSM leadership have responded to this fear by trying to keep the diagnostic thresholds for ‘disorders’ as high as possible (Wakefield and First, 2012) – hence the antagonism to bipolar spectra, or to prodromal psychosis concepts (Frances, 2009).

This solution has failed for 30 years, and it can be proven statistically to be highly likely to fail for another 30 years (Phelps and Ghaemi, 2012). True- or false-positives are reflected statistically as positive predictive values. To have low overdiagnosis, or low false-positives, means to have a high positive predictive value (PPV). PPV is dependent on the sensitivity and specificity of diagnostic criteria; the DSM approach is to make diagnostic criteria harder to meet so as to have high specificity. If spectra are allowed, the concern is that specificity would go down, and with it PPV. But PPV is much more dependent on the baseline prevalence of a condition than the specificity of a diagnostic test (Phelps and Ghaemi, 2012). All psychiatric conditions are low prevalence, in the statistical sense. Even conceived very broadly, bipolar spectrum illness definitions do not exceed 10% of the population (similar to the current broad MDD rates) (Angst, 1998, 2007; Phelps and Ghaemi, 2012). Even if extended by temperaments to 20% of the population, such rates are still low prevalence from the statistical PPV perspective. We have published simulations based on baseline prevalence rates near 10% for bipolar illness in unselected clinical populations, and we have shown that with that kind of low prevalence, one is guaranteed PPV rates of about 50% (Phelps and Ghaemi, 2012). That is, about half of all patients are falsely diagnosed as positive, producing the claim that bipolar illness is an overdiagnosed state (Zimmerman et al., 2008). But the same ‘overdiagnosis’ would have happened with any psychiatric illness because of the impact of low prevalence on PPV, as shown in major epidemiological studies (Smith and Ghaemi, 2010). In other words, this problem is not unique to bipolar illness; it is a problem with all psychiatric conditions. One would need specificities of above 95% to begin to get PPV rates around 70% (Phelps and Ghaemi, 2012), and that kind of high specificity is very uncommon in psychiatric studies, including the best-designed DSM field trials (Clarke et al., 2013; Freedman et al., 2013; Narrow et al., 2013; Regier et al., 2013). Usual specificities are in the 70–80% range, even with our current DSM

criteria, which refuse to recognize spectra for bipolar illness (Phelps and Ghaemi, 2012). Above 90% specificity is difficult to achieve with echocardiograms (Ryan et al., 1993), much less clinical psychiatric interviews.

The solution should be obvious: to increase baseline prevalence. If baseline prevalence for bipolar illness was raised to 50%, then PPV would rise to 90%, assuming the same realistic specificities as currently obtained in psychiatric practice (in the 70–80% range) (Phelps and Ghaemi, 2012). How can we increase baseline prevalence rates? We could do so by examining non-symptom features that increase the prior probability of the condition, even before looking at specific manic or dissociative symptoms. This approach greatly increases true-positive diagnoses, and decreases false-positives (Phelps and Ghaemi, 2012). In bipolar illness, those diagnostic accuracy-enhancing features include a family history of bipolar illness and a severe episodic course with duration of episodes being weeks to months (Phelps and Ghaemi, 2012). As noted, in borderline personality, those diagnostic accuracy-enhancing features include childhood sexual abuse and repeated non-suicidal self-injury (Gunderson, 1984). These features are multiple times more frequent in borderline personality than in bipolar illness (Nock and Kessler, 2006; Zanarini, 2000).

Summary

Concerns about the potential overinclusiveness and vagueness of bipolar spectrum concepts were addressed by describing specific approaches: Akiskal’s subtyping and temperaments, Koukopoulos’ mixed states, and an operationalized definition of bipolar spectrum illness that is as testable as any DSM diagnosis. Concerns about overlap with borderline personality were addressed in a historical and scientific analysis which demonstrated that very different features differentiate the *disease* of bipolar illness (family history of bipolar illness, severe recurrent mood episodes with psychomotor activation) from the *clinical picture* of borderline personality (dissociative symptoms, sexual trauma, parasuicidal self-harm). The term ‘disorder’ was seen as obfuscating an ontological difference between diseases, such as manic-depressive illness, and clinical pictures, such as hysteria/PTSD/dissociation/borderline personality. In sum, bipolar spectrum concepts are historically rooted in Kraepelin’s manic-depressive illness concept and are scientifically testable and can be clearly formulated. Further, they differ in kind from traumatic/dissociative conditions in ways that can be both historically and scientifically established with reasonable clarity.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Declaration of interest

Ghaemi: research grant – Takeda; research consulting – Sunovion.

References

- Akiskal HS (1983) The bipolar spectrum: New concepts in classification and diagnosis. In: Grinspoon L (ed) *Psychiatry Update: The American Psychiatric Association Annual Review, Volume II*. Washington, DC: American Psychiatric Press, pp. 271–292.
- Akiskal HS (2004) Demystifying borderline personality: Critique of the concept and unorthodox reflections on its natural kinship with the bipolar spectrum. *Acta Psychiatrica Scandinavica* 110: 401–407.
- Akiskal HS and Akiskal KK (2005) TEMPS: Temperament Evaluation of Memphis, Pisa, Paris and San Diego. *Journal of Affective Disorders* 85: 1–2.
- Akiskal HS and Pinto O (1999) The evolving bipolar spectrum. Prototypes I, II, III, and IV. *The Psychiatric Clinics of North America* 22: 517–534, vii.
- Akiskal HS, Akiskal KK, Haykal RF, et al. (2005) TEMPS-A: Progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. *Journal of Affective Disorders* 85: 3–16.
- Akiskal HS, Akiskal KK, Lancrenon S, et al. (2006) Validating the bipolar spectrum in the French National EPIDEP Study: Overview of the phenomenology and relative prevalence of its clinical prototypes. *Journal of Affective Disorders* 96: 197–205.
- Akiskal HS, Placidi GF, Maremmi I, et al. (1998) TEMPS-I: Delineating the most discriminant traits of the cyclothymic, depressive, hyperthymic and irritable temperaments in a nonpatient population. *Journal of Affective Disorders* 51: 7–19.
- American Psychiatric Association (1980) *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition. Washington, DC: American Psychiatric Association.
- Angst J (1966) On the etiology and nosology of endogenous depressive psychoses: A genetic, sociologic, and clinical study. *Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie* 112: 1–118.
- Angst J (1998) The emerging epidemiology of hypomania and bipolar II disorder. *Journal of Affective Disorders* 50: 143–151.
- Angst J (2007) The bipolar spectrum. *The British Journal of Psychiatry* 190: 189–191.
- Angst J, Azorin JM, Bowden CL, et al. (2011) Prevalence and characteristics of undiagnosed bipolar disorders in patients with a major depressive episode: The BRIDGE Study. *Archives of General Psychiatry* 68: 791–798.
- Angst J, Gamma A, Bowden CL, et al. (2012) Diagnostic criteria for bipolarity based on an international sample of 5,635 patients with DSM-IV major depressive episodes. *European Archives of Psychiatry and Clinical Neuroscience* 262: 3–11.
- Bassett D (2012) Borderline personality disorder and bipolar affective disorder. Spectra or spectre? A review. *Australian and New Zealand Journal of Psychiatry* 46: 327–339.
- Benazzi F (2000) Depressive mixed states: Unipolar and bipolar II. *European Archives of Psychiatry and Clinical Neuroscience* 250: 249–253.
- Benazzi F (2001) Depressive mixed state: Testing different definitions. *Psychiatry and Clinical Neurosciences* 55: 647–652.
- Benazzi F (2002) Depressive mixed state frequency: Age/gender effects. *Psychiatry and Clinical Neurosciences* 56: 537–543.
- Benazzi F (2005) Mixed depression: A clinical marker of bipolar-II disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 29: 267–274.
- Benazzi F (2006) Borderline personality–Bipolar spectrum relationship. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 30: 68–74.
- Benazzi F (2007) Mixed depression and the dimensional view of mood disorders. *Psychopathology* 40: 431–439.
- Benazzi F and Akiskal HS (2001) Delineating bipolar II mixed states in the Ravenna-San Diego collaborative study: The relative prevalence and diagnostic significance of hypomanic features during major depressive episodes. *Journal of Affective Disorders* 67: 115–122.
- Beumont PJ (1992) Phenomenology and the history of psychiatry. *Australian and New Zealand Journal of Psychiatry* 26: 532–545.
- Bienvenu OJ, Davydow DS and Kendler KS (2011) Psychiatric ‘diseases’ versus behavioral disorders and degree of genetic influence. *Psychological Medicine* 41: 33–40.
- Briere J and Elliott DM (2003) Prevalence and psychological sequelae of self-reported childhood physical and sexual abuse in a general population sample of men and women. *Child Abuse & Neglect* 27: 1205–1222.
- Cassano GB, Rucci P, Benvenuti A, et al. (2012) The role of psychomotor activation in discriminating unipolar from bipolar disorders: A classification-tree analysis. *The Journal of Clinical Psychiatry* 73: 22–28.
- Clarke DE, Narrow WE, Regier DA, et al. (2013) DSM-5 field trials in the United States and Canada, Part I: Study design, sampling strategy, implementation, and analytic approaches. *The American Journal of Psychiatry* 170: 43–58.
- Conus P, Cotton S, Schimmelmann BG, et al. (2010) Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. *Bipolar Disorders* 12: 244–252.
- Coulston CM, Tanius M, Mulder RT, et al. (2012) Bordering on bipolar: The overlap between borderline personality and bipolarity. *Australian and New Zealand Journal of Psychiatry* 46: 506–521.
- Decker HS (2004) The psychiatric works of Emil Kraepelin: A many-faceted story of modern medicine. *Journal of the History of the Neurosciences* 13: 248–276.
- Evans L, Akiskal HS, Keck PE Jr, et al. (2005) Familiality of temperament in bipolar disorder: Support for a genetic spectrum. *Journal of Affective Disorders* 85: 153–168.
- Fliege H, Lee JR, Grimm A, et al. (2009) Risk factors and correlates of deliberate self-harm behavior: A systematic review. *Journal of Psychosomatic Research* 66: 477–493.
- Fossati A, Madeddu F and Maffei C (1999) Borderline personality disorder and childhood sexual abuse: A meta-analytic study. *Journal of Personality Disorders* 13: 268–280.
- Frances A (2009) Dr Frances Responds to Dr Carpenter: A Sharp Difference of Opinion. *Psychiatric Times*, 9 Jul.
- Frances A (2010) DSM in philosophyland: Curiouser and curiouser. *AAPP Bulletin* 17: 21–25. Available at: alien.dowling.edu/~cperring/aapp/bulletin.htm (accessed 8 November 2010).
- Freedman R, Lewis DA, Michels R, et al. (2013) The initial field trials of DSM-5: New blooms and old thorns. *The American Journal of Psychiatry* 170: 1–5.
- Gershon E, Hamovit J, Guroff J, et al. (1982) A family study of schizoaffective, bipolar I, bipolar II, unipolar and normal control probands. *Archives of General Psychiatry* 39: 1157–1167.
- Ghaemi SN (2012) Taking disease serious: Against ‘pragmatic’ nosology. In: Kendler KS and Parnas J (eds) *Philosophical Issues in Psychiatry II: Nosology*. Oxford: Oxford University Press, pp. 42–53.
- Ghaemi SN (2013) *On Depression: Diagnosis, Drugs, and Despair in the Modern World*. Baltimore, MA: Johns Hopkins University Press.
- Ghaemi SN (2008) Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression. *Bipolar Disorders* 10: 957–968.
- Ghaemi SN (2009) *The Rise and Fall of the Biopsychosocial Model: Reconciling Art & Science in Psychiatry*. Baltimore, MA: The Johns Hopkins University Press.
- Ghaemi SN, Ko JY and Goodwin FK (2002) ‘Cade’s disease’ and beyond: Misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Canadian Journal of Psychiatry* 47: 125–134.
- Goldberg JF and Truman CJ (2003) Antidepressant-induced mania: An overview of current controversies. *Bipolar Disorders* 5: 407–420.

- Goodwin FK and Jamison KR (2007) *Manic Depressive Illness: Bipolar Disorders and Recurrent Depression*, 2nd edition. New York, NY: Oxford University Press.
- Goodwin GM, Bowden CL, Calabrese JR, et al. (2004) A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. *Journal of Clinical Psychiatry* 65: 432–441.
- Gunderson J (1984) *Borderline Personality Disorder*. Washington, DC: American Psychiatric Press.
- Haw C, Hawton K, Houston K, et al. (2001) Psychiatric and personality disorders in deliberate self-harm patients. *British Journal of Psychiatry* 178: 48–54.
- Hoch P and Polatin P (1949) Pseudoneurotic forms of schizophrenia. *The Psychiatric Quarterly* 23: 248–276.
- Hoch PH and Cattell JP (1959) The diagnosis of pseudoneurotic schizophrenia. *The Psychiatric Quarterly* 33: 17–43.
- Hyman SE and Nestler EJ (1996) Initiation and adaptation: A paradigm for understanding psychotropic drug action. *American Journal of Psychiatry* 153: 151–162.
- Joyce PR, Light KJ, Rowe SL, et al. (2010) Self-mutilation and suicide attempts: Relationships to bipolar disorder, borderline personality disorder, temperament and character. *Australian and New Zealand Journal of Psychiatry* 44: 250–257.
- Kandel ER (1999) Biology and the future of psychoanalysis: A new intellectual framework for psychiatry revisited. *American Journal of Psychiatry* 156: 505–524.
- Kelsoe JR (1997) The genetics of bipolar disorder. *Psychiatric Annals* 27: 285–292.
- Kendler KS and Prescott CA (2006) *Genes, Environment, and Psychopathology: Understanding the Causes of Psychiatric and Substance Use Disorders*. New York, NY: Guilford Press.
- Kernberg O (1967) Borderline personality organization. *Journal of the American Psychoanalytic Association* 15: 641–685.
- Kernberg O (1968) The treatment of patients with borderline personality organization. *The International Journal of Psychoanalysis* 49: 600–619.
- Klerman G (1986) Historical perspectives on contemporary schools of psychopathology. In: Millon T and Klerman GL (eds). *Contemporary Directions in Psychopathology: Toward the DSM-IV*. New York: Guilford Press, pp. 3–28.
- Koukopoulos A and Tundo A (1992) A mixed depressive syndrome. *Clinical Neuropharmacology* 15(Suppl 1 Pt A): 626A–627A.
- Koukopoulos A, Albert MJ, Sani G, et al. (2005) Mixed depressive states: Nosologic and therapeutic issues. *International Review of Psychiatry* 17: 21–37.
- Koukopoulos A, Sani G, Koukopoulos AE, et al. (2007) Melancholia agitata and mixed depression. *Acta Psychiatrica Scandinavica Supplementum* (433): 50–57.
- Kraepelin E (1907) *Clinical Psychiatry: A Textbook for Students and Physicians*. New York: Macmillan.
- Kraepelin E (1921) Manic-depressive insanity and paranoia. In: Robertson GM (eds) Edinburgh: E & S Livingstone.
- Kretschmer E (1921) [1970] *Physique and Character*. New York: Cooper Square Publishers, Inc.
- Kuiper S, Curran G and Malhi GS (2012) Why is soft bipolar disorder so hard to define? *Australian and New Zealand Journal of Psychiatry* 46: 1019–1025.
- Kukopulos A, Reginaldi P, Laddomada G, et al. (1980) Course of the manic-depressive cycle and changes caused by treatments. *Pharmakopsychiatrie, Neuro-Psychopharmakologie* 13: 156–167.
- Large MM, Nielsen OB and Babidge N (2010) Self-mutilation is strongly associated with schizophrenia, but not with bipolar disorder. *Australian and New Zealand Journal of Psychiatry* 44: 677.
- Leonhard K (1957) *The Classification of Endogenous Psychoses*. New York: Irvington Publishers, Inc.
- Malhi GS (2013) Diagnosis of bipolar disorder: Who is in a mixed state? *The Lancet* 381: 1599–1600.
- Maniglio R (2013) Prevalence of child sexual abuse among adults and youths with bipolar disorder: A systematic review. *Clinical Psychology Review* 33: 561–573.
- Manji HK (1992) G proteins: Implications for psychiatry. *American Journal of Psychiatry* 149: 746–760.
- Manji HK, Moore GJ, Rajkowska G, et al. (2000) Neuroplasticity and cellular resilience in mood disorders. *Molecular Psychiatry* 5: 578–593.
- Micale M (1995) *Approaching Hysteria: Disease and its Interpretations*. Princeton, NJ: Princeton University Press.
- Miklowitz DJ (2010) *Bipolar Disorder: A Family-Focused Treatment Approach*, 2nd edition. New York: Guilford Publications, Inc.
- Molnar BE, Buka SL and Kessler RC (2001) Child sexual abuse and subsequent psychopathology: Results from the National Comorbidity Survey. *American Journal of Public Health* 91: 753–760.
- Narrow WE, Clarke DE, Kuramoto SJ, et al. (2013) DSM-5 field trials in the United States and Canada, Part III: Development and reliability testing of a cross-cutting symptom assessment for DSM-5. *American Journal of Psychiatry* 170: 71–82.
- Nehls N (1999) Borderline personality disorder: The voice of patients. *Research in Nursing & Health* 22: 285–293.
- Nelson JC and Papakostas GI (2009) Atypical antipsychotic augmentation in major depressive disorder: A meta-analysis of placebo-controlled randomized trials. *American Journal of Psychiatry* 166: 980–991.
- Nock MK and Kessler RC (2006) Prevalence of and risk factors for suicide attempts versus suicide gestures: Analysis of the National Comorbidity Survey. *Journal of Abnormal Psychology* 115: 616–623.
- Paris J (2004) Borderline or bipolar? Distinguishing borderline personality disorder from bipolar spectrum disorders. *Harvard Review of Psychiatry* 12: 140–145.
- Perlis RH, Uher R, Ostacher M, et al. (2011) Association between bipolar spectrum features and treatment outcomes in outpatients with major depressive disorder. *Archives of General Psychiatry* 68: 351–360.
- Perris C (1966) A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. *Acta Psychiatrica Scandinavica Supplementum* 194: 15–152.
- Phelps J and Ghaemi SN (2012) The mistaken claim of bipolar ‘overdiagnosis’: Solving the false positives problem for DSM-5/ICD-11. *Acta Psychiatrica Scandinavica* 126: 395–401.
- Prien RF, Klett CJ and Caffey EM (1974) Lithium prophylaxis in recurrent affective illness. *American Journal of Psychiatry* 131: 198–203.
- Regier DA, Narrow WE, Clarke DE, et al. (2013) DSM-5 field trials in the United States and Canada, Part II: Test-retest reliability of selected categorical diagnoses. *American Journal of Psychiatry* 170: 59–70.
- Robins E and Guze SB (1970) Establishment of diagnostic validity in psychiatric illness: Its application to schizophrenia. *American Journal of Psychiatry* 126: 983–987.
- Roth M and Kerr T (1994) The concept of neurotic depression: A plea for reinstatement. In: Pichot P and Rein W (eds) *The Clinical Approach in Psychiatry*. Paris: Synthelabo.
- Ryan T, Segar DS, Sawada SG, et al. (1993) Detection of coronary artery disease with upright bicycle exercise echocardiography. *Journal of the American Society of Echocardiography* 6: 186–197.
- Rybakowski JK, Suwalska A, Lojko D, et al. (2007) Types of depression more frequent in bipolar than in unipolar affective illness: Results of the Polish DEP-BI study. *Psychopathology* 40: 153–158.
- Schildkraut JJ (1965) The catecholamine hypothesis of affective disorders: A review of supporting evidence. *American Journal of Psychiatry* 122: 509–522.
- Shorter E (2006) Hysteria and catatonia as motor disorders in historical context. *History of Psychiatry* 17: 461–468.
- Shorter E (2009) *Before Prozac: The Troubled History of Mood Disorders in Psychiatry*. New York: Oxford University Press.

- Smith D and Ghaemi S (2010) Is underdiagnosis the main pitfall when diagnosing bipolar disorder? Yes. *British Medical Journal* 340: c854.
- Smith DJ, Harrison N, Muir W, et al. (2005) The high prevalence of bipolar spectrum disorders in young adults with recurrent depression: Toward an innovative diagnostic framework. *Journal of Affective Disorders* 84: 167–178.
- Soloff PH, Lis JA, Kelly T, et al. (1994) Risk factors for suicidal behavior in borderline personality disorder. *American Journal of Psychiatry* 151: 1316–1323.
- Spitzer RL, Endicott J and Robins E (1978) Research diagnostic criteria: Rationale and reliability. *Archives of General Psychiatry* 35: 773.
- Tondo L, Baldessarini RJ, Vazquez G, et al. (2013) Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. *Acta Psychiatrica Scandinavica* 127: 355–364.
- Tondo L, Vazquez G and Baldessarini RJ (2010) Mania associated with antidepressant treatment: Comprehensive meta-analytic review. *Acta Psychiatrica Scandinavica* 121: 404–414.
- Turner EH, Matthews AM, Linardatos E, et al. (2008) Selective publication of antidepressant trials and its influence on apparent efficacy. *The New England Journal of Medicine* 358: 252–260.
- Van der Hart O and Dorahy M (2006) Pierre Janet and the concept of dissociation. *American Journal of Psychiatry* 163: 1646; author reply 1646.
- Vöhringer P, Whitham E, Thommi S, et al. (2012) Affective temperaments and clinical practice: A validation study in mood disorders. *Journal of Affective Disorders* 136: 577–580.
- Wakefield JC (1992) Disorder as harmful dysfunction: A conceptual critique of DSM-III-R's definition of mental disorder. *Psychological Review* 99: 232–247.
- Wakefield JC (2007) The concept of mental disorder: Diagnostic implications of the harmful dysfunction analysis. *World Psychiatry* 6: 149–156.
- Wakefield JC and First MB (2012) Placing symptoms in context: The role of contextual criteria in reducing false positives in *Diagnostic and Statistical Manual of Mental Disorders* diagnoses. *Comprehensive Psychiatry* 53: 130–139.
- Wiederman MW, Sansone RA and Sansone LA (1998) History of trauma and attempted suicide among women in a primary care setting. *Violence and Victims* 13: 3–9.
- Woodruff RA, Goodwin DW and Guze SB (1974) *Psychiatric Diagnosis*, 1st edition. New York: Oxford University Press.
- Zanarini MC (2000) Childhood experiences associated with the development of borderline personality disorder. *The Psychiatric Clinics of North America* 23: 89–101.
- Zimmerman M, Ruggero CJ, Chelminski I, et al. (2008) Is bipolar disorder overdiagnosed? *The Journal of Clinical Psychiatry* 69: 935–940.