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Why is soft bipolar disorder so hard to define?

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Introduction

The observation that bipolar disorder (BD) is gradually expanding is not at all new. The boundaries of bipolarity have been gradually shifting outwards from episodic manic depression for decades, starting with the proposal of bipolar II disorder (BD-II) in the 1970s, steadily annexing more and more phenomenology under the aegis of 'soft bipolarity' or the 'bipolar spectrum', and culminating in 'bipolar spectrum disorder', which can be diagnosed in the absence of elevation (Baldessarini, 2000; Ghaemi et al., 2002). Rather than a single illness, we now have a spectrum model that links major depressive disorder (MDD) to BD, in which a steadily greater bipolar diathesis manifests as increased likelihood of subsyndromal mood instability (bipolar disorder not otherwise specified (BD-NOS) or subthreshold BD), hypomania (BD-II) and ultimately mania (bipolar I disorder; BD-I) (Figure 1).

The new bipolar spectrum is a broad church. First, it allows any form of mood instability, including brief hypomanic episodes, cyclothymic or hyperthymic personality, and mood swings within a day, and can even trump personality disorder (Akiskal et al., 2000). Second, it is potentially behind a substantial proportion of depressive illness, where it covers a wide phenomenological field including irritable/dysphoric, anxious, agitated, or atypical symptomatology (Akiskal, 2005), as well as psychosis (Ghaemi et al., 2002), and may therefore drive presentations as distinct as brief depressive episodes with preserved mood reactivity and severe psychotic depression (Ghaemi et al., 2002). It has also been linked to difficult or treatment-resistant depressions via early onset, recurrence, and failure to respond to antidepressants (Ghaemi et al., 2002). Finally, bipolarity has been suggested as a component of nearly every disorder we recognise, from psychosis (Keshavan et al., 2011) to personality disorder (Akiskal et al., 2000), anxiety (Akiskal et al., 2006), attention deficit hyperactivity disorder (ADHD) (Zdanowicz and Myslinski, 2010), eating disorders (Lunde et al., 2009), substance use (Maremmani et al., 2006), autistic spectrum disorder (Ragunath et al., 2011), somatisation (Tavormina, 2011), dissociation (Oedegaard et al., 2008), conversion disorder (Ghosal et al., 2009) and dementia (Ng et al., 2008). It even contributes to whether or not we smoke, drink coffee, or eat chocolate (Maremmani et al., 2011). Perhaps unsurprisingly, in such expansive forms, bipolarity is present in 30–55% of all depressive illness (Akiskal et al., 2000) and in 25% of the community (Angst et al., 2003). More conservative estimates place the lifetime bipolar spectrum prevalence much lower, at approximately 2.5% (Merikangas et al., 2011), but it remains clear that prevalence of bipolar diagnosis in the first world is rising sharply (Moreno et al., 2007).

Unfortunately, such broad-spectrum bipolarity seems to be a troubled diagnosis. As we expand the phenotype to include briefer or less severe mood swings, the diagnostic field steadily shifts away from episodic elevation towards affective instability (Goldberg et al., 2008), which is itself interesting insofar as this is presently a DSM (*Diagnostic and Statistical Manual of Mental Disorders*) criterion for borderline personality disorder (BPD) rather than bipolarity. This also has important diagnostic implications. It is notably unclear who should fall within the new 'soft bipolar' group and how we should dissect that out from personality disorder. The research offers little guidance on this front, either explicitly ignoring the possibility that personality disorder might need to be modelled diagnostically (Angst et al., 2003), or suggesting as-yet unvalidated operationalised criteria (such as the presence of two or more concurrent manic symptoms), which do not address the overlap and produce markedly different prevalence estimates in different settings (Merikangas et al., 2011).

However, it is of even more concern that the shift towards affective instability may be leading to a softening of the way in which existing DSM-IV diagnoses are applied, such that 30–60% of North American patients who are diagnosed with bipolarity in the community subsequently have that diagnosis retracted on formal research assessment (Zimmerman, 2010). As a result, DSM-IV bipolar disorders are now demonstrably overdiagnosed in patients with disorders that phenomenologically overlap with

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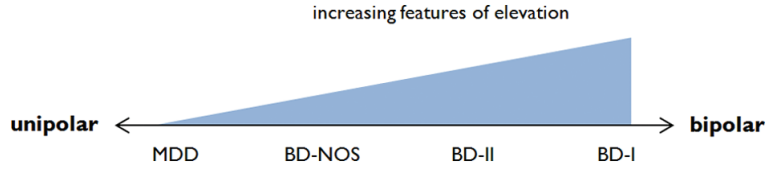
Figure 1. One-axis unipolar to bipolar spectrum model, in which a steadily greater bipolar diathesis manifests as increased likelihood of subsyndromal mood instability (BD-NOS or subthreshold BD), then hypomania (BD-II) and ultimately mania (BD-I). (MDD: major depressive disorder; BD-NOS: bipolar disorder not otherwise specified; BD-II: bipolar II disorder; BD-I: bipolar I disorder.)



bipolarity, such as anxiety disorders, substance use, post-traumatic stress disorder (PTSD) and BPD (Zimmerman et al., 2010). The troubled nature of the field is perhaps best illustrated by the observation that bipolarity is now simultaneously both markedly overdiagnosed (Zimmerman, 2010) and underdiagnosed (Smith and Ghaemi, 2010), a confusing state of affairs that requires some consideration.

It is therefore timely to examine the evidence for broad-phenotype bipolarity and consider both how robust the concept is, and why it appears to be so difficult to define.

Constructing a soft bipolar spectrum

One logic that has been invoked to demonstrate the existence of a soft bipolar spectrum runs as follows. First, it is argued that subthreshold mood instability is an important component of bipolarity, and that therefore the narrow manic depressive phenotype should be broadened (Altshuler et al., 2006). Second, the existence of a large group of patients with subthreshold mood instability is demonstrated (Angst et al., 2003). Finally, unipolar and BDs are connected by demonstration of a near-normal distribution of 'subthreshold manic' symptoms, without any zone of rarity, across MDD and BD (Benazzi, 2003; Cassano et al., 2004). That is to say, symptoms are smoothly distributed, consistent with a single process, rather than discontinuously distributed, as would be expected if two discrete processes were present.

This is an appealing chain of logic, but essentially syllogistic. Crudely stated for effect, the syllogism is that bipolar patients have mood instability, and other groups of patients also have mood instability, therefore that instability is bipolar. In order for this viewpoint to hold true, however, several additional points need to be demonstrated. First, we need to know that 'soft bipolar' or 'subthreshold manic symptoms' are either specific to mania and bipolarity, or that we have adequately distinguished them from other pathologies. Second, we need to be comfortable that 'classic' or narrow-phenotype bipolarity (episodic manic-depressive illness) (Gershon et al., 2009) and broad-phenotype bipolarity (significant mood instability) are essentially different manifestations of the same process, and that they are so intimately related that it is reasonable to use a single framework for describing both. Finally, we need to be confident that the main diagnostic decision we need to model is the distinction between depression and BDs.

We will therefore examine each of these propositions in turn.

Specificity of 'soft bipolarity'

The research construction of the soft bipolar spectrum rests in no small part on the assumption that the categorical symptoms of mania are specific to mania, such that the diagnosis can be disassembled into its component parts and still retain integrity. This assumption is built into both the original epidemiological work which examines distribution of 'subthreshold manic' symptoms (Angst et al., 2003; Benazzi, 2003; Cassano et al., 2004), and into more recent papers which report subthreshold bipolarity as a definite diagnosis on the basis of co-occurrence of as few as two 'manic' symptoms (Merikangas et al., 2011). It is, unfortunately, difficult to support (Malhi et al., 2010). Other disorders can present with symptoms superficially resembling bipolarity, as with the emotional and behavioural dysregulation of BPD (Paris et al., 2007), the pressured thinking of severe anxiety disorders (Provencher et al., 2012) or the distractibility and impulsivity of ADHD (Galanter and Leibenluft, 2008), and these disorders can also occur in the absence of bipolarity.

Similarly, boundaries with normalcy are unclear. In the general population, we do not know what differentiates 'soft bipolarity' from dysphoric mood swings, which occur in almost half of healthy controls (Angst et al., 2003). In adolescence, this difficulty becomes particularly acute, and it is very unclear what differentiates 'soft bipolarity' from developmentally congruent mood instability, as demonstrated by a recent series in which 'hypomanic' symptomatology did not reliably predict either conversion to formal bipolarity or ongoing mental health disturbance (Tijssen et al., 2010).

Markers have of course been identified which suggest a greater or lesser likelihood of bipolarity (Table 1). Such 'bipolar soft signs' (Ghaemi et al., 2002), however, are derived from pure mood disorder samples which compare only depression and BD, and thus have little specificity. For example, BPD is also associated with challenging depression (early onset, recurrent, often brief, often treatment-resistant), post-partum mood disturbance and pseudo-psychotic experiences. Similarly, other proposed markers for bipolarity, such

Table 1. Proposed diagnostic markers for bipolar disorders.

Proposed diagnostic criteria for 'bipolar spectrum disorder' (Ghaemi et al., 2002)

A. At least one episode of major depression
B. No history of spontaneous hypomania or mania
C. Either of the following, plus at least two items from criterion D, or both of the following plus one item from criterion D:
   1. A family history of bipolar disorder in a first-degree relative
   2. Antidepressant-induced hypomania or mania
D. If no items from criterion C are present, six of the following nine criteria are required:
   1. Hyperthymic personality (at baseline, non-depressed state)
   2. Recurrent major depression (> 3 episodes)
   3. Episodes of major depression are brief (< 3 months, on average)
   4. Atypical depression symptoms by DSM criteria
   5. Psychosis during depression
   6. Early age of onset of major depression (< 25)
   7. Post-partum depression
   8. Antidepressant loss of response (acute but not prophylactic response)
   9. Lack of response to > 3 antidepressant trials

Note that these are derived from comparison of unipolar and bipolar disorders. They have not been tested or validated in general psychiatric populations and there is evidence that specificity and predictive power are limited. We do not advocate their clinical use.

Other statistical predictors of bipolarity (Newport et al., 2012; Phelps et al., 2008; Reich et al., 2012)

Euphoric mood instability (as opposed to negative affective instability)
Periods of full remission between episodes
Full and/or rapid response to mood stabiliser medication

Predictors of personality disorder or incorrectly diagnosed bipolarity (Newport et al., 2012; Nilsson et al., 2010)

History of childhood abuse
Disturbed core psychological schemata

DSM: Diagnostic and Statistical Manual of Mental Disorders.

as symptom intensity (Tijssen et al., 2010), euphoric mood instability (Reich et al., 2012), or full remission on mood stabiliser (Newport et al., 2012), are statistically helpful but have unclear clinical predictive power. This difficulty also holds true for the markers which predict personality disorder over bipolarity, such as trauma history (Newport et al., 2012) and maladaptive core psychological schemata (Nilsson et al., 2010).

Specificity of subsyndromal 'manic' symptoms therefore remains unclear, leaving us with a concerning trend towards circularity, in which we have defined the occurrence of isolated 'manic' symptoms as subsyndromal bipolarity, demonstrated their existence, and then stated we have demonstrated a subsyndromal bipolar spectrum. Further, the clinical correlate of lacking a specific symptom profile is that we have no pathognomonic presentation for soft bipolarity and no robust diagnostic heuristic through which we can differentiate 'subsyndromal bipolar' affective instability from non-bipolar affective instability.

Relatedness of narrow and broad bipolarity

In practice, classic manic-depressive illness (narrow-phenotype BD) and subsyndromal mood instability (broad-phenotype BD) do indeed overlap. BD-I is defined by the presence of narrow-phenotype episodes, but also has significant and functionally important inter-episode mood swings (Altshuler et al., 2006), and the two patterns also co-occur in BD-II, albeit with a shift away from narrow phenotype (hypomania rather than mania) towards broad phenotype (greater interval mood instability) (Vieta and Suppes, 2008).

However, it remains unclear that narrow and broad-phenotype presentations are indissociable. Data suggest a degree of dichotomisation between BD-I and BD-II (Vieta and Suppes, 2008), with at least partly separate inheritance, a relative lack of interconversion between the diagnoses, and different illness courses and neurocognitive profiles. Similarly, although treatment data for BD-II remain something of a battleground, and lithium responsiveness may (Malhi, 2010) or may not (Tondo et al., 1998) relate to narrow-phenotype manic depressive illness, it appears that antidepressants are more efficacious and less likely to cause switching into hypomania in BD-II than BD-I (Amsterdam and Shults, 2010).

Data for 'soft bipolar' presentations or the bipolar spectrum are even more limited. Family data show that 'hypomanic personality characteristics' are present in relatives of BD-I patients (Savitz et al., 2008), but these traits are also common in healthy populations (Signoretta et al., 2005) and the majority of patients with 'subthreshold bipolar symptoms' do not develop a formal BD on longitudinal examination. Likewise, although a

quarter of adolescents have 'hypomanic' symptoms, these do not reliably predict conversion to bipolarity at a substantially greater rate than community prevalence, or even an ongoing need for mental health care (Tijssen et al., 2010), suggesting that the broad-bipolar construct in this group is neither clearly linked to classic manic depressive illness nor a longitudinally stable presentation. Finally, treatment data are sparse, but in STAR*D the presence of 'soft bipolar' symptoms did not influence treatment response or outcome (Perlis et al., 2011).

The case of antidepressant-induced mania or hypomania is an interesting subset of 'soft' bipolar presentations, in that it does appear to be a likely precursor of later bipolar diagnosis (Phelps et al., 2008). This may be because it falls more clearly in the narrow phenotype, as it is defined by the occurrence of a mood episode of syndromal intensity and duration, and could thus represent an unmasking of underlying classic manic-depressive illness rather than an extension of the phenotype into new territory.

On a cross-syndromal front, however, the distinction between broad and narrow constructs becomes even clearer. In particular, it becomes evident that not all forms of affective instability are manic-depressive, as evidenced by the marked differences between BD-I and borderline personality in co-occurrence, epidemiology, phenomenology, longitudinal course and treatment response (Bassett, 2012; Coulston et al., 2012; Paris et al., 2007).

It is, therefore, probably not unreasonable to assume that the 'bipolarity' of the soft bipolar spectrum becomes steadily less evident as the definition broadens and moves away from narrow-phenotype manic-depressive illness.

Depression versus bipolarity – binary diagnostics

It is notable that the current bipolar spectrum model only considers the existence of mood disorders, and therefore implicitly collapses the diagnostic field into a binary choice between depression and varying degrees of bipolarity. This assumption is enacted in the research used to demonstrate the spectrum (Benazzi, 2003; Cassano et al., 2004) as well as that used to validate it (Angst et al., 2003), which assumes an illness model where 'unipolarity' and 'bipolarity' are discrete illness processes and the latter is dose-dependently linked to subsyndromal or syndromal 'manic' symptoms. Specifically, the smooth normal distribution of 'manic' symptoms across MDD and BD, to which we referred earlier, may be meaningless if these symptoms are not demonstrably unique to bipolarity (for example, height is also likely to be distributed normally in a mixed unipolar and bipolar population). Likewise, even if there is a partial relationship, the absence of a zone of rarity excludes a dichotomous solution (discrete unipolar versus bipolar) but not a polygenic solution (where subsyndromal mood instability is multifactorially driven). That is to say, the demonstration of the spectrum in its current expansive form rests in part on the flawed assumptions we have challenged earlier.

Moreover, the same assumption of binary diagnostics has substantial clinical implications, as it allows the proposition that markers derived from comparison of unipolar and bipolar depression alone are sufficiently robust for widespread use. In screening, this failure to consider alternate diagnosis results in the development of screening tools that are good for excluding bipolarity (high negative predictive value) but overidentify it in the presence of other disorders (low positive predictive value) (Zimmerman, 2012). Additionally, many 'soft signs' of BD also occur more commonly in personality disordered or traumatised populations, leading to the failure of specificity, which we have already discussed.

Our proposed diagnostic aids, therefore, are limited by their binary diagnostic frame, and their limitations are most acute in precisely the diagnostically difficult territory where we really need them – namely the distinction of bipolarity from other conditions associated with affective instability.

A note on complex trauma

Complex trauma and borderline personality provide an excellent illustration of how these issues play out. These are conditions to which affect dysregulation is central, and which are demonstrably misdiagnosed as bipolarity (Zimmerman et al., 2010). However, they are distinct from manic-depressive illness (Bassett, 2012; Paris et al., 2007), and have an equally distinct explanatory model, in which trauma is linked to autonomic (Corrigan et al., 2011) and neural (Dannlowski et al., 2012) instability, and this in turn creates a sensitised and dysregulated emotional system which fluctuates wildly in the context of disturbed attachment (Choi-Kain et al., 2009), disturbed self (Meares et al., 2011) and relational distress. Understandably, this psychological and relational context is central to the borderline construct (Fonagy, 2000), differs between borderline and bipolar patients (Nilsson et al., 2010), has an emerging neural signature distinct to that of bipolarity (Mauchnik and Schmahl, 2010; Kuiper et al., 2013), and is integral to treatment models in treating traumatised patients (Fonagy, 2000).

'Bipolarisation' of such patients is an understandable consequence of using 'softer' diagnostic models with limited symptom specificity, but represents a reification of phenomenology at the expense of context and meaning (Jureidini, 2012), and is difficult to support on both a biomedical and psychotherapeutic level.

Babies, bathwater and bipolarity

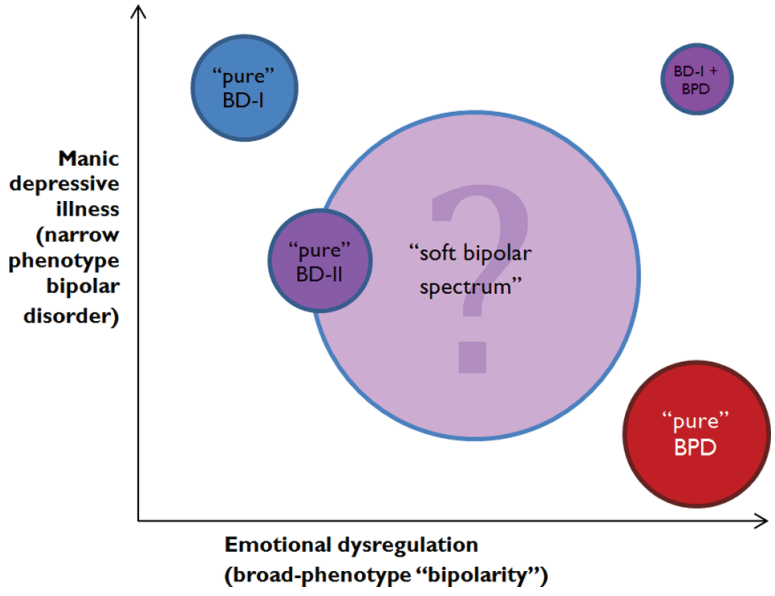
We emphasise that these reservations do not mean that we feel that soft bipolarity does not exist at all or

that it does not require any attention. There are some patients who have a 'subthreshold bipolar' phenotype who either have a familial loading for bipolarity (Savitz et al., 2008) or who eventually convert to BD-I or BD-II (Phelps et al., 2008) and, regardless of diagnosis, patients with severe affective instability are demonstrably unwell and require clinical and research attention.

However, there is a need for more precision in the terminology we use and the way in which we frame the discussion. Manic-depressive illness and severe affective instability can co-occur but are not identical processes, and the latter can occur without the former. The proposed 'soft bipolar spectrum' in the research literature is based much more on temperamental and affective instability than on manic depression, and thus, as the definition softens, the manic-depressive 'bipolar' paradigm becomes less and less relevant. Further, subsyndromal or soft 'bipolarity' is not yet validated as a coherent diagnosis. It likely captures a heterogenous group, some of whom are related to BD-I and some who are not, agreement on its treatment is poor, and it is a very poor predictor of course and outcome. Finally, because soft 'bipolarity' has no clear boundaries, many patients will present cross-sectionally with phenomenology that cannot definitively be determined to be bipolar or not.

The impact of using vague and overinclusive language under such circumstances is substantial. If we use the term 'bipolarity' for the very different broad and narrow constructs, a split evolves. On the one hand, there is a risk of conflating broad and narrow bipolarity and treating a patient who presents with significant affective instability as if they had manic depression, resulting in the overdiagnosis which has been so elegantly demonstrated by Zimmerman and colleagues (2010). On the other, there is a risk that we react against the self-evident dilution of the concept, reaffirm our belief that 'soft bipolarity' is not the narrow-phenotype disorder we professionally grew up with, and dismiss it as personality disorder, with resultant under-recognition and undertreatment.

Figure 2. Putative two-axis model of bipolar spectrum illness (broad and narrow). Disorders are positioned crudely for illustrative purposes, and we acknowledge that 'pure' constructs are artificial. However, BD-I exemplifies the classic narrow phenotype, and BPD can present as a prototypical 'non-bipolar' form of severe emotional dysregulation. BD-II has a lower narrow phenotype loading and a higher loading for interval mood instability. Patients with a high loading on both axes may present as both clear comorbid BD-I and BPD (top right corner), but many 'soft bipolar' presentations will contain smaller contributions from each axis which are difficult to tease out cross-sectionally. (BD-I: bipolar I disorder; BD-II: bipolar II disorder; BPD: borderline personality disorder.)



The exhortation that, on current evidence, we should assess as well as we can, own the uncertainty and take a 'wait and see' approach (Zimmerman, 2011) is absolutely appropriate but unlikely to be enacted on a systemic level. Doctors struggle to hold uncertainty, and are prone to using available heuristics and active decision-making as a way of resolving it (Hall, 2002). Further, on a community level, our decision-making in bipolarity is demonstrably not a strict reflection of diagnostic criteria (Ghaemi et al., 1999), and is vulnerable to process errors and misdiagnosis, which in turn impact treatment choices (Wolkenstein et al., 2011).

The heuristic which we use is thus a critical one, and we cannot simply use the same terminology to describe manic-depressive illness and non-manic-depressive mood dysregulation. If we present an unadultered 'lumping' approach, in which any mood instability is theoretically linked to bipolarity, this will at least to some degree be systemically enacted as overdiagnosis and overtreatment, and there is evidence that this is already occurring. 'Splitting' is difficult when it is not clear that we know where to split, but it may be time to adopt one aspect of the approach used by our colleagues in child and adolescent psychiatry and separate out severe mood dysregulation (Leibenluft, 2011) or broad-phenotype 'bipolarity', from narrow-phenotype bipolarity (Figure 2). This acknowledges

the importance of the construct we are currently referring to as 'soft bipolarity' while relieving it of the apparently false impression that it can be helpfully understood using the heuristic we apply to manic-depressive illness. The parallels of severe mood dysregulation with the emotional dysregulation of personality disorder are immediately apparent, and separating it from narrow-phenotype bipolarity therefore both resolves the clear separation of BD-I and borderline personality (Bassett, 2012; Paris et al., 2007) and maintains the significance and coherence of any shared diathesis between other forms of affective instability (Akiskal et al., 2000; Perugi et al., 2011). It offers a framework for rapid-cycling bipolarity, which clearly shares elements of both broad and narrow phenotypes (Coulston et al., 2012). It also explains why bipolar soft signs (Ghaemi et al., 2002) include different presentations – both the broad-phenotype features of preserved mood reactivity, recurrence and brevity, and the narrow-phenotype features of familiality with BD-I and overlap with psychotic illness. Finally, and most critically, it allows us to separate different phenotypes for research purposes and engage with patients with clinically important mood instability without trying to force them into a narrow-phenotype bipolar treatment paradigm.

Psychiatric diagnosis is subjective and mutable, and this interacts in difficult ways with the changing of diagnostic paradigms. Historically, we have previously reified and then retreated from undue diagnostic expansion of schizophrenia and major depression (Baldessarini, 2000), as well as overinclusive use of psychodynamic theory (Paris, 2005), and the current expansive form of bipolarity is charting an uncomfortably similar course. When we are unable, as a profession, to accurately diagnose a condition (Smith and Ghaemi, 2010), and we are wrong in almost half the cases where we do (Zimmerman, 2010), the diagnosis is in crisis, and we need to correct course rather than accelerating. Irrespective of whether soft bipolarity exists or not, when our construction of it is poorly validated, unreliable, heterogenous, not predictive of outcome and has no defined treatment pathway, we should exercise profound caution before we deploy it clinically.

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