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The clinical diagnosis of bipolar depression

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Abstract

'Bipolar depression' is not a specific type of depression, with most episodes phenotypically weighted to melancholic or psychotic depression. In order to improve our understanding of the etiology and management of bipolar depression, sub-typing heterogeneity should be constrained. A 'top-down' approach to delineate specific sub-typing characteristics is suggested, allowing consideration as to whether 'bipolar depression' differs in expression across bipolar I (BPD I) and II (BPD II) disorders. Current diagnostic systems employ imprecise criteria to differentiate sub-types of BPD, disallowing 'top-down' studies seeking to identify prototypical bipolar depression features.

We describe a categorical 'isomer' model, assisting discrimination between bipolar subtypes and unipolar depressive disorders. In essence, the respective presence or absence of psychotic features differentiates BPD I from BPD II, with a core elevated mood/energy construct delineating BPD from unipolar disorders. Our model allows a 'top-down' approach to clinical diagnosis, *versus* the questionable validity of the bipolar spectrum 'soft signs' approach.

Introduction

'Bipolar depression' is generally defined quite simply – as the depressed phase experienced by an individual who has bipolar disorder (BPD). Thus, the clinical diagnosis generally first requires clarification as to whether an individual has BPD or not. A provisional diagnosis of BPD usually involves the individual describing: (i) clear-cut hypomanic or manic episodes that have a sufficient number of prototypic distinctive features; (ii) a clear onset to their highs – that they can remember a time when mood swings commenced – although we must concede the occasional onset of BPD in childhood; and (iii) that during the 'highs' their usual levels of 'anxiety' disappear as their self-confidence increases in line with the elevated mood state. Thus, by adopting the logic expressed in the first sentence, 'bipolar depression' is effectively the converse depressed state experienced by those with BPD.

However, just as 'depression' is a non-specific term and its clinical expressions can be sub-typed, 'bipolar depression' is not a specific type of depression. Most – but not all – episodes of 'bipolar depression' have a phenotypic picture that is weighted to the melancholic or psychotic depressive picture. Such depressive sub-types have a number of ascriptions, including: (i) having

distinctive symptoms and signs; (ii) having biological determinants that are more relevant than psychosocial determinants; and (iii) that such conditions have more selective responses to physical treatments.

Turning to distinctive symptoms and signs, commonly suggested features [1] include a more severely depressed and non-reactive mood, a depressed state marked by anhedonia and anergia, impaired concentration, psychomotor retardation and/or agitation, appetite and/or weight loss, insomnia (especially early morning wakening), and diurnal variation (with mood and energy worse in the morning). In psychotic depression, psychomotor disturbance is even more severe, mood congruent or incongruent delusions and/or hallucinations are present, and diurnal variation is usually lost, with mood and energy remaining low across the day.

Finally, just as it is a common human experience to develop 'depression' in response to stressors that impact on an individual's self-esteem, those with BPD are not immune to such experiences, and may therefore also develop non-melancholic depressive episodes; in these, the phenotypic picture is marked by the absence of the more specific melancholic features rather than by any class of distinctive features.

If we are to improve our etiological understanding and management of bipolar depression, there is a need to constrain such sub-typing heterogeneity. The remainder of this chapter will consider this key issue – and consider whether there is any *sui generis* bipolar depressive condition or – and more to be expected – distinct over-representation of any type or specific features.

How might we proceed to advance sub-typing of BPD? Theoretically, there are two contrasting ('top down' and 'bottom up') approaches that might lead to delineating any specific sub-typing 'bipolar depressive' characteristics. The former approach would involve studying clearly diagnosed patients with BPD during their depressed phase. The latter might involve studying those with clinical depression and identifying predictors of bipolar status.

Operationalising a 'top down' approach

As noted, while individuals with BPD are not immune to experiencing episodes of 'reactive depression' in response to life's vicissitudes, a 'top down' approach might proceed by selecting groups of individuals with clearly defined BPD, and then identifying the 'characteristic' features experienced by them across multiple depressive episodes. Such an approach emphasises 'characteristic' and 'consistent' features to identify the most prototypic clinical features. As BPD is increasingly sub-divided into bipolar I (BPD I) and bipolar II (BPD II) subtypes, with manic and hypomanic phases respectively, the ideal categorical system would allow consideration as to whether 'bipolar depression' is identical in expression across both bipolar sub-types. This raises the question of how well official classificatory systems (such as the DSM-IV and ICD-10) define and differentiate bipolar sub-types.

The DSM-IV [2] classificatory system has essentially the same criteria for mania and hypomania. Thus, Criterion A for both mania and hypomania involves a "distinct period of abnormally and persistently elevated, expansive, or irritable mood". Criterion B requires three or more (or four or more if the mood is only irritable) of seven listed features. Minimal durations of 7 days for mania and 4 days for hypomania are imposed, although neither of these intervals has been established empirically [3]. If, during the 'high' the individual experiences psychotic features, or if hospitalisation is required, then irrespective of duration, DSM-IV criteria for a manic episode are met. While mania and hypomania require a level of impairment, DSM-IV definitions of 'impairment' are not distinctive across either of the two expressions.

The ICD-10 [4] system contains only one bipolar category ('Bipolar Affective Disorder'), and weights description rather than meeting a set of diagnostic criteria. Hypomania is a non-psychotic state lasting "at least several days", with the associated mood and behavioural changes being more distinctive and persistent than allowed by a diagnosis of 'cyclothymia'. Manic episodes are defined as lasting from 2 weeks to several months and may or may not include psychotic features which, if present, may have mood congruent or mood incongruent characteristics.

Thus, the two categorical diagnostic systems essentially differentiate 'mania' from 'hypomania' by the presence of psychotic features, a longer minimum duration and (in the case of DSM-IV) by hospitalisation. In terms of clinical course, the DSM-IV system characterises BPD I as involving the occurrence of one or more manic episodes or mixed episodes, while BPD II involves at least one hypomanic episode and the occurrence of one or more episodes of major depression. The DSM-IV model essentially positions bipolar depression as 'major depression' – as it effectively does for unipolar depressive conditions. Thus, major depression can exist with or without diagnostic specifiers (e.g., psychotic features, catatonic features, melancholic features, and atypical features), context specifiers (e.g., post-partum onset) and course specifiers (e.g., chronicity, seasonal pattern, or rapid cycling). As major depression is not a specific diagnosis [5] and more an operational strategy to differentiate 'clinical depression' from less substantive depressive disorders, such specifiers are likely to be more salient in determining and quantifying whether 'bipolar depression' is more, or less, likely to be distinctive.

The ICD-10 system [4] adopts a dimensional model for the depressive disorders, operating across severity, persistence, and recurrence parameters. Its so-called 'somatic features' correspond broadly to DSM-IV melancholia criteria, but the Introduction notes that their scientific status is "somewhat questionable", so that such data can be recorded or ignored. Similarly, in light of the imprecise 'criteria' for hypomania ('at least several days') and 'cyclothymia' (where duration and severity criteria are not operationalised), differentiation of BPD from unipolar depressive disorder proves difficult. Thus, the ICD-10 system does not lend itself to 'top down' studies seeking to identify any specific features of bipolar depression.

We have sought to develop a categorical model for BPD and to assist discrimination from unipolar depressive disorders. We first developed [6] a questionnaire (the Mood Swings Survey or MSS), comprising 46 items capturing aspects of 'highs' as generated from a literature review and from clinical experience. In the initial study, 157 depressed outpatients were asked to complete the questionnaire. Of the 101 subjects diagnosed with BPD, 49 received a diagnosis of BPD I by largely respecting DSM-IV criteria of psychosis or hospitalisation (i.e., 61% had had psychotic manic episodes and 37% had been hospitalised when in a mood elevated state), and 52 received a diagnosis of BPD II disorder. BPD I and BPD II groups did not differ by mean age (41 *versus* 37 years), gender, social class, family history of BPD (41% *versus* 38%), nor age of onset of initial elevated mood (24 *versus* 22 years) or initial depression (22 *versus* 20 years). BPD I subjects were significantly more likely, however, to report longer periods of elevated mood.

In completing the MSS, the bipolar groups were asked two probe questions ("Do you ever have mood swings and, as part of such swings, have times when (i) your mood is higher than your usual sense of happiness", and (ii) "Do you feel quite 'wired', 'energised', 'elevated', 'expansive', and possibly 'irritable'?"), and asked to complete the questionnaire for such periods. The probe questions therefore sought to ensure that ratings were for manic or hypomanic episodes rather than merely for periods of happiness. By contrast, the 56 patients with a clinically diagnosed unipolar depressive disorder were asked to complete the same questionnaire (here titled 'Happiness Survey') and invited to think of "times when you are really happy (e.g., your favourite sporting team has won, you're spending a weekend with long-lost friends)". Each questionnaire had identical rating options ('much more than usual', 'somewhat more than usual', and 'no more than usual' scored, 2, 1 and 0, respectively). Items weighted high energy, mood elevation, creativity, disinhibition, mystical experiences, irritation, and anger constructs, but not psychotic features, and therefore sought to measure the core state defining a 'high'.

When questionnaires scores were summed, the 49 BPD I subjects had only marginally higher MSS scores than the 52 BPD II subjects (32.7 *versus* 29.7). The 56 unipolar subjects returned a mean score of 11.2, significantly lower than those with either BPD I or BPD II disorders. We examined the performance of the total score (and later a refined 27-item score) in terms of differentiating BPD and unipolar subjects from each other. Using the total MSS score, ROC analyses established a high level of discrimination (the Area-Under-the-Curve or AUC = 0.93), while at the derived cut-off score of 36 or more, a sensitivity and specificity of 84.3% and 92.6%, respectively, was quantified. Results therefore suggested that the 'core' mood/energy state (quantified by the measure) is likely to differentiate those with BPD from those with unipolar disorder, but not differentiate BPD I from BPD II expressions – again providing support for the MSS to discriminate bipolar from unipolar disorders.

Inspection of individual items indicated that those with BPD were most clearly distinguished from those with unipolar depressive disorders by high

energy and elevated mood items, essentially the converse of melancholic/psychotic depressive states, which (as detailed later) are dominated by psychomotor (including anergic) symptoms and a lowered mood state.

Such data allowed a model to be developed. The core mood/energy construct clearly differentiated bipolar and unipolar disorders, but was insufficient in itself to differentiate BPD I from BPD II conditions. Further, in our initial study, we established that, of those assigned on the basis of being psychotic and/or requiring hospitalisation during a high, 41% had experienced an episode of psychotic depression when depressed. By contrast, none of the BPD II subjects had experienced psychosis during episodes of elevated mood (by definition) and none – the key issue here in developing a model – had experienced psychotic depression when depressed. Such specificity argued for differentiating BPD I and BPD II conditions from each other by the *respective presence or absence of psychotic symptoms.*

Such specificity of psychotic symptoms and the mirror imaging of BPD I and BPD II polar states allows an 'isomer' or 'mirror image' model for distinguishing between BPD I and II disorders, and, of key importance here, having 'top down' potential to inform us about the expression of 'bipolar depression'. In essence, the model (as shown in Fig. 1) recognises that, while the elevated mood/energy state is a core construct of BPD (and shared across both BPD I and BPD II states), it is insufficient to effectively distinguish the two. It is the respective presence or absence of the psychotic 'mantle' that distinguishes BPD I from BPD II. This is a mixed model in that it dimensionalises the core mood/energy construct (increased in 'high' states, decreased in 'depressed' states, and with such changes slightly greater in BPD I subjects than BPD II

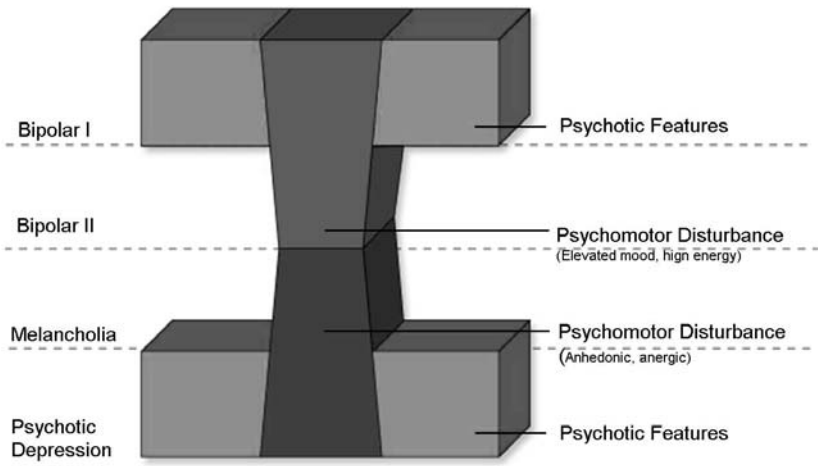

Figure 1. An isomer model capturing psychotic and melancholic depression as mirror images of Bipolar I and Bipolar II disorders, respectively.

subjects), and is categorical in positioning 'psychotic features' as differentiating subtypes of BPD.

The model is also heuristic. It presupposes that those with BPD II oscillate within a narrower band than those with BPD I. While we had previously produced data [7] indicating that those with BPD were highly likely to experience melancholic or psychotic depression when depressed, the isomer model allows more refined hypotheses. It suggests that those with BPD II oscillate between non-psychotic hypomanic and melancholic episodes, while those with BPD I experience psychotic manic episodes and have either psychotic or melancholic episodes when depressed. The model not only allows causal hypotheses to be pursued but provides a platform for testing the relative utility of quite differing drug treatments (antidepressants, mood stabilisers, and antipsychotic drugs) for BPD I and BPD II. Of key relevance here, the model allows comparisons to be made of 'bipolar depression' as experienced by those with differing BPD I and BPD II, as well as comparison to the depression experienced by those with unipolar depression.

Operationalising a 'bottom up' approach

The 'bottom up' approach involves assessing individuals or groups during the depressed phase and considering whether any of the clinical features are indicative or markers of BPD. This approach has also been applied in the absence of the individual reporting clear cut 'highs', particularly by those who model BPD as a non-categorical 'spectrum condition'. As reviewed by Phelps [8], proponents of the dimensional spectrum model allow the existence of some degree of bipolarity even in the absence of clear-cut hypomanic or manic episodes. For example, Ghaemi and colleagues [9] described a number of bipolar 'soft signs' effectively suggesting or allowing a diagnosis of BPD to be suspected on the basis of either (a) the *depressive features*, e.g., having four or more features of major depression; early onset (younger than 25 years) of first episode of major depression; 'atypical' symptoms such as hypersomnia and hyperphagia; or psychotic episodes when depressed; (b) *illness course variables*, e.g., brief episodes of major depression of less than 3 months; and (c) *associated variables*, e.g., a first-degree relative having a diagnosis of BPD; the individual having a hyperthymic personality style; onset of depression in the post-partum period; antidepressant-induced 'highs'; progressive loss of efficacy of an antidepressant (the 'poop out' phenomenon); and three or more unsuccessful antidepressant trials.

Ghaemi and colleagues [9] also provided an algorithm for defining 'bipolar spectrum disorder'. In addition to (i) at least one major depressive episode and no "spontaneous hypomanic or manic episodes" individuals should have either (a) a first-degree relative with a history of BPD or (b) antidepressant-induced manic or hypomanic switching, or, if neither of those features are present, at least 6 of 9 other criteria (essentially those listed in the previous paragraph).

Such a spectrum model is clearly problematic in risking 'over-diagnosis' of false positive bipolar states. As BPD is generally defined as an oscillating state with clearly defined highs and lows, a diagnosis of BPD in the absence of any hypomanic or manic episodes – and merely on the basis of 'soft signs' or proxy features – appears counter-intuitive, and risks intuitive rather than fact-based diagnostic practice. For example, one of those 'soft signs' (a 'hyperthymic' personality style) is worthy of contemplation. As detailed by Jamison [10], it is possible to have a personality style of 'exuberance' without necessitating a diagnosis of BPD. Just as Freud once observed that a cigar can simply be a cigar, sometimes exuberance is simply exuberance, and categorically independent of any 'hypomanic' or 'manic' status. To the extent that BPD is associated with any specific depressive phenotypic picture, then applying a dimensional spectrum model may confound delineation and description of bipolar depression.

An overview of previous studies of bipolar depression

While many individual studies exist that principally focus on differences in particular symptoms or illness correlates, consistency in findings is relatively low. We will first consider possible explanations for such issues before giving an overview of the general findings.

In any attempt to define 'bipolar depression' there are three immediate problems. First, it could be defined, as indicated in the 'top down' section, by studying those with BPD during the depressed phase. However, this descriptive approach is only of modest value as it lacks specificity. The more substantive second problem is whether bipolar depression is 'different' or 'distinctive' from unipolar depression, and the issue here is in considering and studying the appropriate reference group. Let us consider the limitations to any comparison with 'major depression' or 'clinical depression'. As noted earlier, neither represents a pure clinical depressive type, with each effectively capturing heterogeneous depressive conditions, caused (across individuals) by quite differing biological, psychological, and social factors, and subsequently expressed in quite variegated clinical feature patterns. If 'bipolar depression' is a pure type (say ubiquitously 'melancholic') and a sample of those with bipolar depression were compared to those with 'major depression' (with melancholic and non-melancholic constituent representation), then we might expect differentiation from the comparison group. If, by contrast, the comparison group was limited to those with a (unipolar) melancholic depressive episode, few or no differences might be expected. Differences then can be created or obviated by choice of comparison group.

The third problem is that it is unlikely that 'bipolar depression' is a homogenous entity. Based on the isomer noted earlier, we might expect that a sample of those with bipolar depression would include some with psychotic depression, a considerable proportion with melancholic depression, and some with non-melancholic disorders. The extent to which these three differing sub-types

were represented within the bipolar depression sample would also influence comparison with any reference group.

Turning to the literature, this key issue of whether 'bipolar depression' represents a pure type has rarely been considered. We reported [11] an analysis examining whether 'melancholia' was the characteristic sub-type, based on three large data sets of unipolar and patients with BPD recruited over a 15-year period. 'Melancholia' was defined using several diagnostic systems. When comparing BPD and unipolar subjects, the former group were significantly more likely to be diagnosed as having a melancholic depression by DSM-IV criteria (69% *versus* 37%), by the CORE measure [1] (59% *versus* 33%), and by clinical definition (70% *versus* 29%). We undertook logistic regression analyses examining a large number of clinical features, and found that observable psychomotor disturbance (particularly retardation) and pathological guilt were the only two significantly overrepresented features in those with BPD during the depressed phase. Results of these analyses confirm an over-representation of melancholia in the depressed phase of BPD and, via the over-representation of pathological guilt, suggest that psychotic depression is also likely to be represented.

In considering more fine-focused studies, it is more useful to consider an overview report rather than individual studies. One of the most comprehensive reviews was undertaken by Mitchell and colleagues [12] as part of the *International Society for Bipolar Disorders Guidelines Taskforce on Bipolar Depression*. As does much of the literature on BPD, this review focuses on BPD I, and it may be quite unwise to assume that what holds for BPD I can be extrapolated to BPD II. Nevertheless, the review is likely to be the definitive reference for a period. In terms of illness course, the authors suggest that depression is somewhat more likely to be the first state experienced by those initially experiencing BPD. Second, those with BPD tend to experience more depressive episodes over a lifetime than those with a unipolar depressive disorder; however the severity of depression does not appear to differ.

In terms of the depressive sub-type, the authors note an earlier paper that addressed the methodological concern noted early in this section – effectively the need to compare 'apples with apples'. Thus, if bipolar depression is most commonly melancholic in 'type', then those with bipolar depression should be matched in terms of depressive sub-type representation rather than compared with those within a broader diagnostic group (for instance, those with major depression). Mitchell and colleagues [13] compared 39 bipolar depressed patients with 39 unipolar depressed patients, matched for age, sex, and the presence or absence of melancholia as defined by the DSM-IV system. While the groups did not differ in terms of depression severity, those with BPD were more likely to have had a psychotic depressive episode in the past. During the current episode they were more likely to report anhedonia, persistence of depressed mood, and hypersomnia, but less anxiety. In terms of psychomotor disturbance, they did not differ in agitation severity but scored significantly higher on the measure of retardation.

Mitchell and colleagues [12] closely reviewed several other relevant studies and tabulated data (from a large number of studies) on potentially differential clinical features, co-morbid features, course of illness, and family history variables. Of the set of more than 20 clinical features, several were suggested as possibly more likely in those with BPD, including worthlessness, psychotic features, social withdrawal, hyperphagia and hypersomnia, and mood lability. Co-morbid anxiety states and alcohol use were suggested as overrepresented, as was a family history of BPD.

Mitchell and colleagues [12] examined some 40 candidate markers of bipolarity and proposed a 'probabilistic' model for considering a diagnosis of bipolar I depression in an individual experiencing a major depressive episode with no clear prior episodes of mania. In essence, they argued that those with bipolar depression would be more likely to report 'atypical depressive symptoms' (e.g., leaden paralysis, hypersomnia, hyperphagia) while those with unipolar depression would be more likely to report initial insomnia or general insomnia, and appetite and weight loss. Further, they suggested that those with bipolar depression would be more likely than those with unipolar depression to report: i) psychomotor retardation (activity levels in those with unipolar depression would be less likely to be abnormal); ii) psychotic features and/or pathological guilt (whereas those with unipolar depression would be more likely to report somatic complaints); and iii) lability of mood or manic symptoms. Drawing on their literature review, their probabilistic model argued that those with BPD would be more likely to have a positive family history of BPD, to have an early onset of their first depressive episode, and to have had multiple prior episodes of depression, while those with unipolar depression would be more likely to report depressive episodes lasting 6 months or longer.

Most measures assessing depressive phenomenology rate symptoms in terms of their severity (whether self-reported or observer-rated). We have recently completed a study in which patients attending our Depression Clinic were asked to rate their most recent and/or severe depressive episode in terms of its characteristic features. While these results will be reported elsewhere, we will review here the findings of relevance to this chapter.

We examined the most characteristic symptoms as nominated by those with (i) bipolar depression (n = 123), (ii) unipolar melancholia (n = 86), and (iii) unipolar non- melancholic depression (n = 142). The BPD/unipolar and melancholic/non-melancholic decisions were generated by careful clinical assessment. In this analysis, we did not differentiate between BPD I and BPD II. When the rank order of the 32 symptoms (returned by the unipolar melancholic and unipolar non-melancholic groups respectively) was compared, analyses indicated that bipolar patients' prioritising of characteristic symptoms was slightly closer to those with unipolar melancholia than to unipolar non-melancholic depression. Those with bipolar depression were somewhat more likely to report psychomotor disturbance (i.e., difficulty doing basic things like getting out of bed, feeling somewhat paralysed), and somewhat less likely to report irritability and anger than those with unipolar non-melancholic depres-

sion. Other differences between BPD and unipolar non-melancholic subjects included the former as more likely to report diurnal variation in mood (i.e., depressed mood worse in the morning), and concentration difficulties (i.e., brain feeling foggy, thinking slowed).

A synthesis and some speculation

Findings regarding bipolar depression, and in particular as reviewed by Mitchell and colleagues [12], suggest that those with BPD (compared to those with unipolar depression) are more likely to have a family history of BPD, somewhat briefer episodes of depression, and to report depressive symptoms that are generally compatible with melancholic and psychotic depression. That review concluded, however, that rather than report classic 'endogeneity symptoms' such as appetite/weight loss and insomnia (especially early morning wakening) those with BPD are more likely to report the so-called 'atypical features' of hyperphagia and hypersomnia.

Such over-representation of 'atypical depressive features' in those with BPD has long been recognised [14, 15]. However, such features – while common in younger subjects with bipolar depression – are also more common in younger subjects with unipolar melancholia. In one study [16], we focused on the relative proportion of those experiencing hypersomnia *versus* early morning wakening across three differing depressive sub-types (BPD, unipolar melancholia, and unipolar non-melancholic depression) and four age bands (<25 years, 26–35 years, 36–45 years and 46–55 years). Hypersomnia rates decreased as age increased in those with bipolar depression (i.e., 75%, 70%, 43% and 46%) and in those with unipolar melancholia (i.e., 60%, 44%, 43% and 30%) but not in the non-melancholic group (i.e., 76%, 61%, 57% and 66%). Hypersomnia (during depression) has been viewed as an adaptive homeostatic response restoring slow wave sleep during stress [17], and may therefore characterise a general coping response. However, as age increases, those with melancholic depression (whether experiencing a unipolar or bipolar course) may experience more noradrenergic neurotransmission perturbation with age, influencing HPA activity and thus contributing to a differing sleep pattern – the more classic endogeneity feature of early morning wakening. Similarly, we have speculated [15] that hyperphagia may be a general coping response, albeit more commonly reported by those with 'atypical depression', exerting a 'comforting' effect via release of endorphins and multiple other chemical compounds. As they age, those with bipolar depression and unipolar melancholia appear more likely to report the endogeneity symptoms of appetite and weight loss, and again this may reflect the impact of age on contributory monaminergic systems.

Concluding comments

We suggest that the clinical diagnosis of bipolar depression be weighted to a 'top down' approach, in light of many questions about the validity of the bipolar spectrum 'soft signs' approach. This would require ensuring that the individual meets appropriate diagnostic criteria for BPD I or BPD II in terms of their manic or hypomanic episodes respectively, and that they are assessed in relation to characteristic depressive episodes. While bipolar depression appears more weighted to the psychotic and melancholic clinical phenotype, there is the suggestion that so-called atypical features such as hypersomnia and hyperphagia may be over-represented, particularly in younger individuals.

We have detailed an 'isomer model' which suggests that bipolar depression should be studied separately in those with manic and hypomanic episodes, and provided data indicating that, while those with BPD I are at some risk of developing psychotic depression and those with BPD II are likely to develop melancholic episodes, those with BPD II are unlikely to develop psychotic depression.

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