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The Manic-Depressive Spectrum and Mood Stabilization: *Kraepelin's Ghost*

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> Manic-depressive insanity ... includes the whole domain of so-called periodic and circular insanity ... I have become more and more convinced that all of the above-mentioned states only represent the manifestations of a single morbid process.
>
> *Emil Kraepelin* [1]

A century ago, Emil Kraepelin (1856–1926) divided most severe mental illnesses into two classes of disorders: *manic-depressive insanity* (MDI) and *dementia præcox* [1, 2]. He emphasized longitudinal course and outcome to differentiate these conditions, following Karl Kahlbaum's (1828–1899) lead in separating discrete syndromes with different courses from Wilhelm Griesinger's (1817–1868) formerly dominant unitary insanity *(Einheitpsychose)* concept. Kraepelin was driven by a sense of obligation to provide at least a prognosis in the absence of effective treatments [2]. Despite some initial controversy, Kraepelin's dichotomy gained international influence in the early 20th century as a basis for organizing the idiopathic psychotic disorders. However, his descriptive approach and emphasis on major disorders encountered growing competition from psychoanalysis, which considered gradations of illnesses, including intermediate forms or levels of severity between neuroses and psychoses, as well as psycho-etiological hypotheses to explain clinical phenomena.

Kraepelin's influence returned with the efforts of American psychiatrists to develop the descriptive Research Diagnostic Criteria (RDC) and subsequent American Psychiatric Association's major reorganization of its diagnostic schemes in DSM-III, with parallel efforts by the World Health Organization in its ICD-9 and -10. Indeed, current schizophrenia much more closely resembles Kraepelin's *dementia praecox* than Eugen Bleuler's (1857–1939) *group of schizophrenias* [3] and the even broader concepts that emerged in the mid-20th century. In mid-century, too, Kraepelin's MDI was divided into narrowly defined bipolar disorder (BPD) with mania (type I), and an increasingly broadly defined major depressive disorder (MDD) concept. MDD expanded far beyond Kraepelin's recurrent melancholic depressions, and was sustained by general acceptance of drugs labeled and promoted as antidepressants [4]. More recently, DSM-IV broadened BPD to include Kraepelinian hypo-

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mania (type II BPD) and even cyclothymia, as the bipolar/unipolar dichotomy continued to dominate diagnostic standards and clinical practice. As noted by Jürgen De Fruyt and Koen Demyttenaere [5], for several decades BPD has received far less clinical or research attention than MDD, and non-obvious cases of BPD often are misdiagnosed. Mood stabilizers are used less frequently than antidepressants, even for known BPD patients, despite uneven evidence of efficacy of the off-label use of antidepressants for bipolar depression [4–7].

Recently renewed interest in BPD, encouraged by innovative therapeutic options to lithium [8], has rekindled consideration of the validity of the dichotomous (bipolar/unipolar) classification of major mood disorders. Kraepelin conceived MDI broadly as a single disorder of the regulation of arousal and activity as well as mood, with many manifestations and levels of symptomatic and functional severity, marked by an unstable or chaotic longitudinal course [1, 2, 9]. His concept relied heavily on Kahlbaum's *course* criterion of recurrence with substantial recovery between acute illness episodes of varied and typically pathoplastic forms [10], rather than a cross-sectional criterion of manic versus depressive symptomatic *polarity* [11]. Recurrent, especially melancholic, depression was included in Kraepelin's mature, late concept of MDI, as were cyclothymia and even MDI-related temperaments [1, 2].

Currently, a growing number of clinical investigators are returning to the Kraepelinian MDI concept in proposing a broad *bipolar spectrum*, with intermediate forms between BP-I disorder and indubitable cases of severe, melancholic, and recurrent MDD as well as other less well-characterized forms of less severe depression and dysthymia [5, 12, 13]. Often, such diagnostic concepts are seen as requiring a choice between *either* a categorical, *or* a spectrum model [13]. Associated conceptual simplifications can yield antagonistic camps, and more controversy than enlightenment. In his thoughtful review of evidence supporting categorical and dimensional or spectrum concepts of major mood disorders, Franco Benazzi [13] outlines an alternative to the either-or approach. He proposes that extreme clinical archetypes in a mood spectrum may indeed allow for separate, categorically conceived mood disorders, whereas intermediate variants may best be described dimensionally. He also emphasizes the significance of states involving simultaneous or rapidly shifting admixtures of manic and depressive features (mixed states). Indeed, such mixed states appear to have been important in encouraging Kraepelin's broad MDI concept through their systematic study by his younger colleague, Wilhelm Weygandt (1870–1939) in Heidelberg in the mid 1890s [14].

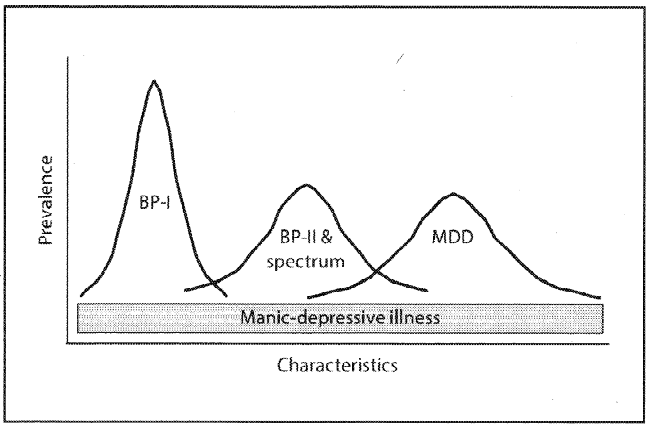

Fig. 1. Proposed model of the distribution of manic-depressive disorders, including classic type I BPD (lifetime prevalence ca. 1–2%), disorders included in current DSM-IV MDD (prevalence ca. 2–5%, or even less if only more classic, recurrent, melancholic-endogenomorphic syndromes are included), and an emerging intermediate group ('bipolar spectrum disorders'), that represents expanded bipolar II syndrome, marked mainly by depressive features and recurrence, but with relatively subtle bipolar features including broadly defined hypomania and cyclothymia (at a lifetime prevalence, also of ca. 2–5%, that may be similar to that of MDD).

We agree with Benazzi's proposal [13] that many cases of psychiatric syndromes appear to be distributed in a dimensional manner, in that individuals vary in clinical presentations: some cases share most features, others some, and still others almost none. As Darwin noted about individuals in species, case variations are distributed continuously [15]. This basic biological fact does not invalidate categories, but limits them to distributions of cases whose features overlap little with other cases. A central question to be established empirically is *how much overlap* exists in the distribution of cases of BPD and MDD. If Kraepelin was correct, distributions of characteristics BPD and MDD cases should overlap considerably; if the DSM-III/IV approach is correct, there should be little overlap. Benazzi concludes that the available evidence indicates some overlap, perhaps justifying the use of a bipolar spectrum concept, yet allowing for useful BPD and MDD groupings for a substantial proportion of archetypical cases marked by indubitable mania versus seemingly pure, severe, recurrent depression. An alternative model would consider a distinctly bipolar I group, and a more secure, relatively severe, melancholic or endogenomorphic and recurrent MDD, with a third group

between them that shares features of both (fig. 1). This mid-group would include DSM-IV BP-II syndrome [16] and its expanded forms – in our opinion, the essence of the bipolar spectrum.

As De Fruyt and Demyttenaere [5] point out, important scientific and clinical concerns need to be addressed before the narrow DSM-III/IV BPD concept is abandoned [17] in favor of a broader bipolar spectrum model, or consideration of a possible third group of disorders intermediate between classic BP-I and classic, relatively severe and recurrent MDD syndromes. Indeed, MDD might well include a 'unipolar spectrum' that seems implicit in its modern, broadly defined, form. Scientifically, biological studies in psychiatry have been hampered by a primitive, essentially clinical-descriptive, and possibly arbitrary, nosology [5, 17, 18]. More than a century of research in major mood and psychotic disorders has failed to define a pathophysiology, let alone a plausible etiology, of these conditions [18]. This lack of progress may be due to heterogeneity, for example, in the extraordinarily broad current MDD and former schizophrenia concepts. Even type I BPD is a highly pleiotropic and chaotic condition within as well as between individuals. If BPD were broadened to subsume even more heterogeneous phenotypes, there is a risk of hampering progress in genetic and other biological investigations [17–19]. Similar concerns apply to experimental therapeutics. Huge sums and efforts are expended in demonstrating minor superiority of particular psychotropic medicines over older treatments or placebos in many conditions, including mood and psychotic disorders [4, 7, 8]. To some extent, this impasse may reflect clinical heterogeneity implicit in *both* categorical and dimensional diagnoses, as well as the considerable clinical non-specificity of most psychotropic medicines [7, 8], leading to difficulty in predicting individual responses to particular treatments.

Clinically, one must ask what kind of bipolar spectrum is being proposed, and why. Is it to be a spectrum of mania-hypomania or of depression [20], of psychosis [21], of impulsivity [22], of anxiety [23], temperament [24], or of all of these dimensions [25]? We need evidence to view the bipolar spectrum along some of these dimensions and not others. A mood spectrum, as opposed to specific diagnoses, may encourage a more individualized and morbidity-targeted, rather than the categorical approach to psychiatric treatment now used to support use of antidepressants for 'depression', and mood stabilizers' for 'bipolar disorder'.

De Fruyt and Demyttenaere [5] identify and applaud a major recent upswing in research on BPD, while noting continued though diminishing disparity between levels of research funding, publications, and controlled therapeutic trials for BPD compared to MDD. They also note that this increase in interest has emerged along with major advances in the use of drugs developed for other purposes (epilepsy, schizophrenia) to treat BPD, as has occurred in association with previous therapeutic advances [4, 26, 27]. They also opine that this expanded research effort has not yielded greater clarity about the essence of BPD or its delimitation from other disorders [5]. Instead, they point out that many widely accepted assumptions about BPD are being thrown into doubt. The contrast between a relatively pure BP-I syndrome and a bipolar spectrum, and the place for mixed manic-depressive states, remain particular dilemmas.

The emphasis in their report [5] as well as that by Benazzi [13] is on *expansion* of the BPD concept and evolution of a spectrum of putatively related disorders that invade some of the territory occupied by MDD and perhaps other disorders. Another possibility is that MDD, as broadly conceived in DSM-III/IV, may be more of a problem than BPD. It, too, needs critical reconsideration, and either narrowing or subdivision to account for conditions ranging from mild ambulatory dysphorias to malignant, psychotic melancholias requiring urgent hospitalization. Distinguishing bipolar-like components marked by unstable or cyclic mood shifts, increased energy and activity, or anger is at least worth considering as a potentially useful step in such a process [13]. We agree with De Fruyt and Demyttenaere [5] that a critical test of the bipolar spectrum concept will be adequate head-to-head comparisons of the therapeutic effects of antidepressants and mood stabilizers.

De Fruyt and Demyttenaere [5] suggest, and we [28] again agree, that the term 'mood stabilizer' is serviceable if more or less equated with long-term prophylactic efficacy rather than specific effects on mania or bipolar depression. As anticipated earlier by interactions of the colloquialism 'antidepressant' with emergence of the broad modern concept of MDD [4], they also note [5] that the pharmaceutical industry and clinicians have taken advantage of the vagueness of 'mood stabilizer' as a clinical colloquialism to promote and use agents with limited or unproved effects on various components and consequences of BPD – particularly on the debilitating and potentially lethal depressive component, and on long-term mood stabilization [8]. Currently, less demanding and less expensive putative surrogate measures are widely accepted in lieu of direct and compelling evidence of long-term prophylaxis for BPD and of favorable modification of long-term morbidity or improved health. Such surro-

gate measures include induction of relapses by removing treatments relatively soon after clinical recovery from an acute episode of mania or bipolar depression, or delaying time to a single new major relapse [8, 28–30].

Regarding antidepressants, De Fruyt and Demyttenaere [5] argue that their off-label, empirical, and plausible, but wishful, use for treating bipolar depression is a major example of a practice that lacks a secure evidence base. In turn, they rightly point out, lack of empirical data invites 'expert opinion' as well as 'pharmaceutical propaganda and disease mongering' [5]. They note that reviews may differ little in the evidence considered, but derive different interpretations from that evidence – 'the story or opinion ... being more important than the facts' [5]. Yet the extremely widespread use of antidepressants to treat patients with known BPD (let alone those with unrecognized BPD) occurs without regulatory recognition or specific approval and without pharmaceutical marketing, as is implied by 'disease mongering'. Moreover, the published reviews cited as examples by De Fruyt and Demyttenaere [5] do differ in the evidence they consider and in the weight given to studies of differing scientific merit, and not only in story-telling [31, 32].

We suggest that the evident overuse of antidepressants in BPD reflects an assumption by clinicians and patients that all depressive conditions should respond similarly to drugs labeled as 'antidepressants', as well as representing a humane response to the clinically compelling but currently-ineffectively treated depressive and mixed phases of BPD [33, 34]. We suspect that, if BPD patients were not systematically excluded from trials of antidepressants, use of antidepressants to treat bipolar depression might be much less than it is. On the other hand, treating them without appropriate use of mood-stabilizing agents could well prove dangerous to both patients and investigators.

Finally, perhaps we should not be too concerned if, as De Fruyt and Demyttenaere [5] suggest, 'clinicians are left with too many choices', or if growing research leads to more questions than answers. A crucial role of scientific inquiry is to challenge questionable assumptions or false, misleading, or inadequate old ideas, whether or not identifying superior new ideas; new concepts are unlikely to emerge without their predecessors being challenged. In the process of disproving old beliefs, confusion often occurs and uncertainty may well increase. Nevertheless, scientific uncertainty is preferable to unscientific certainty [35].

In sum, Dr. Benazzi's broad review of published evidence suggests that a century of controversy may be approaching scientifically justifiable conclusions. Most cases of mood disorders probably are distributed on a spectrum, yet archetypical cases also are common and perhaps best conceptualized categorically. We agree that dimensionality may make sense for the nosology of mood disorders, but its introduction requires conceptual and empirical rigor, lest BPD suffer a similar fate as the broad, and both scientifically and clinically unworkable, concepts of old 'schizophrenia' and modern 'MDD'. Drs. De Fruyt and Demyttenaere [5] rightly relate a recent upswing in research to greater uncertainty about many aspects of BPD. Appropriate resolution requires more research, with special attention to diagnostic groupings and to definitions of mood-stabilization. We also suggest that increasing uncertainty is a good sign, and that knowing that one does *not* know is an essential first step toward progress in seeking more valid knowledge about the nature of BPD and its safer and more effective treatment.

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