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Bipolar Depression: An Orphan Syndrome?

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Depressive phases in bipolar, manic-depressive disorder are emerging as a most important challenge for contemporary psychiatry, but a syndrome that, until recently, has lacked adequate consideration in clinical and therapeutic research (1). Since the pervasive acceptance of the heterogeneous concept major depressive disorder in the standard international nomenclature since 1980 (2), there has been insufficient emphasis on defining specific types of major depression, their diagnosis and separate clinical assessment, and their optimal treatment. In particular, depressive components of bipolar disorders have often been considered similar to nonbipolar (unipolar) forms of major depression, including an expectation that antidepressant medicines should be used routinely for their treatment (3,4).

Instead, bipolar depression is a distinct syndrome. Depression as well as dysthymic, dysphoric, and mixed (manic-depressive) states (notably, dysphoric mania or hypomania and agitated depression) are major and probably dominant features of bipolar disorder (1). Depression represents the highest proportion of time ill in type I (with mania) as well as type II (with hypomania and prominent depression) bipolar disorders (5,6). Depression in bipolar disorder has unique and strong familial risk of bipolar disorder itself, as well as of depression and psychosis (7). Bipolar disorder also has a substantially younger average onset-age (type I < type II) than unipolar depression, and family history of mood disorder is more likely with lower age at onset of bipolar disorder (8). A classic form of bipolar depression is a withdrawn-anergic state (similar to so-called "atypical" depression in unipolar depression), but states of dysphoria or agitation, and mixing of depressive with anxiety or hypomanic features also occur, and postpartum depression or psychosis is commonly followed by a diagnosis of bipolar disorder (7,9). In addition to the challenge of differentiating unipolar major depression from bipolar depression, a difficult differential diagnosis is between bipolar depressive and mixed states. Mixed-states were first systematically described in 1895 by Wilhelm Weygandt, then a junior colleague of Emil Kraepelin's at the University of Heidelberg (10). Many cases of bipolar mixed states are misdiagnosed as "depression" and treated with

Table 1: Characteristics of bipolar depression

Depression is most prevalent initial episode
Initial polarity is highly predictive of future morbidity
Often misdiagnosed as unipolar major depression, especially early
Prevalent family history of mood or bipolar disorders
Onset is earlier than in unipolar depression (earlier, more familial)
Often associated with postpartum depression or psychosis
History of hypomania often missed (needs independent verification)
Multiple recurrences are usual; rapid-cycling has an excess of depression
Depression is the most prevalent long-term morbidity in bipolar disorder
Anergic-retarded depression: classic, but often agitated, anxious or psychotic
Mixed-states often misdiagnosed as depressive
High co-morbidity (substance abuse, anxiety disorders) and disability
Very high suicide risks, especially in or following mixed-states
High antidepressant demand by patients and for clinicians
Spontaneous mood switching is common (not much more with antidepressants)
Mood-stabilizers, antipsychotics underused, antidepressants overused
Costs are much higher than in unipolar major depression

antidepressants, which can make them dangerously worse (11-13); others are considered forms of mania and even included in trials of antimanic treatments (14). Characteristics that are much more prevalent in bipolar than unipolar depression include: pathological mood-elevation (switching) or lability with antidepressant treatment, familial bipolar disorder, "borderline" personality traits, substance abuse, mixed-states, psychosis, anergic (atypical) symptoms, multiple previous depressive episodes, and onset before age 30 (15) (Table 1).

Approximately one-quarter of depressed patients eventually meet diagnostic criteria for bipolar disorder. Depression is the predominant initial presentation (84% of cases) and long-term morbidity in type II bipolar disorder; depression also is a prevalent initial presentation in type I bipolar disorder (49%), and in the majority (63%) of cases of bipolar disorder overall (16,17). These tendencies make it important clinically, though challenging, to differentiate bipolar from unipolar depression as early as possible with any new patient, in order to formulate a rational prognosis and treatment plan. Nevertheless, currently the delay from an initial depressive episode to correct diagnosis and appropriate treatment of bipolar disorder averages 8-10 years internationally, and is even longer when bipolar disorder begins in adolescence (11-12 year delay) or at preadolescent ages (12-16 years) (8,18). Such delays commonly involve overuse of antidepressants, based on incorrect diagnosis of unipolar depression (19,20). More dangerously, delay of correct diagnosis can be fatal in that fully half of long-term suicidal acts among persons eventually diagnosed with bipolar disorder occur within the first 2-4 years of the illness (21). Such delay is particularly ominous given the very high rate of suicide among both type I and type II bipolar disorder patients (ca. 0.36%/year, with a male:female ratio of approximately 1.6 [0.44/0.28]), with standardized mortality ratios (SMRs) estimated at over 20 times above rates in the general population (0.36/0.015=24) (21-25). In addition, ratios of attempts/suicides (A/S) are much lower in bipolar disorder than in the general population, reflecting greater lethality of methods and intent (25,26). Mortality also is increased in bipolar disorder owing to moderately elevated SMRs (2-3-fold) for co-occurring common general medical disorders in older bipolar disorder patients (27,28). However, owing to the numbers of persons involved, counts of deaths per year due to suicide or other violence and that associated with medical illnesses are about the same (27). In turn, much of the excess mortality in bipolar disorder is strongly associated with its depressive components, with highest risks associated with current or past mixed-states (23-26).

Another characteristic of depressive first-lifetime episodes of bipolar disorders is that they have powerful prognostic value. Initial depression (as well as anxiety and mixed-states), strongly predict a later excess of depressive morbidity, and predicts depression as the predominant polarity of recurrences, long-term (5,16,17,29). There is also an association of initial depression in bipolar disorder with later suicidal behavior (25). Initial depression in bipolar disorder also predicts a future illness-course marked by predominant cycles of depression followed by hypomania or mania and then a euthymic interval ("DMI" course-pattern vs. its opposite, "MDI") (30). The DMI course-pattern is associated with inferior treatment responses to mood-stabilizers, relatively poor long-term prognosis, and greater risk of mania when given a mood-elevating agent (antidepressant, stimulant, corticosteroid) (30).

It is remarkable to acknowledge that, even with the growing number of apparently effective mood-altering and mood-stabilizing treatments, clinically treated patients diagnosed with type I or type II bipolar disorder or unipolar major depressive disorder all experience morbidity in 40%-50% of weeks of long-term follow-up (5,6). More remarkably, three-quarters of this unresolved morbidity is depressive (5,6). Evidently, treatments for manic and psychotic aspects of bipolar disorder are far more effective than treatments for depressive components of the disorder (3). It is not surprising that antidepressants are, by far, the most prominent class of psychotropic drugs given to treat bipolar disorder patients, particularly those diagnosed with type II, in which hypomania is far less a problem than depression, and less dangerous than mania of bipolar I disorder (31-33). Indeed, the suffering that

accompanies bipolar depression often drives both patients and clinicians to attempt to treat it with antidepressants (3).

Experienced clinicians are often uncomfortable to treat bipolar depression with an antidepressant or other mood-elevating agents, especially in type I bipolar disorder, in which mania, psychosis, and dangerous behavior may result (34,35). Indeed, such clinical concerns and associated risk-aversion, as well as a tendency to conflate all types of "major depressive disorders", probably contribute to the paucity of experimental investigation of new treatments for bipolar depression. Our systematic review of risks of mood-switching during treatment with an antidepressant suggest that this concern is probably exaggerated, though understandable from the perspective of risk-avoidance (12). That is, the added risk of hypomania or mania with an antidepressant is only slightly (ca. 2%) above that without such treatment (15%-16% vs. 13%-14%), owing to a high rate of natural shifting of mood in bipolar disorder patients, especially with type I disorder (12). Curiously, as a statistical artifact, the relative (percentage) increase of new hypomania or mania in "unipolar" (i.e., misdiagnosed) major depressive disorder is much higher with an antidepressant added (ca. 6% vs. 1%-2%), owing to a low base rate of undiagnosed bipolar disorder among depressed patients (12). Even though the objective evidence of switch-risk in bipolar I syndrome during treatment with an antidepressant is not much above spontaneous rates of mood-switching, when the treatment and the outcome are associated, there is a potential for medical liability. Interestingly, however, many cases of "depression" (or anxiety disorder) are rediagnosed as bipolar disorder when hypomania or mania emerges during treatment. This phenomenon appears to be more probable with younger illness-onset, if only because bipolarity in older patients is likely to have been recognized earlier (13,36). An important, but still inadequately tested question is the extent to which drugs with proved (lithium) or putative (carbamazepine, lamotrigine, valproate) mood-stabilizing or antimanic (antipsychotics) actions can prevent or minimize the severity of pathological mood-elevation associated with antidepressant treatment in bipolar disorder. Clinical practice assumes this to be the case, but randomized, controlled trials to test this plausible expectation are lacking. Moreover, clinical data on the point are misleading since mood-switching rates actually are slightly higher with a mood-stabilizer added—evidently, a classic case of "confounding by indication": those who need mood-stabilizers get them (12). Since there are both clinical and liability risks in mania associated with (not necessarily "caused by") antidepressant treatment, factors associated with such risk should be considered in clinical assessment of new depressed patients at risk of misdiagnosis. They include: family history of bipolar disorder, onset of depression before age 25, perhaps ≥4 depressive episodes in the past 10 years, certain temperament traits (hyperthymic, cyclothymic, irritable), prior mood-switching with mood-elevating agents, and current agitation or possible "mixed" features even if the hypomanic component is subtle (15).

The value of antidepressant treatment for bipolar depression, despite its highly prevalent empirical use, remains controversial (4,19,20,34,35). Some controlled trials found no benefit when an antidepressant was added to a standard mood-stabilizing regimen, or given as a monotherapy in acute bipolar depression (37,38). On the other hand, in more than a dozen, randomized, controlled trials antidepressants not only were superior to a placebo (33), but showed effect-sizes at least as large as those found in trials for unipolar major depressive episodes (32). That is, response rates with antidepressants were superior to placebo by 52% in bipolar depression and somewhat less, 39%, in unipolar depression (32,33). In addition, 10 studies compared antidepressant vs. placebo responses in depressed patients diagnosed with bipolar depression or a unipolar major depressive episode in the same controlled trials, finding only 5% better outcomes in unipolar over bipolar depression (31). We also analyzed outcomes of large samples of depressed patients treated clinically with an antidepressant (with or without mood-stabilizers) in a European mood-disorder center, with the caveat that cases with current agitation were excluded (15). Measures of symptomatic improvement, clinical response (≥50% improvement), attaining clinical

remission, and weeks to remission were similar among bipolar-I, bipolar-II, and unipolar major depressive disorder patients, with slightly superior outcomes in the bipolar cases. In contrast, switching into hypomania or mania occurred in 8% (type I) to 17% (type II) in bipolar disorder patients and in ≤1% of nonbipolar cases (15). A possibly critical aspect of this study was that depressed patients with any type of mood disorder who showed clinically apparent agitation or suggestions of hypomanic behaviors were excluded from treatment with an antidepressant (15).

Another unresolved question is whether long-term addition of an antidepressant to mood-stabilizing regimens in bipolar disorder patients can reduce risks of depressive recurrences and not increase risk of mania. This and other long-term treatments aimed at preventing recurrences of bipolar depression remain poorly evaluated scientifically. A review of findings from 12 long-term trials in which an antidepressant was included or not found a moderate, statistically significant reduction in risk of new depression, by 27%; however, risk of new episodes of hypomania or mania increased highly significantly by 72%, and the respective estimated numbers-need-to-treat (NNT=11) versus to-harm (NNH=7) yielded an unfavorable apparent cost/benefit ratio (7/11) (39). Despite the evidence reviewed, the place of antidepressants in treating bipolar depression remains unsettled (4). Many expert clinicians consider use of antidepressants for bipolar-II depression with relatively low clinical and liability risks, and even consider them in depressions arising in bipolar-I disorder patients, provided that alternative treatments have failed, the depression is severe or frequently recurring, and a mood-stabilizer that has been effective for the patient is in place, and there is no current agitation or even mild hypomanic symptoms (4,15).

A final issue pertains concerns arising from post-hoc meta-analyses of registration-trials of new antidepressants by the US Food and Drug Administration (FDA), as well as large clinical cohort studies involving serotonin reuptake inhibitors. Both sets of findings suggested higher rates of suicidal ideation and perhaps attempts (no deaths) versus placebo treatment among juvenile and young adult depressed patients (some whom are likely later to be diagnosed with bipolar disorder), as well as lower risks in older adults, and no effect overall without age-stratification (40-42). To date, it remains unproved whether antidepressant treatment increases or decreases rates of suicide in depressed patients, and it is unknown whether effects like those found by FDA in juvenile and young adult patients might be of particular concern in rarely studied bipolar depression. To date, the only treatment with substantial evidence of reducing risks of suicide and potentially life-threatening attempts in bipolar disorder patients is long-term treatment with lithium (43,44). It is less clear whether other proposed mood-stabilizing treatments, notably anticonvulsants, have such effects (45,46).

Given uncertainties about the value and risks of antidepressant treatment of bipolar depression, there is growing interest in alternatives. Meta-analysis was applied to the findings from the remarkably few randomized, controlled trials (approximately 20 for all non-antidepressants) that have been reported for this condition, and virtually only for acute bipolar depression (47). Ranked by apparent efficacy, the most promising treatments were: olanzapine+fluoxetine ≥ valproate ≥ quetiapine ≥ lurasidone ≥ olanzapine alone, whereas carbamazepine, lithium, lamotrigine, ziprasidone, and aripiprazole had lesser outcomes and were not statistically effective. However, many agents were tested in only 1 or 2 trials, making conclusions highly tentative. Currently, valproate among anticonvulsants, and olanzapine+fluoxetine, lurasidone, and quetiapine appear to be particularly promising, but all of these treatments and lithium require further study, especially for long-term treatment with prophylactic intent against bipolar depression.

In conclusion, bipolar depression is a complex, difficult, often disabling, sometimes fatal disorder, the treatment of which remains remarkably inadequately studied, suggesting its status as an "orphan syndrome." This status probably reflects failure to distinguish specific types of "major depression" and their optimal treatments, possibly related to efforts to maintain broad markets for antidepressants, as well as efforts to avoid clinical and liability risks of mania arising during treatment with an antidepressant. Encouraging signs

include recent introduction of several treatments specifically aimed at bipolar depression (notably, in historical order: lamotrigine, olanzapine+fluoxetine, quetiapine, and lurasidone) (3). Successful clinical management of bipolar depression requires clinical expertise, experience, and flexibility, with greater reliance on mood-stabilizing and antipsychotic treatments than antidepressants, and with constant vigilance for the high risks of suicide that accompany bipolar depression.

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