Morbidity in Depressive Disorders

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Levels of residual morbidity in mood disorder patients followed up long-term under community conditions of treatment are remarkably high [1]. Both unipolar major depressive disorder (MDD) and bipolar disorder (BD) patients were ill 40–50% of follow-up time; in BD patients, three-quarters of that residual morbidity was depressive [1]. These striking findings encourage further consideration of aspects of mood disorders that might contribute to such outcomes in an era of supposedly effective modern treatments. Selected topics considered here include basic conceptualizations and diagnoses of mood disorders, risk factors associated with their natural history, and characteristics of available treatments, with an emphasis on BD.

Conceptualizations about Mood Disorders

Kraepelin's introduction of the broad category of manic-depressive illness in the mid 1890s was followed by efforts to differentiate and define limits of potentially separable syndromes included in the original concept [2, 3]. These efforts led to differentiation of BD and unipolar

MDD as relatively young, 20th century concepts [2–4]. Separation by polarity was encouraged in part by the discovery of selectively effective antidepressant and anti-manic treatments a half century ago [5]. However, several recent trends may contribute to limiting optimization of this differentiation. First, modern therapeutics complicated the matter by assuming that 'major depression' in both syndrome types is generally similar and presumably responsive to 'antidepressants' – assumptions that are increasingly challenged [5–7]. Second, the introduction of the concept of MDD with DSM-III in 1980 involved lumping a broad range of depressive conditions into a single group after excluding mania or hypomania. Distinctions between depressive phases of BD and MDD were not addressed initially, but their symptomatic, longitudinal, epidemiological, and therapeutic differences are increasingly recognized [2, 8–12]. Third, blurring the distinction between unipolar and bipolar depression is encouraged by renewed consideration of elements of hypomania in many depressive illnesses [13–15], as noted a century ago [2, 3]. We propose that the breadth and heterogeneity of the MDD concept and the insufficient distinction between depressions of bipolar and unipolar

Table 1. Long-term morbidity in clinically treated mood disorder subjects

Diagnosis	Studies, n	Subjects, n	Exposure, years	Time ill, % (95% CI)				
				depression	mania	other	total	depressed
<i>MDD</i>								
Major depression	14	2,479	12.8 (7.93–17.7)	46.0 (34.0–58.0)	–	–	46.0 (34.0–58.0)	100
<i>BD</i>								
Bipolar I	12	2,760	7.78 (3.53–12.0)	30.6 (23.9–37.3)	10.3 (7.68–12.8)	5.73 (1.94–9.52)	43.7 (37.5–49.9)	69.6 (60.4–78.9)
Bipolar II	8	822	8.28 (2.18–14.4)	35.9 (23.1–48.7)	5.54 (1.57–9.50)	2.76 (2.14–3.38)	43.2 (35.2–51.1)	81.2 (71.3–91.0)
Bipolar NOS	3	354	2.54 (0.01–5.07)	50.1 (0.0–112)	8.80 (–)	3.00 (–)	54.4 (6.70–100)	89.3 (0.0–288)
All bipolar	15	3,936	7.27 (4.43–10.1)	35.4 (28.5–42.3)	8.51 (6.31–10.6)	4.44 (1.92–6.96)	44.9 (40.1–49.7)	76.4 (69.4–83.3)

Depression: includes dysthymia. Mania: includes hypomania. Other: largely anxiety syndromes. NOS = Not otherwise specified. Data adapted from Forte et al. [1] (2015), with permission.

mood disorders have impeded their optimal clinical management and greatly constrained progress in biomedical research on depressive disorders.

Based on the proportion of time ill, depression is the dominant morbidity of type I BD, the major clinical feature of type II BD, and the essence of MDD. Mania and hypomania contribute less to time ill in BD as depressive episodes generally are longer-lasting, and modern treatments for mania are more effective than for bipolar depression [2, 5]. Of patients presenting initially with depression, perhaps a quarter are later considered to have BD – often indicated when (hypo)mania first appears during treatment with an antidepressant, commonly in juvenile or early adult years [16, 17]. Over 60% of first episodes in BD are depressive, contributing to early difficulty in differentiating it from unipolar MDD [2, 16, 17]. Initial depressive as well as severe (DSM-IV) mixed manic-depressive states in BD are followed by an excess of later depression [18]. Depression in unipolar MDD and both types I and II BD not only is clinically significant itself but also contributes importantly to disability, substance abuse, and mortality due to both suicide and co-occurring medical illnesses [2, 19–21]. Again, depressive components account for three-quarters of the 40–50% long-term time ill in BD patients treated by contemporary community standards, and virtually all of similar unresolved morbidity in unipolar MDD [1] (table 1).

A fundamental clinical challenge in dealing with depressive illnesses is the timely differentiation of depression associated with BD, so as to guide appropriate treatment. Typically, latency from the onset of initial depression to appropriate treatment of BD is 5–10 years, or even longer following juvenile onset [2, 16, 17]. Diagnosis is

particularly difficult in type II BD since hypomania is often overlooked or viewed by patients as nonpathological or even desirable. Independent, verifying information from a family member or close friend can help greatly, as might specific screening for hypomania [22]. Differentiation of BD from MDD is supported by evidence of BD, such as (a) multiple family members with mood disorder, suspected mania, or ‘nervous breakdown’, (b) young onset of depression with multiple, especially brief, recurrences, (c) postpartum mood disturbance or psychosis, (d) classically anergic-retarded (‘atypical’) depression, but sometimes with prominent anxiety, agitation, anger, or psychosis, (e) co-occurring substance abuse or anxiety syndromes or (f) excessive or rapid mood elevation after exposure to an antidepressant, stimulant, or corticosteroid [2, 16, 17].

Antidepressant Drugs

Since the 1960s, treatment of depression in both MDD and BD has relied heavily on the use of antidepressants. Such treatment in MDD is reasonably effective for acute depressive episodes, at least of moderate severity [3, 4, 23]. Evidence is also emerging for its long-term effectiveness in preventing relapses and recurrences, with less secure findings regarding psychotherapies [24]. Nevertheless, responses to antidepressants vary greatly among MDD patients [5, 25, 26], probably reflecting clinical and pharmacokinetic heterogeneity, and responses to antidepressants in BD are poorly studied but widely considered inferior [5–7]. In 142 randomized, controlled trials reported since 1980, an average ($\pm$ SD) of $54 \pm 11\%$ of depressed MDD subjects initially improved by at least 50%

with antidepressant treatment over 7.2 weeks compared to $37 \pm 11\%$ of those randomized to placebo (1.46-fold difference) [23]. Improvement of symptoms was even more modest (49 ± 45 vs. $36 \pm 10\%$; 1.36-fold difference) [23]. Rates of attaining clinical remission within 2–3 months in such trials were typically 10–20% lower than rates of response and achieved by fewer than one-third of MDD patients in some studies [5, 27]. In 37 long-term controlled trials in MDD, the pooled recurrence rates with antidepressant versus placebo were 25 ± 13 versus $56 \pm 22\%$, indicating more than 2-fold superiority of antidepressants but also that a quarter of patients diagnosed with unipolar MDD were not protected from major recurrences over 2 years of follow-up [24]. An unknown proportion may also have experienced additional subsyndromal morbidity. Long-term antidepressant treatment in MDD is associated with rising rates of recurrence of depression over several years, although drug-placebo differences appear to be quite stable when treatment is maintained [28].

Improved outcomes in the treatment of depression might evolve by clarifying the relative efficacy of particular treatments as well as by closer matching of specific treatments to types of patients (e.g. mild vs. severe, anxious or agitated, psychotic, bipolar) [5]. However, the assessment of candidate antidepressants has traditionally been broad, and efforts to rank specific agents by efficacy or tolerability have proved challenging [5, 23]. Meta-analytic summaries across separate trials of specific antidepressants yield pooled outcomes that overlap statistically, as might be expected from heterogeneous sampling within and among trials [5, 23]. Head-to-head comparisons of specific treatments are desirable but rare, in part for lack of commercial interest in direct comparisons with competitors' products. Emerging efforts involve *indirect* comparisons (comparing separate trials of treatment A vs. B and C vs. B to infer possible differences between A and C) by network meta-analysis [29, 30]. These increasingly popular techniques require caution in that the conditions of trials compared need to be more closely matched than is usually feasible [31]. Potentially useful matching of specific treatments with types of depressed patients might also be supported by analyses of massive but largely dormant databases arising from commercial and academic treatment trials to compare responses and clinical features. Although commercial interest in broad indications and markets for antidepressants is understandable, better differentiation of specific treatments is needed to guide rational clinical selection among their growing numbers and may also be useful for marketing.

Bipolar Depression

The short-term use of antidepressants to treat episodes of acute depression in BP remains highly controversial, and relevant research evidence is both surprisingly limited and inconsistent, reflecting the paucity of therapeutic research for this important syndrome over the past half century [5, 6]. Conclusions arising from systematic, meta-analytic reviews of placebo-controlled antidepressant trials in acute bipolar depression vary with the evidence considered [6]. We reviewed 12 such controlled trials and, unexpectedly, found significant superiority of antidepressants of various types over placebo, with more than a 50% net difference [32, 33]. We also found 10 controlled trials in which antidepressants were tested in both BD and unipolar depressed subjects under the same conditions, with <5% better pooled outcomes among unipolar cases [34]. In uncontrolled clinical observations of over 1,000 cases, selected only to exclude patients with agitation or elements of current hypomania, responses and recovery among depressed BD patients were not less than among unipolar cases and possibly slightly superior [35]. Nevertheless, several randomized, controlled trials have found no advantage for treating bipolar depression by adding an antidepressant over a placebo to ongoing mood-stabilizing treatments [6]. Evidence for long-term, depression-preventing effects of antidepressants in BD is even scarcer, usually involves combinations with mood stabilizers, and is generally unsupportive of the routine addition of an antidepressant to a mood-stabilizing treatment regimen [5, 36, 37].

In general, the extremely limited study of antidepressant treatment in BD contrasts strikingly with the abundant evidence for the short- and long-term effects of antidepressants in unipolar MDD [4, 5, 23, 24]. The basis of this disparity is uncertain, but it has encouraged reserving antidepressant treatment in BD for certain conditions. These include (a) type II BD, (b) more years ill, (c) depressive first episodes, (d) melancholic features, (e) multiple recurrences, (f) more depressions/year, (g) lack of family history of affective illness and (h) lack of hypomanic features or agitation [35, 38, 39].

The use of antidepressants in BD has also led to great, but possibly exaggerated, fear of inducing manic or psychotic states with the risk of harmful or dangerous behavior and associated legal liability, particularly in type I BD. There is surely an effect of inducing (hypo)mania soon after introducing an antidepressant to treat bipolar depression, but the risk increase is surprisingly small, owing to high rates of spontaneous 'mood switching' not associ-

Table 2. Potential sources of limited effectiveness of treatments for MDD and BD

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- Diagnosis: bipolar depression or mixed-state vs. unipolar depression
 - Comorbid medical illnesses
 - Co-occurring life stressors
 - Treatment-resistant form of illness: DMI course, rapid cycling, prominent mixed states in BD, psychotic depression
 - Untreated co-occurring psychiatric conditions: anxiety syndromes, substance abuse, personality disorder
 - Limited effectiveness of treatment: antidepressants, mood stabilizers, antipsychotics, psychotherapies
 - Overuse of antidepressants, underuse of mood-stabilizing agents, overuse of untested drug combinations
 - Adverse effects of treatment: (hypo)mania, emotional instability, rapid cycling with antidepressants, excessive sedation, other adverse effects of mood stabilizers
 - Inadequate adherence to recommended treatment (side effects, regimen complexity, absence of acute symptoms, patient skepticism about recurrence risks, cost)
 - Relapse/recurrence following discontinuation of antidepressants, mood stabilizers, or antipsychotics, especially rapidly and in pregnancy
 - Potential adverse effects of repeatedly starting, stopping, and changing treatments (cause and effect are not always clear)
 - Insufficient or infrequent clinical supervision, monitoring, clinical or family support, and psychotherapy
 - Poverty, insufficient access to health care
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DMI: pattern in which depression is followed by (hypo)mania and then a stable interval.

ated with treatment. The increased risk may be as small as 5% (from 10–12% spontaneous mood elevation to 12–15% with antidepressants) [40]. Paradoxically, the differential risk is greater among persons diagnosed with ‘unipolar MDD’ (perhaps doubling from a base rate of <5%), owing mainly to a previous nondiagnosis of BD [40] or prior to a first (hypo)manic episode. The expectation that combining a mood stabilizer or antipsychotic with an antidepressant will prevent mood switching in BD is both plausible and widely accepted but lacks adequate proof [40].

Risk Factors for Poor Outcome

Given that unsatisfactory responses to treatments for depression in both BD and MDD are a major problem, it is of interest to identify factors, especially modifiable ones, that may contribute to poor responses (table 2). In BD, the long-term predominance of depression and recurring mixed manic-depressive states are associated with inferior

treatment responses and outcomes [41]. It remains to be seen how recently broadened criteria for mixed features in depression or (hypo)mania will impact outcomes and treatment responses [42–45]. Generally, mixed features, even a few hypomanic features in major depression, have been associated with relatively poor response to antidepressants and unfavorable outcomes [42]. This circumstance seems to encourage trials of mood-stabilizing or antipsychotic agents [46]. In addition, BD patients who usually show a long-term pattern in which depression is followed by (hypo)mania and then a stable interval (‘DMI’ pattern) tend toward a worse overall prognosis and inferior treatment response compared to the opposite (‘MDI’) pattern [47]. Rapid cycling is also strongly associated with poorer prognosis and lesser response to mood-stabilizing treatments, usually involves an excess of depressive episodes, and is markedly worsened by sustained antidepressant treatment [48–50]. Counterintuitively, however, a delay in starting treatment or the number of previous recurrences seem to have little effect on long-term responses to treatment in either MDD or BD, although prolonged treatment delay can severely compromise clinical status [51, 52]. In addition, the long-term loss of effectiveness of antidepressant treatment (tolerance) appears to be uncommon [53]. Additional factors are associated with unsatisfactory treatment of depression in both MDD and BD (table 2). These include probable limitations of the effectiveness of available treatments but also less than vigorous treatment and inconsistent treatment adherence, especially long-term when acute symptoms are no longer present [5, 54–57]. The use of even moderate doses of antidepressants for more than a few weeks is not easily achieved, and such inadequate treatment surely contributes to apparent ‘treatment resistance’ and on inclination to try new or added treatments [58–61].

Depression, perhaps particularly in BD, typically involves a high demand for antidepressant treatment by patients and their families, who are often fearful of depressive relapses, and clinicians are under great pressure to provide it. There is an associated tendency to underuse mood-stabilizing agents to treat BD patients [5, 58]. In large US insurance database surveys, antidepressants were the most prevalent (three-quarters of cases) initial monotherapy for patients diagnosed with BD, regardless of their most recent clinical state. In addition, antidepressants were continued longer than any other treatment except lithium, and all monotherapies usually ended by adding other agents [5, 58]. Typically limited antidepressant responses in BD as well as in MDD often lead to polytherapy, with multiple medicines given in combinations

that are usually inadequately evaluated for additional efficacy and safety, with higher burdens of adverse effects and cost [5, 6, 57, 60]. In addition to the overuse of antidepressants and complex treatment regimens encouraged by incomplete clinical responses in mood disorders (often after *inadequate* trials of monotherapies), erratic treatment adherence involves repeated discontinuation and restarting [56, 57].

Rapid or abrupt discontinuation of antidepressants, and indeed of most psychotropic drugs, is followed by a rapid return of the illness being treated [62–65] as well as physiological withdrawal reactions, particularly with sedatives and short-acting SRIs or SNRIs [66]. Complex and especially changing treatments are associated with, and might contribute to, an unstable long-term course of BD (table 2). In addition, relapse of mood and other disorders associated with drug discontinuation can contribute to misleading interpretations of experimental therapeutic studies, especially in trials involving relatively rapid discontinuation of initially effective treatments in subjects ('enrichment' samples) recovering from acute depression, with inflated relapse rates associated with discontinuation to placebo [24, 67]. The potentially adverse impact of both polytherapy and erratic starting and stopping on the clinical status in mood disorders requires study, despite great difficulties in separating causes and effects (table 2).

Emerging Treatments

Progress to more effective biomedical and psychosocial treatments for MDD (aimed at reducing the substantial remaining morbidity) has been slow but includes some promising developments, as reviewed elsewhere [68, 69]. Alternatives to antidepressants also are emerging for depression in BD [70, 71]. Prominent among these are agents with demonstrated or putative antimanic or mood-stabilizing potential, including several originally developed as anticonvulsants or antipsychotics. Among anticonvulsants (carbamazepine, divalproex, and lamotrigine), evidence for benefits in acute bipolar depression is weak [72], although lamotrigine has some protective effect against depressive recurrences [5, 73]. Benefits in bipolar depression have also emerged with some atypical antipsychotics originally developed to treat schizophrenia and mania, including olanzapine combined with fluoxetine, quetiapine, lurasidone, and perhaps cariprazine [5, 74–77]. Such treatments offer the additional benefit of lacking the risk of inducing (hypo)mania (some can induce akathisia or agitation), with little effect or possible

benefits for suicidal behaviors [78, 79]. Lithium remains an essential option for long-term prophylaxis in BD and may be more effective than valproate [7, 80] and better tolerated than quetiapine [81]. Lithium is also the only treatment, except clozapine in schizophrenia, with substantial evidence of antisuicidal effects [21, 82]. Despite its demonstrated value, lithium remains underutilized, probably due to the inconvenience of the need for medical monitoring of safe serum lithium concentrations and the fear of potential adverse thyroid and renal effects, but also due to aggressive marketing of more commercially attractive alternatives. Remarkably, the testing of lithium for short-term effects in acute bipolar depression is almost nonexistent, and the rare evidence available does not support its efficacy for that indication [72].

Additional options have included various combinations of lithium, mood-stabilizing anticonvulsants, atypical antipsychotics, and antidepressants [70, 72]. Some combinations have at least preliminary evidence of greater efficacy than with the individual treatments [80, 83–85]. ECT may be useful in both manic and depressive phases of BD [86]. A growing number of experimental treatments with possible benefits in bipolar depression have also been considered [70, 87–90]. Examples include (a) ketamine, (b) dopamine agonists including pramipexole, especially in type II BD, (c) moderately intense light treatment, (d) brief periods of sleep deprivation, (e) triiodothyronine, (f) memantine, (g) N-acetylcysteine, (h) L-methylfolate, (i) minocycline, (j) scopolamine, (k) transcranial direct-current brain stimulation, (l) vagal nerve stimulation, and (m) repetitive transcranial magnetic stimulation.

Another dimension of rational clinical management of depressed patients is to attend to co-occurring conditions that may contribute to depression, including social and economic stressors, general health, co-occurring anxiety, and misuse of alcohol or drugs. In addition, supportive care and cognitive-behavioral psychotherapy are likely to be useful clinically, and have research support for both unipolar MDD and BD [24, 71–95].

Conclusions

It is important to emphasize that the long-term effectiveness of available treatments for both unipolar and bipolar types of major depression is more limited than is often appreciated. Both BD and MDD patients treated by current community standards appear to be unwell 40–50% of the time in long-term follow-up, and the great

majority of that unresolved morbidity is depressive [1]. Indeed, the lack of effective methods for the treatment and prevention of bipolar depression, shortcomings of antidepressant treatment in MDD, and maintaining treatment adherence are leading therapeutic challenges for modern psychiatry. For decades, there seems to have been a tacit, but highly questionable, assumption that major depressive syndromes are more or less similar clinically and therapeutically, leading to a stunning paucity of controlled studies of treatments for acute depression in BD and even fewer for the prevention of recurrences. Promising recent developments include leads to innovative treatments for MDD and efforts to develop and test treatments for bipolar depression.

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Acknowledgments

This study was supported by a grant from the Bruce J. Anderson Foundation and by the McLean Private Donors Research Fund (to R.J.B.), a grant from the Aretæus Foundation of Rome (to L.T.), the Interdisciplinary Investigation Program (PIA) of the Chilean National Commission for Science and Technology Investigation (CONICYT; Anillos ACT1414), and a research grant from the Clínica Alemana de Santiago (to J.U.).

Disclosure Statement

No author or any immediate family member has financial relationships with commercial organizations that might present an apparent conflict of interest in the material presented.

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