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REVIEW

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Bipolar depression: a major unsolved challenge

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Abstract

Depression in bipolar disorder (BD) patients presents major clinical challenges. As the predominant psychopathology even in treated BD, depression is associated not only with excess morbidity, but also mortality from co-occurring general-medical disorders and high suicide risk. In BD, risks for medical disorders including diabetes or metabolic syndrome, and cardiovascular disorders, and associated mortality rates are several-times above those for the general population or with other psychiatric disorders. The SMR for suicide with BD reaches 20-times above general-population rates, and exceeds rates with other major psychiatric disorders. In BD, suicide is strongly associated with mixed (agitated-dysphoric) and depressive phases, time depressed, and hospitalization. Lithium may reduce suicide risk in BD; clozapine and ketamine require further testing. Treatment of bipolar depression is far less well investigated than unipolar depression, particularly for long-term prophylaxis. Short-term efficacy of antidepressants for bipolar depression remains controversial and they risk clinical worsening, especially in mixed states and with rapid-cycling. Evidence of efficacy of lithium and anticonvulsants for bipolar depression is very limited; lamotrigine has long-term benefit, but valproate and carbamazepine are inadequately tested and carry high teratogenic risks. Evidence is emerging of short-term efficacy of several modern antipsychotics (including cariprazine, lurasidone, olanzapine-fluoxetine, and quetiapine) for bipolar depression, including with mixed features, though they risk adverse metabolic and neurological effects.

Keywords: Bipolar disorder, Depression, Disability, Morbidity, Mortality, Suicide, Treatment

Background: depression in bipolar disorder

Nosological uncertainties

Debate concerning Kraepelin's broadly inclusive concept of manic-depressive illness (MDI) continued to 1980 with a first formal separation of a distinct *bipolar disorder* (BD) with mania from nonbipolar major depressive disorder (MDD) in DSM-III (Trede et al. 2005; Baldessarini et al. 2015). Tension continues between lumping mood syndromes and separating various depressive and bipolar subtypes, and considering a "spectrum" of disorders ranging from more or less pure depression to archetypical BD, leading to profound therapeutic ambiguities (Cuellar et al. 2005; Goodwin and Jamison 2007; Baldessarini 2013; Yildiz et al. 2015; Tondo et al. 2018).

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Current status of bipolar depression

Adequate understanding, timely diagnosis, and effective short- and long-term treatment of depressive episodes in BD patients are critically important but remarkably insufficiently resolved (Baldessarini et al. 2010c). Clinical significance of bipolar depression is underscored by strong association with overall morbidity, other co-occurring psychiatric conditions (notably anxiety and substance-abuse disorders), disability, and excess mortality owing largely to suicide in young patients and intercurrent medical illness in older patients (Ösby et al. 2001, 2018; Tondo et al. 2014, 2016; Baldessarini et al. 2020).

Diagnosis

Clinical challenges include difficult and often long-delayed diagnostic differentiation of depression as an initial presentation of BD vs. a manifestation of nonbipolar MDD. Accurate diagnosis and appropriate treatment

typically are delayed by 6–8 years, and even longer following juvenile onset (Post et al. 2010; Bschor et al. 2012; Drancourt et al. 2013; Tondo et al. 2014). Depression is initially considered as unipolar MDD in as many as 40% of patients later diagnosed with BD (Stensland et al. 2008; Shen et al. 2018). Such uncertainty is heightened as depression is the most prevalent presenting polarity in BD, (Goodwin and Jamison 2007; Baldessarini et al. 2014; Yildiz et al. 2015). Moreover, excess future depression in BD can be anticipated by initial episodes of anxiety or mixed-states as well as of depression (Baldessarini et al. 2012, 2014, 2020).

BD patients commonly fear, seek to avoid, to report, and to seek clinical help for depression. Contrarily, they may not recognize moderate increases of mood, energy, activity, or libido as hypomanic symptoms as clinically relevant, and may even prefer such states. Diagnostic uncertainty is especially likely early in the illness-course and without corroborating information from a family member or close friend (Vöhringer and Perlis 2016).

In perhaps 12–17% of cases, BD is not recognized until there is a mood "switch" into hypomania or mania ("[hypo]mania"), either spontaneously or with exposure to a mood-elevating substance (Tondo et al. 2010; Baldessarini et al. 2013; Barbuti et al. 2017). Other indirect factors suggesting a diagnosis of BD include: (a) familial mania, psychosis, "nervous breakdown," or psychiatric hospitalization; (b) early illness-onset, commonly with depression; (c) cyclothymic temperament; (d) multiple recurrences (e.g., ≥ 4 depressive episodes within 10 years); (e) depression with prominent agitation, anger, insomnia, irritability, talkativeness, other "mixed" or hypomanic features, or psychotic symptoms; (f) clinical "worsening," especially with mixed features during an antidepressant treatment; (g) suicidal ideation and acts; and (h) substance abuse (Tondo et al. 2014; Vöhringer and Perlis 2016).

Depression in overall morbidity

Of note, overall time in depressive phases of BD, and duration of depressive episodes are much greater than in mania or hypomania ("[hypo]mania") (Kupka et al. 2007; De Dios et al. 2010). Moreover, morbidity has been surprisingly high in BD despite supposedly effective treatment. Indeed, BD patients averaged 45% of time ill during long-term follow-up, and depression accounted for 72% of time-ill, and somewhat more with BD-II (81%) than BD-I (70%) (Forte et al. 2015) (Table 1).

Table 1 Depressive morbidity in clinically treated bipolar disorder subjects. Data adapted from Forte et al. (2015), based on systematic review of studies involving adult patients treated by community standards

Measure	Bipolar I	Bipolar II	All bipolar
Studies	12	8	15
Subjects	2760	822	3582
Exposure (years)	7.78 [3.53–12.0]	8.28 [2.18–14.4]	7.89 [5.47–12.6]
%-Time depressed	30.6 [23.9–37.3]	35.9 [23.1–48.7]	31.8 [23.7–39.9]
Total %-time ill	43.7 [37.5–49.4]	43.2 [35.2–51.1]	43.6 [37.0–49.8]
%-of illness depressed	69.6 [60.4–78.9]	81.2 [71.3–91.0]	72.3 [62.9–81.7]

Data are means with 95% confidence intervals [CI]. Depression includes major episodes plus dysthymia

Morbidity and disability

Disability

Given the high proportion of time in depression among BD patients, depression is likely to be associated with dysfunction and disability, including limited academic achievement and decreased employment success. Perhaps 80% of BD patients experience some work-loss, and 30–40% experience prolonged unemployment during adult working years—much of that disability associated with depression (Zimmerman et al. 2010; Arvilommi et al. 2015).

Co-occurring psychiatric disorders

Psychiatric conditions commonly encountered in BD patients include substance-abuse and anxiety disorders, as well as various personality disorders and temperament types (Goodwin and Jamison 2007; Pavlova et al. 2015; Preti et al. 2016; Messer et al. 2017; Stokes et al. 2017; Vázquez et al. 2017b; Post et al. 2018). Such concomitant conditions may meet standard diagnostic criteria, but whether they should be considered separate, "comorbid" disorders vs. expressions of the range of psychopathology of BD remains unresolved (Yildiz et al. 2015; Vázquez et al. 2017b). Multiple diagnoses risk contributing to complexity and potential incoherence of treatment choices to compromise clinical care.

General-medical morbidity and mortality

BD patients have increased risk of many general-medical disorders, including vascular conditions, with increased morbidity, disability and diminished longevity (McIntyre et al. 2007; Correll et al. 2017; Fornaro et al. 2017). In addition, obesity, diabetes, migraine, and some infectious diseases are more prevalent among BD patients (McIntyre et al. 2007; Almeida et al. 2018). With BD, risk of myocardial infarction was 37% greater (88% among women), stroke 60%, and congestive heart failure nearly 230% greater than in age-matched general populations (Wu et al. 2015; Fornaro et al. 2017; Tsai et al. 2017). Cardiovascular diseases are particularly frequent in association with BD disorder (Table 2) (Correll et al. 2017). Mediating

Table 2 Risk of cardiovascular diseases in bipolar disorder patients vs. general population. Data adapted from Correll et al. (2017)

Outcome	Studies	Subjects	HR [95% CI]	*p*-value
Congestive heart failure	1	1397	2.27 [1.49–3.45]	< 0.0001
Cardiovascular mortality	3	179,651	1.65 [1.10–2.47]	0.02
Cerebrovascular disease	4	6,673,266	1.60 [0.99–2.57]	0.05
Any cardiovascular disease	10	7,058,912	1.57 [1.28–1.93]	< 0.0001
Coronary artery disease	4	6,808,812	1.16 [0.76–1.78]	0.49

Based on longitudinal studies with 8.4 [range: 1.8–30) years of follow-up. Hazard ratio (HR) is adjusted for six potential confounders; ranked by HR

factors include obesity, inactivity, diabetes or metabolic syndrome, and increased inflammatory factors—all with increased prevalence among BD patients (Vancampfort et al. 2013; Halaris 2017; Tsai et al. 2017), and at least in part attributable to treatments which may contribute to these risks (Baldessarini 2013; Correll et al. 2015).

With many general-medical disorders, BD patients have more adverse clinical outcomes and diminished life-expectancy, with all-cause mortality up to 15-times above general population rates, and rising (McIntyre et al. 2007; Ösby et al. 2018; Hällgren et al. 2018; Staudt-Hansen et al. 2019). Life-expectancy with BD is reduced by 12–15 years (Chesney et al. 2014). Factors associated with this decreased longevity include co-occurring substance abuse, smoking, and being overweight, unmarried, and having limited access to adequate medical care (Hjorthøj et al. 2015; Brietzke et al. 2017; Dickerson et al. 2018). The decreased longevity may be particularly associated with depression (Dickerson et al. 2018).

Bipolar depression and suicide

Suicidal risks

The reported international annual suicide rate averages 15.4/100,000 (0.015%/year), with wide regional variation (WHO 2018). The standardized mortality ratio (SMR) for suicide in BD is about 20 (Baldessarini et al. 2019a). By diagnosis, suicide risk ranks: bipolar disorders (BD-I = BD-II; especially with mixed or psychotic features) ≥ severe major depressive disorder with hospitalization > moderate depression among outpatients (Bachmann 2018; Hällgren et al. 2018; Baldessarini et al. 2019a). Risk for suicide and attempts is especially high in days following discharge from psychiatric hospitalization, in association with delay or lack of appropriate aftercare (Olfson et al. 2016; Large and Swaraj 2018; Forte et al. 2019).

In mood-disorder patients depressive-dysphoric phases are more associated with suicide than other illness states, especially if accompanied by mixed (hypomanic) features, co-occurring substance abuse, and following previous suicidal acts (Tondo et al. 1999, 2018; Baldessarini et al. 2019b). General population rates of suicide *attempts* average 0.2–0.6% per year, or approximately 36-times the suicide rate, and over 1%/year in BD (Kessler et al. 2005; Nock et al. 2008; Tondo et al. 2016; Baldessarini et al. 2019b). The ratio of suicide attempts/suicides (A/S), an *index of lethality* lower with more lethal intent or method, is only 5–10 in BD and MDD, or about five-times above lower than that for the general population (Tondo and Baldessarini 2015; Baldessarini et al. 2019b).

Among both BD-I and BD-II patients, especially with mixed or psychotic features, risk of suicidal behavior is among the highest of all psychiatric disorders despite supposedly effective treatments (Baldessarini et al. 2019b). This disparity almost certainly reflects great difficulty of treating depressive and mixed states in BD (Baldessarini et al. 2010c; Saunders and Hawton 2013; Forte et al. 2015). The remarkably prolonged delay of recognition and intervention in BD, sometimes for more than a decade, contrasts strikingly with observations that half of long-term risk of suicidal acts among BD patients occurred within the first 2–3 years of illness (Tondo and Baldessarini 2014, 2015).

Suicide and treatment with antidepressants

Suicide cannot be "treated" but only prevented (Table 3). Research on treatments aimed at suicide prevention, not surprisingly, is very limited because of clinical and ethical problems arising if an inactive or ineffective treatment, such as placebo, were compared to an experimental intervention, with death as a potential outcome. In addition, it is virtually impossible to know when a suicide has been prevented, whereas suicidal acts or surrogate measures can be counted. Rarity of suicide, even among psychiatric patients, encourages research reliance on more prevalent measures related to suicide, including suicidal ideation, threats, self-injurious acts, or emergency interventions. However, the typically distant relationship of such measures to suicide limits their value in testing for therapeutic effects on suicide itself. Relating treatments to suicidal risks is further complicated by uncertain long-term adherence to recommended treatments (Isometsä 2005; Simon and Hales 2012; Baldessarini 2013; Ahmedani et al. 2014). Treatments for BD considered for possible suicide-prevention include antidepressants, anticonvulsants and lithium, antipsychotics, ECT, and psychosocial interventions (Table 3).

Table 3 Treatments aimed at reducing suicidal risk in bipolar disorder patients

Intervention	Timing	Findings	Comments
Antidepressants	Short-term benefits are not clear; long-term effects are virtually untested	Research findings are inconclusive. Suicidal risk may increase with agitation, and in youth but may be lower in older adults	Studies lack long-term randomization with suicidal acts as an explicit outcome measure
Antipsychotics	Short-term benefits are not adequately tested. Clozapine is probably beneficial long-term in schizophrenia (with FDA approval) but untested in BD	Except for clozapine, testing remains inadequate and inconclusive	Effects of clozapine rely mainly on a single randomized trial vs. olanzapine, without reduction of mortality
Anticonvulsants	Short-term effects are not established; long-term benefits have been proposed	Valproate most studied; anticonvulsants may be less effective than lithium	Studies lack suicidal acts as an explicit outcome
Lithium	Very likely effective long-term	Consistent decrease of risk of suicide and attempts in controlled and uncontrolled studies; not clear if effect is via reducing risk of depression, impulsivity, or specific anti-suicidal action	Even randomized trials lack suicidal behavior as explicit outcome measure. Long-term acceptance and tolerance suggests some self-selection; potentially toxic on overdose
Other pharmacological treatments	Only short-term effects have been tested	Ketamine can reduce suicidal ideation; effects on suicidal behavior are untested; newer NMDA agents untested	Ketamine has a short-term antidepresant effect in BD
Other somatic treatments	If there are benefits, they are probably short-term	ECT, magnetic, vagal nerve, or deep-brain stimulations can benefit depression	Inadequate testing vs. suicidal behavior specifically
Psychotherapies	Effects not established, but widely assumed to be helpful clinically	Cognitive-behavioral, dialectic and interpersonal methods best studied, but research results for suicide are inconclusive	Psychotherapy involves self-selection

References to relevant studies are provided in the text

Strong association of suicidal behavior or acts with depression suggests that treatment with antidepressants might reduce suicidal risk, though most studies have yielded inconsistent evidence. Most were not designed to test for suicidal behavior as an explicit outcome measure rather than as an incidental and passively reported "adverse event" (Möller 2006; Tondo and Baldessarini 2015; Baldessarini et al. 2020). Too, some patients can *worsen* clinically when given an antidepressant, and the treated depressive episode can be accompanied by agitation, dysphoria, restlessness, irritability, anger, insomnia, behavioral disinhibition, or other mixed features, with increased risk of suicidal behavior (Tondo et al. 1999, 2018; Maj et al. 2006; Simon and Hales 2012; Pacchiarotti et al. 2013). In addition, abrupt or rapid discontinuation of antidepressant treatment markedly increases early risk of new depression, and might increase suicidal risk (Baldessarini et al. 2010b).

Several studies have found only minor associations of antidepressant treatment and suicidal behaviors, mainly with MDD (Beasley et al. 1991; Acharya et al. 2006; Möller 2006; Tondo et al. 2008; Khan et al. 2011; Tondo and Baldessarini 2015; Braun et al. 2016). Other findings noted increased risk of suicidal acts in juveniles and young adults but decreased risk in older adults (Hammad et al. 2006; Laughren et al. 2006; Bridge et al. 2007; Barbui et al. 2009; Saunders and Hawton 2013; Braun et al. 2016). However, most such studies lacked explicit, validated, predefined outcome measures pertinent to suicide.

In our experience, emergence of new suicidal behaviors among mood-disordered adults treated with sustained antidepressant treatment in clinical settings was infrequent, involving perhaps 5/1000 patients/year (Tondo et al. 2008). Nevertheless, risks of clinical worsening with antidepressants, as well as the possibility that acute depression may be the initial episode of BD, should be considered and monitored at any age, especially early in antidepressant treatment.

Lithium treatment and suicide

An association of reduced risk of suicides and attempts during long-term treatment with lithium in BD is supported consistently by most (Müller-Oerlinghausen et al. 2006; Baldessarini and Tondo 2008; Tondo and Baldessarini 2014, 2015, 2018; Roberts et al. 2017; Smith and Cipriani 2017; Felber et al. 2018), but not all studies (Marangell et al. 2008; Oquendo et al. 2011). At least 10 placebo-controlled, randomized trials not specifically designed with suicide risk as the primary outcome measure, but involving more than 110,000 person-years of risk, found five- to sixfold reductions in suicidal acts (Tondo et al. 1998, 2001; Angst et al. 2005; Cipriani et al. 2005; Baldessarini et al. 2006; Lauterbach et al. 2008; Khan et al. 2011). Based on such studies, several expert reports recommend long-term lithium treatment to limit risk of suicidal behavior in BD patients (Wasserman et al. 2012; Lewitzka et al. 2013; Yatham et al. 2018).

Anticonvulsants and suicide

Few studies directly compare suicidal risks during treatment with alternatives to lithium, including anticonvulsants, and findings are largely inconsistent and inconclusive (Thies-Flechtner et al. 1996; Goodwin et al. 2003; Yerevanian et al. 2007; Baldessarini and Tondo 2009; Chen et al. 2019). The FDA (2008) proposed that some anticonvulsants may even be associated with increased risk of suicidal behavior, at least in epilepsy patients, though probably not in psychiatric applications (Yerevanian et al. 2007; Gibbons et al. 2009). Meta-analysis of suicidal behavior with lithium vs. several anticonvulsants (mainly valproate) in six direct comparisons involving over 30,000 patients found nearly three-fold greater reductions with lithium (Baldessarini and Tondo 2009).

Antipsychotics and suicide

Antipsychotic drugs remain little-evaluated for effects on suicidal behavior (Simon and Hales 2012). However, one study found no difference in relatively short-term risk of suicides or attempts during treatment of > 10,000 psychotic patients with either first- or second-generation antipsychotics (FGAs or SGAs) vs. placebo (Khan et al. 2001). In addition, mortality risk was not increased in nearly 109,000 schizophrenia subjects given antipsychotic drugs (Schneider-Thoma et al. 2018), but was greater without antipsychotic treatment in another study of over 2200 such patients (Tiihonen et al. 2006). The InterSePT study comparing suicide-related behavior in schizophrenia patients at high risk for suicide provided strong support for an antisuicidal effect of clozapine compared to olanzapine (Meltzer et al. 2003). Clozapine has not been evaluated adequately in the treatment of BD patients, although it may have antimanic or mood-stabilizing effects (Li et al. 2015). Studies of SGAs with antidepressant effects in BD patients, in particular, require assessment for effects on suicide.

Other treatments and suicide

Evidence is growing that the glutamate NMDA-receptor antagonist ketamine and its active *S*-enantiomer (esketamine) can exert rapid, short-term reduction of suicidal ideation along with rapid reduction of symptoms of depression, including in BD patients, although effects on suicidal behavior are uncertain (Parsaik et al. 2015; Grunebaum et al. 2017; Wilkinson et al. 2018).

There is considerable uncertainty about how to continue use of racemic or *S*-ketamine following initial benefits, and some concern that its discontinuation may provoke adverse clinical responses (Schatzberg 2019). ECT often appears to be lifesaving in suicidal emergencies but lacks evidence of sustained antisuicidal efficacy (Fink et al. 2014). Other methods of external electrical or magnetic stimulation of brain, vagal nerve stimulation, and deep brain stimulation are being investigated or introduced for the treatment of otherwise treatment-resistant depression but remain to be tested adequately for specific effects on suicidal behavior, particularly in BD.

Additional interventions of potential value include emergency hospitalization (Zalsman et al. 2016) as well as psychotherapies, in particular cognitive-behavioral, dialectic, and interpersonal methods, which can improve depressive symptoms and may reduce suicidal risk (Brown et al. 2005; Zalsman et al. 2016; McCauley et al. 2018; Baldessarini et al. 2020). However, results from studies of psychosocial interventions may be limited by the self-selection of patients who adhere to such prolonged treatments.

Treatment of bipolar depression

As noted, depressive, dysthymic, and mixed states account for the majority of illness-burden in BD, and are strongly predicted by initial depressive, mixed, or anxious episodes (Goodwin and Jamison 2007; Yildiz et al. 2015; Forte et al. 2015; Baldessarini et al. 2014, 2019a). Remarkably few treatments are proved to be highly and consistently effective in acute episodes of bipolar depression, and there is even less evidence supporting substantial long-term protection from recurrences (Table 4). In particular, there is continued controversy about the value and risks of antidepressant drugs in bipolar depression (Pacchiarotti et al. 2013; McGirr et al. 2016). Lack of highly effective treatments encourages widespread drug-combinations and other off-label treatments largely untested for effectiveness and safety.

Relative paucity of experimental treatment studies for bipolar depression may reflect a broadly accepted view that "major depression" is similar in its clinical characteristics as well as treatment responses in BD and MDD (Baldessarini 2013). Instead, their characteristics differ, e.g., in family history, sex-distribution, onset-age, long-term diagnostic stability, episode duration, recurrence rates, and treatment-responses (Baldessarini et al. 2010a, c). The assumption of similarity probably contributes to the rarity of direct comparisons of treatment responses with depression in BD vs. MDD, and leaves bipolar depression as a leading challenge for psychiatric therapeutics (Goodwin et al. 2016; Baldessarini et al. 2019b, 2020).

Table 4 Placebo-controlled trials for acute depression in bipolar disorder

Treatments	Subjects (n)	Responders/subjects (%)		RR [95%CI]
		Drug	Placebo	
Anticonvulsants [10 trials, 3 agents]	1281	313/657 [47.6%]	181/624 [29.0%]	1.61 [1.39–1.87]
Antidepressants [12 trials, 11 agents]	1895	383/803 [48.9%]	419/1092 [38.4%]	1.32 [1.07–1.62]
Antipsychotics [13 trials, 6 agents]	6044	2135/3859 [55.3%]	904/2185 [41.4%]	1.28 [1.09–1.51]
Lithium [1 trial, 1 agent]	265	85/136 [62.5%]	72/129 [55.8%]	1.12 [0.92–1.37]
Pooled/totals [36 trials, 21 agents]	9485	2926/5455 [54.4%]	1576/4030 [39.4%]	1.37 [1.30–1.44]

Dropout rates (average: 32.9% [28.0–37.8]) were similar across treatments and with drug or placebo. Response typically involved ≥ 50% improvement in depression symptom ratings. By separate random-effects meta-analysis, antidepressants were statistically more effective than placebo (RR = 1.32 [1.07–1.87]; $z = 2.65$, $p = 0.008$), as were the other agents (RR = 1.34 [1.17–1.53]; $z = 431$, $p < 0.0001$). The overall weighted average drug vs. placebo difference (RR = 1.37) was highly significant ($\chi^2 = 196$, $p < 0.0001$). Antidepressant dose averaged 172 [146–198] mg/day imipramine-equivalent (Baldessarini 2013). Antidepressant monotherapy trials yielded greater drug/placebo differences than with addition to a mood-stabilizer (RR = 1.64 [1.05–2.56] vs. 1.18 [0.96–1.46]). Of note, in 23/36 trials (63.9%) drug was *not* statistically superior to placebo. Results are ranked by drug/placebo Risk Ratios (RR). [References: Nemeroff et al. (2001); Tohen et al. (2003); Shelton and Stahl (2004); Agosti and Stewart (2008); McElroy et al. (2010); McGirr et al. (2016); Yatham et al. (2018); Vázquez et al. (2017a); Baldessarini et al. (2019b)]

Antidepressants for bipolar depression

Ease and relative safety of treating depressive episodes with modern antidepressants, and strenuous efforts to minimize or avoid depression by BD patients and clinicians, have made antidepressants the leading treatment provided to BD patients (Baldessarini et al. 2008, 2019b). Nevertheless, there is a striking paucity of therapeutic experimentation and inconsistent findings, despite more than a half-century of use of antidepressant drugs to treat "depression," with particularly serious gaps regarding dysthymia and dysphoria, mixed features, and long-term prophylaxis for bipolar depression (Ghaemi et al. 2008, 2010; Sidor and MacQueen 2012; Baldessarini 2013; Pacchiarotti et al. 2013; Fountoulakis et al. 2017; Liu et al. 2017a; Gitlin 2018). Many experts advise caution in using antidepressants, particularly for BD-I patients to avoid potentially dangerous mood-switches, and encourage their use, if necessary, only with mood-stabilizing agents or SGAs, and without current mixed features or agitation (Pacchiarotti et al. 2013; Tondo et al. 2013; Goodwin et al. 2016; Yatham et al. 2018).

Well-designed, controlled, monotherapy trials of antidepressants for acute bipolar depression are surprisingly

few, vary in size and quality, and yield inconsistent findings (Table 4) (Vázquez et al. 2011; Tondo et al. 2013; Gitlin 2018; Yatham et al. 2018). Two large trials found no additional improvement in bipolar depression by adding paroxetine or bupropion to mood-stabilizing or antipsychotic drugs (Sachs et al. 2007; McElroy et al. 2010). Two meta-analyses including these and the few other relevant trials supported possible efficacy of various antidepressants in bipolar depression (Gijsman et al. 2004; Vázquez et al. 2013); another did not (Sidor and MacQueen 2012). Several direct comparisons found similar antidepressant responses in depressed BD and MDD patients (Vázquez et al. 2011). Another comparison of clinical responses in large samples of depressed BD-I, BD-II, or MDD patients also found only minor differences in response or remission and low risk of mood-switching in these disorders, provided that subjects with agitation or even minor mixed features were excluded (Tondo et al. 2013).

Impressions that antidepressants may be less effective in acute bipolar depression than in MDD may, to some extent, reflect adverse effects of treatment, including worsening of agitation, anger, or dysphoria, interpreted as failure of depression to respond (Tondo et al. 2013). Our findings from available randomized, controlled trials support the impression that antidepressant treatment has yielded a significant, 32% superiority over placebo for acute bipolar depression, with moderately high heterogeneity of outcomes (Table 4). Despite this limited and inconsistent body of research, it is evidently widely assumed clinically that antidepressants may be appropriate for some BD patients, and especially safe for BD-II depression (Baldessarini et al. 2008; Amsterdam and Shults 2010; Undurraga et al. 2012; Altshuler et al. 2017; Gitlin 2018). Selection of BD candidates for clinical antidepressant treatment may usefully be guided by previous beneficial and tolerated responses, relatively less severe or nonrapidly cycling illness, relatively few previous depressions, lack of switching from depression to mania, or of current agitation or even minor mixed features (Pacchiarotti et al. 2013; Tondo et al. 2013; Baldessarini et al. 2019b). Research on biomarkers associated with response to antidepressants is ongoing and may help in identifying more effective treatments for various types of depression (Gadad et al. 2018).

Antidepressants and mood switching

There is widespread concern that antidepressant treatment for bipolar depression risks switching into potentially dangerous agitation or mania, especially in BD-I (Bond et al. 2008; Undurraga et al. 2012). Such risk is more associated with the long-term BD course-pattern of depression followed by mania before a stable interval ("DMI") than the opposite ("MDI") (Koukopoulos et al. 2013). However, it is difficult to distinguish spontaneous from antidepressant-associated switching in BD, mean rates of which are similar (13.8% [12.2–15.3] vs. 15.3% [14.5–16.1]) (Tondo et al. 2010). Though it is plausible to expect mood-stabilizing and antipsychotic drugs to prevent mood-switching with antidepressants, required randomized comparisons are lacking (Tondo et al. 2010; Baldessarini et al. 2019b). Trials of antidepressants have found little difference in risk of new mania between antidepressants and placebo, with or without a mood-stabilizer included, although exposure times were short (Liu et al. 2017a). However, one study found that switching in BD was 2.8-times greater within 9 months after adding an antidepressant, but not if a mood-stabilizer also was used (Viktorin et al. 2014), and switching risk was increased in the rare long-term trials with an antidepressant included in treatment (Ghaemi et al. 2008).

An evident clinical consensus is that antidepressants be used for BD only cautiously, with short-acting agents given in moderate, slowly increased doses, briefly, and with effective mood-stabilizing co-treatment, while monitoring for emerging hypomania. It seems prudent that antidepressants, especially tricyclics and some SNRIs, be used very cautiously for bipolar depression, especially in BD-I patients, and perhaps avoided altogether with a history of mood-switching during antidepressant treatment, rapid-cycling without antidepressant treatment, or if mixed symptoms are present (Tondo et al. 2010; Pacchiarotti et al. 2013).

Mood-stabilizers

Several anticonvulsants have been used widely for BD, based on secure evidence of short-term antimanic effects (carbamazepine and valproate) or long-term reduction of risk of depressive recurrences (lamotrigine) (Baldessarini 2013; Geddes and Miklowitz 2013; Reinares et al. 2013). Such treatment choices are encouraged by seeming simpler than treatment with lithium (Baldessarini 2013; Vázquez et al. 2014). For divalproex monotherapy, 4 small trials suggest possible value in acute bipolar depression (Table 4), but it remains FDA-unapproved for depression or long-term treatment in BD. Evidence that lamotrigine is effective in acute bipolar depression rests on pooling inconsistent data, including from individually failed trials vs. placebo (Table 4) (Solmi et al. 2016). Lamotrigine is FDA-approved only for long-term prophylaxis in BD, with partial effectiveness against recurrences of depression but little efficacy against acute or recurrent mania (Frye et al. 2011; Baldessarini 2013). Moreover, slow dose-increases to avoid potentially serious dermatological reactions limit practicality of off-label use of lamotrigine in acute bipolar depression. Evidence concerning carbamazepine for short- or long-term use for bipolar

depression is very limited (Table 4), and controlled trials for other anticonvulsants in BD are lacking (Reinares et al. 2013; Selle et al. 2014).

Despite use of lithium as a fundamental treatment for BD for more than six decades, and its position as a first-line treatment in some expert guidelines (Goodwin et al. 2016; Yatham et al. 2018), it remains virtually untested for acute bipolar depression. Lithium was included as a third-arm of a trial in acute bipolar depression designed primarily to test quetiapine, with little benefit (Table 4) (Young et al. 2010). Nevertheless, lithium has some long-term effectiveness against recurrences of bipolar depression as well as greater prophylactic effects against [hypo] mania (Baldessarini 2013; Bschor 2014; Yatham et al. 2018), and benefits in mixed episodes in BD (Sani and Fiorillo 2019). Moreover, as noted, lithium may reduce risk of suicide substantially in BD patients (Tondo et al. 2001; Baldessarini et al. 2006; Cipriani et al. 2013; Tondo and Baldessarini 2014, 2018; Song et al. 2017).

Second-generation antipsychotics

SGAs, including cariprazine, lurasidone, olanzapine-fluoxetine, and quetiapine are currently the only FDA-approved medicines for short-term treatment of acute depressive episodes in BD (Baldessarini 2013; Selle et al. 2014; Earley et al. 2019; Ragguett and McIntyre 2019). Of these, only quetiapine has outperformed placebo consistently in several trials, with similar results for doses of 300 vs. 600 mg/day, and only the lower dose is FDA-approved (McElroy et al. 2010). Olanzapine-fluoxetine was superior to placebo, whereas olanzapine alone was less effective (Tohen et al. 2003). Unsurprisingly, as both olanzapine and quetiapine are antimanic, they have yielded somewhat *lower* risks of mood-switching than placebo (Selle et al. 2014). Most of these responses in acute bipolar depression have been modest (Table 4), and possible long-term protective effects require further study. Of note, beneficial effects in bipolar depression are not a class-effect of all SGAs (Taylor et al. 2014). In effective doses, antipsychotics risk adverse effects that include excessive sedation as well as distressing restlessness (akathisia) (Brown et al. 2006; Tamayo et al. 2010). Although risks of tardive dyskinesia with most SGAs are far lower than with FGAs (Tarsy et al. 2010; Carbon et al. 2017), their greatly increasing use and broadening indications may risk increased numbers of cases of even this uncommon adverse outcome (Pompili et al. 2016). Moreover, risks of weight-gain, type-2 diabetes, and other features of metabolic syndrome (hyperlipidemia, hypertension) are encountered with some SGAs (particularly olanzapine and quetiapine), sometimes rapidly (Centorrino et al. 2012; Baldessarini 2013; Vázquez et al. 2015). These medically important adverse effects tend to limit the potential value of SGAs for prophylactic treatment against recurrences of bipolar depression (Vázquez et al. 2014, 2015; Fountoulakis et al. 2017). In summary, cariprazine, lurasidone, and quetiapine, as well as olanzapine-fluoxetine are effective in acute bipolar depression, though with some risks, and they need further testing for long-term, prophylactic effects against bipolar depression.

Other treatments

Growing numbers of novel pharmacological treatments for depression are under investigation; some may be of value in BD, including drugs that act at synaptic transmission systems mediated by amino acid neurotransmitters glutamate and GABA. They include the NMDA-glutamate receptor antagonist ketamine and newer pharmacologically similar agents (e.g., apimostinel, rapastinel) (Dhir 2017; Garay et al. 2017; Grady et al. 2017; Grunebaum et al. 2017; Ragguett et al. 2019; Wilkinson and Sanacora 2019). Given apparent association of postpartum mood disorders and BD (Liu et al. 2017b), neurosteroids that interact with $GABA_A$ receptors and found effective for postpartum depression (e.g., brexanolone) may be of interest for bipolar depression (Martinez-Botella et al. 2017; Scott 2019). Agents of less certain value include polyunsaturated fatty acids, anti-inflammatory agents, and probiotics (Vázquez et al. 2017a).

Among nonpharmacological treatments, acute bipolar depression is responsive to ECT (Itagaki et al. 2017; Perugi et al. 2017; Bahji et al. 2019), although optimal treatment to follow successful ECT remains uncertain. Other biomedical treatments may be of value in bipolar depression. Intense light therapy and sleep deprivation are plausible candidates that require adequate testing in BD (Tseng et al. 2016; Suzuki et al. 2018). Vagal nerve stimulation (VNS) is FDA-approved for treatment-resistant depression, with evidence of efficacy in depression of BD and MDD (Cimpianu et al. 2017; Conway et al. 2018), though with some risk of inducing mania (Salloum et al. 2017). Repeated transcranial magnetic stimulation (rTMS) and various forms of electrical stimulation of brain from the surface or through stereotaxically placed deep-brain electrodes remain experimental for bipolar depression (Nierenberg et al. 2008; Vázquez et al. 2017a; Widge et al. 2018; Filkowski and Sheth 2019).

Finally, several manual-based, replicable forms of psychotherapy, alone or added to antidepressants, have shown promise for treating BD patients (Bouwkamp et al. 2013; McMahon et al. 2016; Salcedo et al. 2016; Lovas and Schuman-Olivier 2018; Yatham et al. 2018).

Table 5 Current status of depression in bipolar disorder

Depression in bipolar disorder (BD) is the major residual psychiatric morbidity with available treatments, accounting for three-quarters of the 40–50% long-term time-ill
Unresolved morbidity, and especially depression, is associated with excess medical morbidity, including metabolic syndrome and cardiovascular disease, with increased mortality
Suicide risk in BD is similar in types I and II BD, greater than in most other psychiatric disorders, ca. 20-times above general population rates, and strongly associated with depression, especially with agitation (mixed-dysphoric states), and in the days–weeks following hospital discharge
Predicting suicide in BD clinically is limited regarding individuals and timing
Treatments proposed to prevent suicidal behavior in BD include lithium, clozapine, and possibly ketamine and psychotherapies, which all require further study
Therapeutics of bipolar depression is far less well developed than for nonbipolar major depression, probably reflecting lack of recognition of differences between bipolar and unipolar depression
The short-term value and safety of antidepressant treatment for bipolar depression remains controversial, and long-term value remains virtually untested; it is best avoided with ongoing dysphoric agitation or mixed features
Some modern antipsychotics are effective in bipolar depression short-term; lithium and lamotrigine have modest prophylactic value long-term but are not adequately tested short-term; other anticonvulsant mood-stabilizers have very limited evidence of short- or long-term efficacy in bipolar depression
All available treatments for bipolar depression have risks of adverse metabolic or neurological effects; valproate and carbamazepine are also highly teratogenic

Conclusions

Depression, dysthymia, and dysphoria in BD represent major, only partially solved, clinical challenges (Table 5). As the main unresolved illness in treated BD, bipolar depression is associated with excess morbidity as well as mortality from co-occurring general-medical disorders and very high suicide risk. Suicide risk in BD exceeds general-population rates by 20-fold and is strongly associated with depressive phases, especially with mixed or psychotic features. Treatments proposed to reduce suicide risk notably include lithium. Treatment of bipolar depression is far less well investigated than MDD, and the value and tolerability of standard antidepressants for bipolar depression remain controversial. Evidence of efficacy in bipolar depression of mood-stabilizing agents, including lithium and several anticonvulsants (except lamotrigine, long-term) remains far less substantial than for several SGAs. All available pharmacological treatments used for bipolar depression have limited efficacy and risk adverse metabolic or neurological effects. Overall, we strongly encourage renewed efforts to consider bipolar depression as distinct from depression in MDD and to seek more effective treatments especially for long-term prophylaxis aimed at reducing morbidity and mortality.

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