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REVIEW

Overview of antidepressant treatment of bipolar depression

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Abstract

Bipolar depression remains a major unresolved challenge for psychiatric therapeutics. It is associated with significant disability and mortality and represents the major proportion of the approximately half of follow-up time spent in morbid states despite use of available treatments. Evidence regarding effectiveness of standard treatments, particularly with antidepressants, remains limited and inconsistent. We reviewed available clinical and research literature concerning treatment with antidepressants in bipolar depression and its comparison with unipolar depression. Research evidence concerning efficacy and safety of commonly used antidepressant treatments for acute bipolar depression is very limited. Nevertheless, an updated meta-analysis indicated that overall efficacy was significantly greater with antidepressants than with placebo-treatment and not less than was found in trials for unipolar major depression. Moreover, risks of non-spontaneous mood-switching specifically associated with antidepressant treatment are less than appears to be widely believed. The findings encourage additional efforts to test antidepressants adequately in bipolar depression, and to consider options for depression in types I *vs.* II bipolar disorder, depression with subsyndromal hypomania and optimal treatment of mixed agitated-dysphoric states – both short- and long-term. Many therapeutic trials considered were small, varied in design, often involved co-treatments, or lacked adequate controls.

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Introduction

Background

Bipolar disorder (BD) is a disabling, recurrent or chronic condition associated with functional impairment, psychiatric and somatic co-morbidity and premature mortality (Angst et al., 2002; Krishnan, 2005; Kupfer, 2005; Roshanaei-Moghaddam and Katon, 2009; de Hert et al., 2011; Leboyer et al., 2012). Lifetime prevalence was recently estimated to exceed 4% of the general population (Merikangas et al., 2007). Depressive, dysthymic and mixed (dyphoric-agitated) states contribute importantly to the total illness-burden of type I (with mania) and II (with hypomania) BD, and these components of future morbidity are predicted by similar first lifetime episodes (Baldessarini et al., 2010a, b, c, 2012). Several longitudinal studies indicate that the proportion of total time in depressive components of BD (averaging 75% of a total of 54% of weeks ill) is far greater than in manic or hypomanic phases, despite use of available treatments (Judd et al., 2002; Post et al., 2003a; Joffe et al., 2005; Paykel et al., 2006; Kupka et al., 2007; Baldessarini et al., 2010a, c). Depressive components of BD are associated with high morbidity (Baldessarini et al., 2010a, b; Leboyer et al., 2012), co-morbidity (Kilbourne et al., 2004; Bauer et al., 2005a, b), disability (Keck et al., 2008; Rosa et al., 2010), mortality (Ösby et al., 2001; Angst et al., 2002; Roshanaei-Moghaddam and Katon, 2009; Baldessarini et al., 2010d) and high levels of clinical and economic burdens to patients and their families (Kupka et al., 2007; Baldessarini et al., 2010d). In addition, both types I and II BD are associated with very high rates of suicide (about 20 times above rates in the general population) and other violent causes of death especially among young patients (Ösby et al., 2001; Tondo et al., 2003, 2007; Novick et al., 2010; Undurraga et al., 2012b), as well as similar total annual numbers of deaths associated with medical co-morbidity in older patients, albeit at far-lower standardized mortality rates (2–3 times above rates in the general population) than for suicide (Ösby et al., 2001; Tondo et al., 2003, 2007; Novick et al., 2010).

Despite the high prevalence and the major public health, clinical and economic significance of bipolar

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depression, few treatments are proved to be highly and consistently effective in acute episodes or to provide major prophylactic protection from recurrences of this major component of BD. The prevalent, related, dysthymic and dysphoric mixed-states of BD are even less extensively studied. These circumstances leave the depressive components of BD among the most critical, unsolved challenges for contemporary psychiatric therapeutics (Baldessarini, 2013).

Status of antidepressants for bipolar depression

Opinions concerning the value of antidepressants to treat bipolar depression vary markedly and reflect the strikingly limited and inconsistent state of available research-based information. Specific clinical recommendations from international academic guidelines and expert consensus statements differ substantially in their assessments of the value and safety of antidepressants for the treatment of acute episodes of bipolar depression (National Institute for Health and Clinical Excellence, 2006; Goodwin, 2009; Yatham et al., 2009; Grunze et al., 2010; Nivoli et al., 2011). Commonly, they call for caution in the use of antidepressants or give priority to various mood-stabilizing agents or second-generation antipsychotics, in contrast to the very prevalent and sustained use of antidepressants in clinical practice (Baldessarini et al., 2007a, 2008; Angst et al., 2011; Heeren et al., 2011; Pacchiarotti et al., 2011a; Post et al., 2011; Lorenzo et al., 2012).

Well-designed, controlled trials of antidepressants for acute bipolar depression are rare, vary in size and quality and their findings have been notably inconsistent (Gjisman et al., 2004; Frye et al., 2011; Vázquez et al., 2011; Sidor and MacQueen, 2011, 2012; Amit and Weizman, 2012; Bauer et al., 2012; Fountoulakis et al., 2012). Concerns about inducing mania surely contribute to the routine exclusion of patients with identified BD from controlled trials of antidepressant drugs, contributing to the dearth of investigations of bipolar depression. Evidence of long-term, prophylactic benefit of antidepressants is even more limited, with greater concerns about increased long-term risk of mania, emotional destabilization or more rapid cycling of mood-states (Ghaemi et al., 2003, 2008, 2010; Leverich et al., 2006; Post et al., 2006; Pacchiarotti et al., 2011b; Sussman et al., 2012; Valentí et al., 2012). One meta-analysis of 12 heterogeneous, short-term trials that included both BD I and II patients in acute depression found that antidepressants of various types yielded a rather large apparent superiority in pooled response-rates *vs.* placebo or other control treatments, averaging 86% [95% confidence intervals (CI) 49–130] and for remission rates, 41% (95% CI 11–80; Gjisman et al., 2004). A meta-analytic review that included more recent trials found only small and non-significant pooled differences in short-term outcomes of randomly assigned treatment with antidepressants *vs.* placebo, with respect either to responses (18%; 95% CI −1 to 44) or remission (20%; 95% CI −2 to 47; Sidor and MacQueen, 2011). Even more recent updates also found little evidence for efficacy of antidepressants in acute bipolar depression (Amit and Weizman, 2012; Sidor and MacQueen, 2012).

Of particular note, two of the largest, well-designed trials found no added benefit associated with treatment with a serotonin reuptake inhibitor (SRI) antidepressant or bupropion (Sachs et al., 2007; McElroy et al., 2010). The first involved adding bupropion, paroxetine or placebo to ongoing treatment with mood-stabilizing or antipsychotic agents for 6 months in BD patients recovering from an acute episode of depression; lack of superior attainment of sustained remission with the antidepressants suggested that their addition to mood-stabilizing treatments afforded little additional benefit. The second, short-term trial compared depressed BD subjects randomized to paroxetine or placebo in trial-arms of a larger comparison with quetiapine, which was non-dose-dependently superior to placebo, whereas paroxetine was superior to placebo only in some outcomes and less effective than quetiapine. These trials have been taken as evidence that antidepressants may be ineffective for many depressed BD patients and other controlled trials have yielded inconsistent and conflicting findings.

Despite the limited and largely inconclusive nature of evidence concerning the efficacy and safety of antidepressants for bipolar depression, they may well be the most common clinically employed treatments for BD (Baldessarini et al., 2007a, 2008). This practice probably arises from the highly questionable assumption that 'major depressive episodes', whether in bipolar or non-bipolar disorders, are similar in their characteristics and treatment responses. We propose that the inconclusive state of available evidence concerning antidepressants in bipolar depression justifies further effort to update the status of randomized, controlled trials (RCTs) of antidepressant treatment in acute bipolar depression. The primary aim of this report was to consider available reported RCTs in order to update the available evidence, and also to compare the findings in BD with a recent, comprehensive meta-analysis of RCTs for acute, unipolar major depression (Undurraga and Baldessarini, 2012). We also consider other aspects of antidepressant treatment of BD patients as well as noting alternative treatment-approaches that have emerged recently or remain under investigation.

Method

We performed a comprehensive literature search for reports on treatments for bipolar depression, focusing on RCTs of antidepressants in acute major depressive episodes in patients diagnosed with type I or II BD. To identify RCTs of antidepressants, we carried out a systematic search of several literature databases (PubMed,

Table 1. Randomized, placebo-controlled trials of antidepressants in acute depression in bipolar disorders

Trial	Bipolar types	Duration (wk)	Dropouts (%)	Antidepressant dose [mg/d (Imi-eq)]	Treatments	Responders/cases [*n*/*N*(%)]	
						Antidepressant	Placebo
Cohn et al. (1989)	I+II	6	53.9	50 (250)	Flx *vs.* Pbo±Li	26/30 (86.7%)	11/29 (37.9%)
Cohn et al. (1989)	I+II	6	53.9	188 (188)	Imi *vs.* Pbo±Li	17/30 (56.7%)	11/29 (37.9%)
Nemeroff et al. (2001)	I+II	10	23.3	33 (165)	Li±ACs:+Prx *vs.* Pbo	15/33 (45.5%)	15/43 (34.9%)
Nemeroff et al. (2001)	I+II	10	23.3	167(167)	Li±ACs:+Imi *vs.* Pbo	14/31 (45.2%)	15/43 (34.9%)
Tohen et al. (2003)	I+II	8	33.9	39 (195)	OFC *vs.* Pbo	46/82 (56.1%)	108/355 (30.4%)
Shelton and Stahl (2004)	I+II	12	40.2	28 (140)	MS+Prx±Rsp *vs.* Pbo±Rsp	5/20 (25.0%)	3/10 (30.0%)
Agosti and Stewart (2007)	II	6	6.0	255 (255)	Imi *vs.* Pbo	13/23 (56.5%)	5/22 (22.7%)
Agosti and Stewart (2007)	II	6	6.0	65 (162)	Pnz *vs.* Pbo	13/25 (52.0%)	5/22 (22.7%)
Sachs et al. (2007)	I+II	12	56.8	300 (165) or 30 (150)	Bup or Prx+MS *vs.* Pbo+MS	42/179 (23.5%)	51/187 (27.3%)
McElroy et al. (2010)	I+II	8	33.9	20(100)	Prx *vs.* Pbo	65/118 (55.1%)	64/121 (52.9)
Overall ($n=10$ trials)	I+II	8.4±2.5	34.2±18.4	179±47 (Imi-eq)	Antidepressants±Others *vs.* Pbo	256/571 (44.8%)	288/861 (33.4%)

ACs, Anticonvulsants; Bup, bupropion; Flx, fluoxetine; Imi, imipramine; Imi-eq, Imi-equivalent dose (mg/d); Li, lithium carbonate; MS, mood-stabilizers (Li or ACs); OFC, olanzapine–fluoxetine combination; Pbo, placebo; Pnz, phenelzine; Prx, paroxetine; Rsp, risperidone.

Many of these 10 randomized comparisons involve complex treatments, often with ongoing mood-stabilizers, and types I *vs.* II bipolar disorder subjects are not considered separately. The crude, overall response rates differ highly significantly, and favour antidepressants by 34.1% ($\chi^2=17.7$, $p<0.0001$).

PsycINFO, EMBASE and ClinicalTrials.gov). Search terms included various combinations of 'antidepressant', 'bipolar depression', 'bipolar disorder', 'controlled trial', 'major depression', 'efficacy', 'randomized controlled trial' and 'treatment'. In addition, we reviewed citations in identified reports and systematic reviews on this topic (Gjisman et al., 2004; Frye et al., 2011; Vázquez et al., 2011; Sidor and MacQueen, 2011, 2012; Amit and Weizman, 2012; Bauer et al., 2012; Fountoulakis et al., 2012). This search initially identified 1250 reports of potential interest, of which 160 were considered sufficiently relevant as to require detailed review. This process yielded a total of 25 reports of controlled trials. Of these, 10 fulfilled selection criteria: (1) acute phase of major depressive episodes in types I or II BD diagnosed by standard, internationally accepted diagnostic criteria, with $\geqslant$10 patients/trial-arm; (2) randomized treatment; (3) antidepressant as monotherapy or add-on to mood-stabilizing treatment; (4) placebo control (±other comparators); (5) double-blinded; (6) neither concerning special populations such as juvenile or geriatric patients nor limited by subject-count or weeks of treatment. Another 15 trials were considered separately and not included in the reported meta-analysis.

Findings from trials meeting the preceding selection criteria were then subjected to categorical, random-effects meta-analyses (Stata®; StataCorp, USA) to determine antidepressant/placebo response-rate (usually defined as $\geqslant$50% improvement in depression ratings) ratios (RR) and rate differences (RD) with their 95% CI; we also tested for publication-bias and estimated number-needed-to-treat (NNT, as 1/RD).

Results

A summary of findings from the 10 placebo-controlled antidepressant trials meeting inclusion criteria identified during November 2012 is provided in Table 1. They involved a total of 1432 patients diagnosed with bipolar depression. These trials are few, heterogeneous in patient characteristics, duration and in additional treatments allowed, making conclusions highly tentative. Nevertheless, the crude pooled response rate with antidepressant treatment was 44.8% (256/571) *vs.* 33.4% (288/861) with placebo ($\chi^2=17.7$, $p<0.0001$). Random-effects meta-analysis indicated a relative RR=1.43 (95% CI 1.11–1.84), indicating significant superiority of antidepressants ($z=2.76$, $p<0.006$). The RD also was significant [0.164 (95% CI 0.049–0.280); $z=2.79$, $p=0.005$] and the corresponding NNT was 6.2 (95% CI 3.6–6.7). Publication bias was not found by inspection of a funnel-plot nor significant statistically [Egger's coefficient=3.79 (95% CI −0.58 to 8.16); Fig. 1].

For comparison, the results of this meta-analysis for bipolar depression were compared with results of a comparable meta-analysis of findings from 142 placebo-controlled RCTs for antidepressants in unipolar major

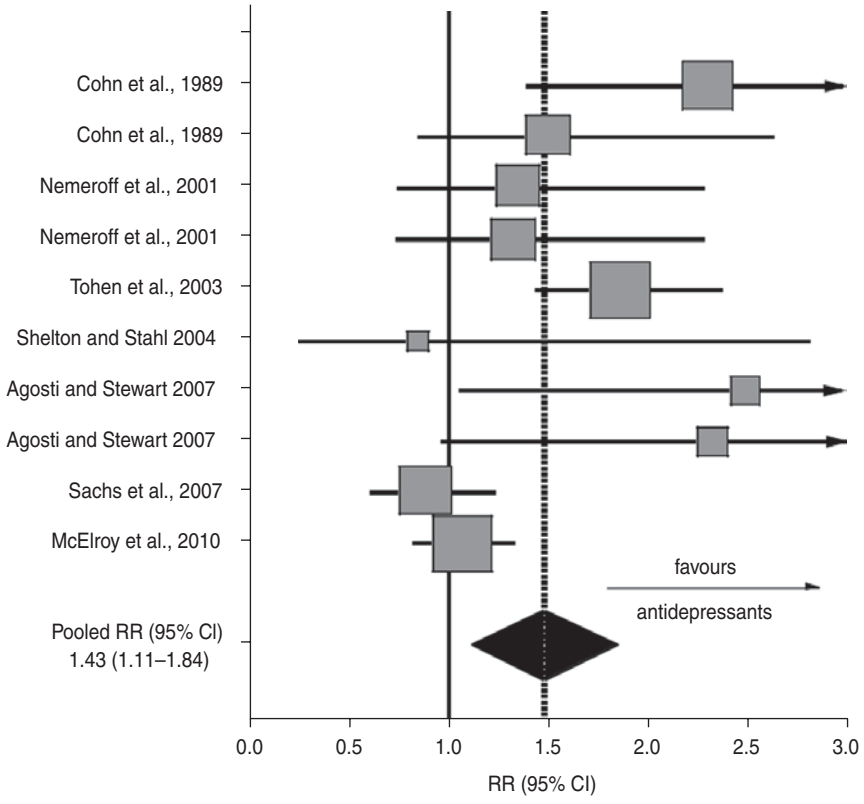

Fig. 1. Meta-analytic summary of 10 randomized, comparison trials in seven studies of short-term efficacy of antidepressants *vs.* placebo controls in acute bipolar depression (reports summarized in Table 1). Horizontal bars = 95% confidence intervals (CI); vertical solid bar = null value [response-rate ratio (RR) = 1.0] and dotted line = pooled drug/placebo RR; box size is proportional to the weight of each trial. The overall drug/placebo response (typically ⩾50% improvement in depressive symptom ratings) rate ratio (RR; black diamond) was 1.43 (95% CI 1.11–1.84), a significant difference (z = 2.76; $p = 0.006$), with an estimated number needed to treat (reciprocal of response-rate difference) of 6.1 (95% CI 3.6–20.5).

depressive disorder reported between 1980 and 2010 (Undurraga and Baldessarini, 2012). Although the outcomes in BD were inferior statistically (with much more limited power), the actual values of ratings of efficacy (RR and RD), as well as NNT estimates, were similar in both diagnostic groups (Table 2).

We also considered reported rates of mood-switching into hypomania or mania in the studies analysed (not shown). These rates (with 95% CI) varied markedly by treatment-type, ranking: imipramine [26.7 (1.88–51.5)%]; modern antidepressants [SRIs or bupropion: 7.31 (2.79–11.8)%]; placebo [6.15 (3.47–8.83)%], with or without additional mood-stabilizing treatments, during an average exposure time of 2 months. This risk with imipramine was high, but with modern antidepressants it was only 1.16% greater than with placebo (spontaneous switching), although these differences were not statistically significant and need further study.

Findings from 15 other trials in depressed BD patients did not meet all study-inclusion criteria but several, involving an antidepressant *vs.* a comparison treatment, were of potential interest and are summarized as follows. Himmelhoch et al. (1991) found the monoamineoxidase (MAO) inhibitor tranylcypromine to be a significantly superior antidepressant to imipramine in bipolar depression (responders: 21/28 *vs.* 10/28; $p = 0.003$), but lacked a placebo control. Tohen et al. (2003) found an olanzapine–fluoxetine combination to be superior to olanzapine monotherapy (responders: 46/82 *vs.* 137/351; $p = 0.005$; this arm was excluded from meta-analysis as not comparing an antidepressant to placebo). Amsterdam and Shults (2005) compared three treatments to placebo in a small trial (eight or nine subjects/arm) involving types I and II, depressed BD patients: fluoxetine monotherapy; olanzapine monotherapy; their combination; placebo. Changes in depression ratings did not differ statistically but lacked statistical power. Brown et al. (2006) compared olanzapine–fluoxetine to lamotrigine without a placebo (responders: 141/205 *vs.* 122/205; $p = 0.05$). Schaffer et al. (2006) compared citalopram to lamotrigine (responders: 4/10 *vs.* 2/10; $p = 0.33$). Nolen et al. (2007) compared tranylcypromine [responders: 5/8 (62.5%)] to lamotrigine [4/11 (36.4%)] in treatment-refractory bipolar depressed patients (RR = 1.72; not significant, but underpowered). Amsterdam and Shults (2008) compared venlafaxine to lithium (responders: 20/43 *vs.* 8/40; $p = 0.01$). In six of these seven trials, treatments that included an

Table 2. Meta-analytic findings from placebo-controlled trials in acute bipolar *vs.* unipolar major depression

	Measure (95% CI)	
Measures	Bipolar	Unipolar
Trials	10	142
Antidepressant/control RR	1.43 (1.11–1.84)	1.42 (1.38–1.48)
Antidepressant/control RD	0.164 (0.049–0.280)	0.125 (0.111–0.141)
NNT	6.2 (3.6–6.7)	8.0 (7.1–9.1)

CI, Confidence intervals; RR, response-rate ratios; RD, rate differences; NNT, number needed to treat.
Data are derived from Table 1 for bipolar and from Undurraga and Baldessarini (2012) for unipolar trials in acute depression (1980–2010).

antidepressant were more effective in bipolar depression than active comparators [by random-effects meta-analysis, pooled RR = 1.49 (95% CI 1.17–1.89); z = 3.22, $p = 0.001$; six out of six trials, individually, involved significant differences; NNT = 6.4 (95% CI 3.6–10.2)]. In addition, van der Loos et al. (2009) compared adding lamotrigine or placebo to lithium (responders: 33/64 *vs.* 19/60; $p = 0.025$); non-responders also failed to respond to later, unblinded addition of paroxetine (van der Loos et al., 2010). Finally, several trials compared different antidepressants in bipolar depression and found no differences in responses, but lacked placebo controls (Bocchetta et al., 1993; Sachs et al., 1994; Grossman et al., 1999; Young et al., 2000; Silverstone, 2001; Post et al., 2006).

Discussion

Antidepressant responses

The present primary meta-analysis indicated statistically significant overall efficacy of antidepressants *vs.* placebo in acute bipolar depression (Table 2), although we found only 10 trials meeting inclusion criteria, with variable conditions and findings across trials. There was also a rather low overall rate of response with antidepressant treatment (45%), but an unremarkable pooled response with placebo (33%; Table 1) that is similar to trials in unipolar depression (Undurraga and Baldessarini, 2012). This outcome may reflect some selection of BD patients who are clinically complex and may be experiencing depression despite mood-stabilizing treatments, although one would expect treatment-resistant sampling to yield low placebo- as well as drug-associated responses. Notably, the pooled antidepressant/placebo RR and differences in bipolar depression were not less than those found in a recent, comprehensive meta-analysis of RCTs in unipolar major depression [BD: RR = 1.43 (95% CI 1.11–1.84) *vs.* unipolar: RR = 1.42 (95% CI 1.38–1.48); Table 2; Undurraga and Baldessarini, 2012]. Our recent review of only 10 reports of direct comparisons of bipolar and unipolar depressed subjects also found very little difference in rates of response to antidepressant treatment by diagnosis (Vázquez et al., 2011). Moreover, the overall RR for mood-stabilizers *vs.* placebo in 18 RCTs in acute bipolar depression was only 1.30 (95% CI 1.16–1.44; van Lieshout and MacQueen, 2010), suggesting that mood-stabilizers may not be more effective than antidepressants and further underscoring the need for more effective treatments during depressive phases of BD.

The evidence of overall clinical efficacy of antidepressants in bipolar depression found in the present meta-analysis as well as in six out of six other RCTs comparing an antidepressant to various alternatives other than placebo-controls, if valid, raises questions about the striking dearth of trials of antidepressants in bipolar depression, in contrast to the large number of trials in patients diagnosed with unipolar major depression reported since the late 1950s (Undurraga and Baldessarini, 2012; Undurraga et al., 2012c). One possible basis of this striking research imbalance may be concern about the safety of antidepressant treatment in BD, especially type I, with risks of mania, psychosis and potentially dangerous behaviours associated with 'mood- switches.' Such concerns are suggested by the near-absence of RCTs in bipolar depression with corporate sponsorship identified in the present literature-search (a rare example being a study of the MAO inhibitor moclobemide by Silverstone, 2001) and the status of bipolarity as a routine exclusion criterion from most antidepressant trials. Such concerns probably also limit clinical use of antidepressants, particularly in type I BD patients (Heeren et al., 2011; Lorenzo et al., 2012; Undurraga et al., 2012a; Valentí et al., 2012).

Antidepressant treatment for BD patients is also encouraged by hoped-for, long-term prophylactic benefits against depressive recurrences, even though such effects remain unproved (Altshuler et al., 2003;

Goldberg et al., 2007; Sachs et al., 2007; Ghaemi et al., 2008, 2010; Baldessarini et al., 2010d; Frye et al., 2011). Evidence for prophylactic effects of sustained antidepressant treatment, even in non-bipolar recurrent depressive illnesses, remains limited and ambiguous, with risk of confounding effects of discontinuing ongoing antidepressant treatment (Altshuler et al., 2003; Baldessarini et al., 2007a, 2008, 2010c; Vieta, 2008; Vöhringer and Ghaemi, 2011; Baldessarini, 2013).

Risks of mood 'switching'

There has been concern about pathological activation of mood and behaviour during treatment with antidepressants, stimulants or other mood-elevating drugs for many years (Wehr and Goodwin, 1979; Peet, 1994; Wehr et al., 1988; Nemeroff et al., 2001; Vieta et al., 2002; Ghaemi et al., 2003, 2004, 2008, 2010; Post et al., 2006; Goldberg et al., 2007; Licht et al., 2008; Valenti et al., 2012). This concern arises mainly from treatment trials that are largely anecdotal and lack controls to test for a direct relationship between elevated mood and antidepressant treatment, as opposed to spontaneous mood-shift characteristics of BD (Licht et al., 2008; Tondo et al., 2010). It is notable that risks of switching in the reports reviewed earlier were remarkably low when modern antidepressants were involved, and barely greater than during parallel treatment with a placebo. However, these samples include many type II BD patients, whose risk of readily identified and clinically dangerous switching appears to be limited and may be influenced further by prevalent use of mood-stabilizing co-treatments.

In a recent, comprehensive review of studies of spontaneous mood-switching and that associated with antidepressant treatment, rates of spontaneous hypomania or mania among patients diagnosed with a BD (type I or II), without exposure to an antidepressant were high (13.8% over an average of several months), but little-higher (15.3%) with antidepressants (Tondo et al., 2010). Another recent review (Sidor and MacQueen, 2012) reported pooled switch rates of 8% with either antidepressant or placebo treatments in RCTs for bipolar depression [RR = 1.03 (95% CI 0.70–1.52)], indicating no difference between spontaneous and antidepressant-associated risks. These observations suggest that clinical concerns about risky mood-switching may be greater than is warranted.

It may be possible to predict risks of excessive mood-elevation during antidepressant treatment to some extent. Factors including previous mood-switching during antidepressant treatment, rapid-cycling ($\geqslant$4 recurrences/yr), younger onset-age, presence of co-morbid anxiety or substance-use disorders, may contribute to risk of antidepressant-associated mood-switching but require further study (Ghaemi et al., 2010; Perlis et al., 2010; Angst et al., 2011; Biernacka et al., 2012; Cazard and Ferreri, 2012; Post et al., 2012; Tondo et al., 2012; Valentí et al., 2012). In addition, as suggested in the present meta-analysis, tricyclic antidepressants may have a higher risk of inducing mood-switches than most modern antidepressants, at least in adults, although SRI may have a higher risk among pre-pubertal juveniles (Martin et al., 2004; Baldessarini et al., 2005; Tondo et al., 2010). The impression that bupropion may have an especially low risk of inducing mood-switches may arise from its having been marketed, for safety, with dosing limits well below those found to be effective in its initial RCTs (Baldessarini, 2013). There is also some evidence that MAO inhibitors may have a relatively low risk of inducing mood-switching (Himmelhoch et al., 1991; Tondo et al., 2010).

The presence of unrecognized initial subsyndromal hypomanic symptoms may contribute to poor responses to antidepressant treatment, even in patients diagnosed with unipolar depression (Ghaemi et al., 2003; Post et al., 2003b; Sharma et al., 2005; Calabrese et al., 2006; Goldberg et al., 2007; Sachs et al., 2007; O'Donovan et al., 2008; Phelps et al., 2008; Frye et al., 2009; Baldessarini et al., 2010d; Correa et al., 2010; Angst et al., 2011; Pacchiarotti et al., 2011b; Perlis et al., 2011; Rihmer and Gonda, 2011; Rybakowski, 2012). This hypothesis parallels the view that bipolar depression is less treatment-responsive than unipolar depression – a conclusion that can be questioned based on the present findings (Table 2). Moreover, it is not clear to what extent unfavourable outcomes represent lack of response or actual worsening by induction of excessive activation. States with a mixture of agitation and dysphoria can sometimes be difficult to differentiate as a mixed-state *vs.* 'worsening depression,' and may occur only transiently, especially in early antidepressant treatment (Pompili et al., 2005; Tondo et al., 2012).

Many clinicians rely on plausibly expected, protective effects of ongoing mood-stabilizing treatments to limit risks of mood-switching when an antidepressant is given to a BD patient. However, evidence concerning putative protective effects of mood-stabilizers against mania or hypomania during treatment with antidepressants remains inconclusive and the point requires further, randomized-controlled trials (Licht et al., 2008; Tondo et al., 2010).

Additional treatments for bipolar depression are being considered, but most remain experimental (Table 3). Exceptions with regulatory approval include olanzapine–fluoxetine and quetiapine for acute bipolar depression, as well as lamotrigine for long-term prevention mainly of depressive recurrences, and quetiapine as a long-term adjunctive treatment with lithium or valproate (Table 3; Baldessarini, 2013). These approved treatments carry very low risks of mood-switching, but the effectiveness of lamotrigine is limited and the sedative and adverse metabolic effects of olanzapine and quetiapine can be substantial (Frye et al., 2011;

Table 3. Treatments for bipolar disorder: emphasis on bipolar depression

Agents	Indications in BD	Status for bipolar depression	References
Antidepressants	None for BD; indication for 'major depression' widely assumed to include bipolar depression	Clinically used	Amit and Weizman (2012), Sidor and MacQueen (2011, 2012)
Aripiprazole	Mania, mixed-states and recurrences	Mainly negative findings; not approved for bipolar depression	Thase et al. (2008); Cruz et al. (2010), De Fruyt et al. (2012)
Asenapine	Mania, mixed-states	Experimental; some evidence	Cruz et al. (2010), De Fruyt et al. (2012)
Carbamazepine	Mania or mixed-states	Not approved for bipolar depression	Reinares et al. (2012)
Deep brain stimulation	Treatment-resistant depression	Experimental; some evidence	Rizvi et al. (2011)
Dopamine agonists[a]	Proposed for bipolar depression	Experimental; some evidence	Howland (2012)
Divalproex	Mania	Not approved for bipolar depression	Reinares et al. (2012)
Electroconvulsive treatment	Major and bipolar depression; mania	Clinically used; FDA Class III medical device	Dierckx et al. (2012)
Gabapentin	None for BD	Not approved for bipolar depression	Reinares et al. (2012)
Glutamate NMDA-antagonists[b]	Treatment-resistant & bipolar depression	Experimental; some evidence	Owen (2012), Zarate et al. (2012)
Lamotrigine	Recurrences (mainly *vs*. depression)	Not approved for bipolar depression	Reinares et al. (2012)
Levetiracetam	None for BD	Not approved for bipolar depression	Saricicek et al. (2011)
Light therapy (intensive)	Depression, seasonal affective depression	Experimental	Poon et al. (2012)
Lithium salts	Mania, recurrences	Not approved for bipolar depression	Baldessarini (2013)
Lurasidone	Mania	Not approved for bipolar depression	De Fruyt et al. (2012)
Modafinil, *R*-modafinil	None for BD	Experimental; some evidence	Frye et al. (2007); Calabrese et al. (2010)
Olanzapine	Mania, mixed-states, maintenance	Some evidence; approved in Japan	Cruz et al. (2010), De Fruyt et al. (2012), Tohen et al. (2012)
Olanzapine + Fluoxetine	Treatment-resistant and acute bipolar depression	FDA-approved	Cruz et al. 2010, De Fruyt et al. 2012
Omega-3 fatty acids and other 'nutriceuticals'	Proposed for bipolar depression	Experimental; some evidence	Keck et al. (2006), Sarris et al. (2011), Torrey and Davis (2012)
Pregabalin	None for BD	Experimental; some evidence	Reinares et al. (2012)
Psychostimulants[c]	Proposed adjuncts	Experimental	Parker and Brotchie (2010); Howland (2012)
Psychosocial interventions	Major depression; maintenance treatment	Clinically used	Fountoulakis (2010), Lolich et al. (2012)
Quetiapine	Mania, mixed-states, acute bipolar depression; long-term with lithium or valproate	FDA-approved	Cruz et al. (2010), De Fruyt et al. (2012)
Repeated transcranial magnetic stimulation	Major depression	Experimental	George et al. (2013)
Risperidone, Paliperidone	Mania, mixed-states, maintenace (risperidone) with lithium or valproate	Experimental; some evidence	Cruz et al. (2010), De Fruyt et al. (2012)

Table 3 (*Cont.*)

Agents	Indications in BD	Status for bipolar depression	References
Sleep deprivation	Major depression	Experimental	(Poon et al. 2012)
Thyroid hormones	Proposed for bipolar depression	Experimental	Bauer et al. (2005a, b)
Topiramate	None for BD	Not approved for bipolar depression	Reinares et al. (2012)
Vagal nerve stimulation	Chronic or recurrent depression	FDA-approved	Rizvi et al. (2011)
Ziprasidone	Mania, mixed-states, maintenance with lithium or valproate	Experimental; some evidence; not recommended for bipolar depression	Cruz et al. (2010), De Fruyt et al. (2012), Yatham et al (2013)

BD, Bipolar disorder; FDA, Food and Drug Administration; NMDA, N-methyl-D-aspartic acid.

[a] Includes bromocriptine, pramipexole.

[b] Ketamine, memantine, riluzole.

[c] Amphetamines, methylphenidate.

Proposed treatments are considered 'experimental' for bipolar depression if there are some supportive studies.

Centorrino et al., 2012). Evidence to support use of anticonvulsants to treat acute bipolar depression is limited, and as noted earlier, may be even less effective than antidepressant treatment (Calabrese et al., 2008; van der Loos et al., 2009; van Lieshout and MacQueen, 2010; Muzina et al., 2011; Reinares et al., 2012).

Conclusions

This overview was encouraged by the status of bipolar depression and related clinical states of dysthymia and dysphoria, as well as mixed-states of various types and levels of clinical severity, as major contributors to residual morbidity, disability and excess mortality of BD patients, even with application of available treatments aimed at mood-stabilization. It is remarkable that controlled trials for these clinically very important conditions remain limited and inadequate to support firm recommendations for treatment and optimal clinical management. The present review adds to the conclusion that placebo-controlled trials of antidepressants in acute bipolar depression remain rare. Nevertheless, trials that were identified yielded evidence of significant overall efficacy of antidepressants in bipolar depression that, remarkably, was not less than in unipolar depression. These findings, and the paucity of compellingly effective alternatives, encourage continued study of antidepressants in bipolar depression.

Further studies are required to advance therapeutic practices, despite difficulties that may be encountered, including fears of potentially dangerous activation during antidepressant trials, and uncertain commercial interest in the topic of bipolar depression as distinct from non-bipolar major depressive disorder. Needed is clarification of the efficacy and safety of antidepressants of different types and doses in various forms of depressive morbidity in bipolar or bipolar-like disorders. Specifically, head-to-head comparisons are needed to compare the short and long-term efficacy and safety of antidepressants *vs*. lithium, selected anticonvulsants and modern antipsychotic agents, given in monotherapy and in controlled combinations. Unresolved questions include whether some agents proposed for use in treating BD may worsen some aspects of mood, behaviour, or general health, including through excessive sedative effects or weight-gain and metabolic syndrome. The hypothesis that mood-stabilizing treatments can limit risk of antidepressant-associated mania also requires RCT to test this plausible but still-unproved concept. A major unresolved question is whether particular aspects of psychopathology, including mild, subsyndromal hypomanic features or elements of mixed-states that would not meet currently widely employed, but narrow, diagnostic criteria are indeed predictive of poor responses to antidepressants in bipolar depression, and whether such an effect is a reflection of a syndrome-type or an effect of current agitation.

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Statement of Interest

None.

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