Use of adjunctive stimulants in adult bipolar depression

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Abstract

Bipolar depression represents a high priority research field, due to its pervasiveness, and high economic and personal (suicidality, impaired function, quality of life) costs, and the limited evidence base to inform therapeutics. Mood stabilizers and second-generation antipsychotics for bipolar depression are commonly only partially effective, and their side-effects may overlap with depressive symptoms such as hypersomnia, daytime drowsiness, fatigue, psychomotor retardation, and weight gain. Moreover, the use of antidepressants in bipolar depression is controversial due to concerns regarding the risks of inefficacy or switching to mood elevation. Stimulants and related compounds such as modafinil and armodafinil have on occasion been used as adjuncts in bipolar depressed patients with encouraging results, but their use is limited by the paucity of systematic evidence of efficacy and safety. The present review aims to provide an updated perspective on the use of stimulants and stimulant-like medications in adult bipolar depression, considering not only recent randomized controlled trials, but also open naturalistic studies, in order to clarify the strengths and limitations of using these agents.

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Key words: Armodafinil, bipolar depression, methylphenidate, modafinil, stimulants.

Introduction

Bipolar disorder (BD) is a common (Merikangas et al. 2007), severe, disabling and chronic illness that profoundly adversely impacts the lives of patients and their families (Judd et al. 2008). While mood stabilizers (lithium, divalproex, carbamazepine, lamotrigine) and second-generation antipsychotics can effectively and rapidly overcome the core symptoms of mania, bipolar depression remains the major source of suffering for most patients, being the most pervasive illness phase, and associated with the greatest symptom burden and disability (Judd et al. 2002; Kupka et al. 2007). In addition, treating bipolar depression is particularly challenging, with mood stabilizers and second-generation antipsychotics commonly yielding inadequate efficacy and safety/tolerability, respectively. Moreover, antidepressants may be less effective in bipolar compared to unipolar depression, and may induce mania, rapid cycling, mood destabilization, and increased suicidality (Ghaemi et al. 2003; Grunze, 2008; Grunze et al. 2010; Yatham et al. 2009). For these reasons, there is a compelling need for additional treatment options with proven efficacy and safety/tolerability in bipolar depression.

Stimulants and related stimulant-like compounds such as modafinil and armodafinil (hereafter referred to collectively as stimulants) can promote alertness and wakefulness, reduce fatigue, attenuate excessive appetite, and perhaps even improve mood through a variety of mechanisms of action distinctive from those of mood stabilizers, second-generation antipsychotics, and antidepressants (Connolly & Thase, 2011). Some of these compounds may even have cognition enhancing actions (Turner et al. 2003, 2004a, b).

Stimulants include a heterogeneous group of medications (e.g. amphetamines, methylphenidate, modafinil, armodafinil) with diverse chemical composition and biological functions. While methylphenidate possesses structural similarities to amphetamine, and both agents target the dopamine transporter, subtle pharmacological differences exist, such as amphetamines being dopamine transport substrates whereas...
methylphenidate is a dopamine transport blocker (Sulzer et al. 2005). On the other hand, the stimulant-like agent modafinil is thought to act primarily on dopamine and norepinephrine neurotransmission with secondary elevations of serotonin, glutamate and histamine as well as effects on orexigeneric transmission (Minzenberg & Carter, 2008). Moreover, modafinil, unlike amphetamines and methylphenidate, exhibits only weak affinity for the dopamine uptake carrier site and does not stimulate dopamine release in animal models (de Sére´ville et al. 1994; Lin et al. 1992; Mignot et al. 1994), perhaps contributing to it having less abuse liability compared to stimulants (Warot et al. 1993).

In view of their clinical profiles and mechanisms of action, stimulants have been considered as alternative or adjuncts to antidepressants in mood disorder patients by clinicians who have assessed their safety and effectiveness in case reports and case series dating back to the 1970s. Indeed, several reviews have assessed the use of stimulants in major depression (Candy et al. 2008; Chiarello & Cole, 1987; Orr & Taylor, 2007; Satel & Nelson, 1989), although controlled monotherapy and adjunctive trials to date have had positive/mixed results (Candy et al. 2008; DeBattista et al. 2003; Fava et al. 2005).

Stimulants have been assessed in a variety of mood disorders, although not always through systematic investigation. Thus, stimulants have been assessed in: treatment-resistant depression (Buhagiar & Cassar, 2007; Feighner et al. 1985; Patkar et al. 2006), psychotic unipolar depression (Huang et al. 2008), depression associated with medical conditions (Masand et al. 1991; Rosenberg et al. 1991; Roy & Bernier, 1999; Woods et al. 1986) including cancer (Rozans et al. 2002), respiratory disturbances (Rothenháusler et al. 2000), human immunodeficiency virus (HIV) infection (Thomas & Lipsky, 2000; White et al. 1992), or medical treatments like interferon (Camacho & Ng, 2006). Furthermore, stimulants in general and methylphenidate, in particular, have been used in geriatric depression (Katon & Raskind, 1980; Wallace et al. 1995), post-stroke depression (Lazarus et al. 1992), BD with comorbid attention deficit hyperactivity disorder (ADHD) (Hamrin & Bailey, 2001) including child studies (Findling et al. 2007; Scheffer et al. 2005) and adolescent studies (Zeni et al. 2009), acute mania (Garvey et al. 1987; Schoennecht et al. 2010) and even depression with comorbid methamphetamine abuse (Camacho et al. 2010).

On the one hand, many of the aforementioned reports appear to suggest at least some support for the use of stimulants in specific depressive disorders with poor response to first-line treatment. On the other hand, however, most authors recommend considerable caution due possible risk of treatment-induced mood destabilization (Connolly & Thase, 2011; Ketter & Wang, 2010a,b; Shopsin & Gershon, 1978). In bipolar depression, the need for cautious use of stimulants is particularly advisable (Wingo & Ghaemi, 2008).

Bipolar depression is commonly associated with fatigue and somnolence (Angst et al. 2006; Mitchell et al. 2001, 2008; Perlis et al. 2009) as well as cognitive impairment, with such problems being documented across the bipolar spectrum (Bora et al. 2011; Solé et al. 2011; Yates et al. 2011). Therefore, stimulants which promote alertness and wakefulness and potentially enhance cognitive function appear to be potential treatment options in bipolar-depressed subjects not responding to first-line treatment (Shelton & Reddy, 2008). However, the risk of treatment-induced manic/hypomanic switches limits the routine use of these agents in bipolar depression (Carlson et al. 2004; Ketter & Wang, 2010a,b; Wingo & Ghaemi, 2008).

Prior reviews of stimulants have focused on effectiveness in unipolar major depressive disorder and treatment-resistant unipolar depression, so that the adjunctive use of these compounds in adults with bipolar depression has been less extensively and specifically documented. However, recent randomized controlled trials (RCTs) (Calabrese et al. 2010; Frye et al. 2007) indicate the need to review the use of these medications in bipolar depression, particularly in view of the paucity of therapeutic options for and the clinical consequences of bipolar depression (Post, 2005; Post et al. 2003; Tondo et al. 2003).

Methods

Literature for this narrative overview was identified by searching Medline and Cochrane Library in two steps. First, a search was performed identifying articles published in English and related to the use of stimulants in BD and unipolar major depressive disorder in order to detect reports combining unipolar and bipolar patients. In particular, the key words ‘stimulant’, ‘stimulants’, ‘psychostimulant’, ‘psychostimulants’, ‘amphetamine’, ‘ampetamines’, ‘methylphenidate’, ‘modafinil’, and ‘armodafinil’ were variably combined with the terms ‘bipolar disorder’, ‘bipolar depression’, ‘major depressive disorder’, ‘major depression’ and ‘treatment-resistant depression’. A second search was conducted in the area of safety and tolerability with the key words ‘stimulant’, ‘stimulants’, ‘psychostimulant’, and ‘psychostimulants’.
variously combined with the terms ‘tolerability’, ‘safety’, ‘side-effects’, ‘adverse events’, ‘mania’, ‘suicide’, and ‘cycle acceleration’. The ultimate aim of the literature search was to specifically identify efficacy and safety studies on the use of stimulants in adult bipolar depression.

Search publications included meta-analyses, RCTs, naturalistic and retrospective studies, case series, case reports and clinical reviews. In order to enhance the focus of the review, single case reports were not included in the analysis. Furthermore, a manual (non-computerized) search for further relevant articles was conducted examining references of publications retrieved from the computerized search. Additional information was explored in recently published guidelines on BD treatment and conference proceedings (Grunze et al. 2010; Yatham et al. 2009).

Results

After excluding studies not specifically focused on adult bipolar depression, nine studies were identified, reviewed in detail and tabulated. These included one open uncontrolled study of amphetamines, four open uncontrolled studies of methylphenidate, four studies (including three open uncontrolled studies and one RCT) of modafinil, and one RCT of armodafinil. Stimulants were in almost all instances used as adjunctive treatment. A brief section of early reports and case series on amphetamines is preliminarily presented, followed by reviews of reports organized by compound type (i.e. methylphenidate, modafinil, armodafinil) in chronological order.

Early reports and case series

In spite of the paucity of systematic investigations, the clinical use of stimulants in BD and bipolar depression dates back over 70 yr (Carlson et al. 2004). In the late 1930s, a pioneering report showed that open treatment with benzedrine – an amphetamine sulfate – yielded some benefit in a case series of 20 bipolar-depressed patients, and although some individuals had increased irritability, none had an actual treatment-induced manic switch (Davidoff & Reifenstein, 1939).

During the late 1970s and 1980s, a few case reports supported the use of stimulants added to tricyclic antidepressants or lithium for bipolar-depressed subjects with poor responses to prior treatments (Bannet et al. 1980; Drimmer et al. 1983; Meyers 1978). Subsequently, some cases of BD and comorbid ADHD with poor response to standard treatments were reported to be successfully treated with adjunctive stimulants (Schaller & Behar, 1998).

In 1991, Fawcett and colleagues reported their clinical experience combining a stimulant (either pemoline or dextroamphetamine) with a monoamine oxidase inhibitor (MAOI) in 32 depressed patients (mainly outpatients, including some bipolar subjects) refractory to standard antidepressant pharmacotherapy. Of note, 78% of these patients experienced at least 6 months of symptom remission with treatment combination and 40% of the long-term responders were bipolar patients (Fawcett et al. 1991). However, 6 out of 32 patients, including unipolar-depressed subjects, experienced manic/hypomanic episodes. In addition, concerns about serious adverse effects when combining stimulants with MAOIs limits the clinical utility of this approach (Feinberg, 2004).

Methylphenidate

Methylphenidate is a short-acting stimulant with a structure resembling that of endogeneous catecholamines (Biederman, 2000). It increases synaptic availability of the monoamine neurotransmitters nor-epinephrine, serotonin and dopamine by blocking their uptake as well as by increasing their release (Candy et al. 2008). Current United States Food and Drug Administration (US FDA) indications for methylphenidate include the treatment of ADHD and narcolepsy (Chavez et al. 2009; Thomas & Lipsky 2000). Clinical reports of the use of adjunctive methylphenidate in BD and adult bipolar depression are summarized in Table 1.

In 2000, El-Mallakh conducted a 12-wk open study of adjunctive methylphenidate in 14 depressed bipolar subjects (including 10 with bipolar I disorder) with a baseline Hamilton depression scale (HAMD; Hamilton, 1960) score of at least 15 (El-Mallakh, 2000). Methylphenidate (10–20 mg/d) was added to a stable mood stabilizer regimen, and mean ± S.D. HAMD scores dropped from 16.9 ± 1.79 at baseline to 9.4 ± 9.73 at endpoint. Symptom severity decrease on the Psychiatric Symptom Assessment Scale (PSAS; Bigelow & Berthot, 1989) was even more consistent: from 17.9 ± 5.63 to 4.8 ± 7.47. Of note, it was observed that early improvement predicted ongoing improvement and the response by week 1 foretold final outcome. Three individuals dropped out secondary to anxiety, agitation and hypomania, respectively. Taken as a whole, results showed that methylphenidate was effective and relatively safe for the treatment of bipolar depression.

In 2004, Carlson and colleagues reported a retrospective case series of eight subjects with BD (five with BDI and three with BDII) treated with adjunctive
Table 1. Summary of published studies (not including single case reports) with adjunctive methylphenidate in bipolar depression

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study design</th>
<th>Sample feature</th>
<th>Treatment group dose</th>
<th>Study length</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>El Mallak (2000)</td>
<td>Open, prospective study</td>
<td>14 bipolars (10 BDI, 3 with prior alcohol abuse); depressed despite mood stabilizers</td>
<td>Adjunctive methylphenidate (10–20 mg/d)</td>
<td>12 wk</td>
<td>44% decrease in mean HAMD score. 3 discontinued – 1 each due to anxiety, agitation, hypomania</td>
<td>Adding methylphenidate to mood stabilizers may be somewhat effective and relatively safe</td>
</tr>
<tr>
<td>Carlson et al. (2004)</td>
<td>Open, retrospective case series</td>
<td>8 bipolars (5 BDI, comorbidities other than ADHD allowed); depressed despite variable concomitant medications</td>
<td>Adjunctive methylphenidate (10–20 mg/d) or amphetamines (unspecified doses)</td>
<td>Mean 18 months (range 11–24)</td>
<td>Robust mean CGI-BP improvement (2.9) with prolonged treatment. No switching</td>
<td>Adding methylphenidate/amphetamine to various medications may be effective and relatively safe</td>
</tr>
<tr>
<td>Lydon &amp; El-Mallakh (2006)</td>
<td>Open, retrospective chart review</td>
<td>16 bipolars (9 BDI, 5 also with ADHD); depressed despite mood-stabilizing agents, BZs</td>
<td>Adjunctive methylphenidate mean dose 16.3 mg/d (range 5–40 mg/d)</td>
<td>Mean 14 months (range 1–60)</td>
<td>Most had attenuation of depression and inattention. (Generally mild) adverse events in 62% – irritability in 19%, agitation in 13% – no mania/hypomania, cycling exacerbation, substance abuse induction</td>
<td>Adding methylphenidate to mood stabilizers and BZs may be effective in most patients and relatively safe</td>
</tr>
<tr>
<td>Parker &amp; Brotchie (2010)</td>
<td>Open, prospective case series of 50 mood (including bipolar) disorder patients</td>
<td>27 bipolars (5 BDI) with history of persistent and/or recurrent treatment-resistant depression; depressed despite (in most) psychotropic medication</td>
<td>Adjunctive (mostly) methylphenidate (10–60 mg/d, modal 20 mg/d) or dextroamphetamine (few cases)</td>
<td>Mean 57 wk (range 6–250) (among patients continuing stimulant drug at final review)</td>
<td>34% distinct improvement in depression, 30% some improvement in depression, 36% no improvement in depression and/or side-effects. Rapid positive responses, only rare loss of efficacy. Significant side-effects in 18% – mostly minor, but 1 mania; switching rare and limited to bipolars</td>
<td>Adding methylphenidate to other psychotropics may be variably effective and relatively safe</td>
</tr>
</tbody>
</table>

BDI, Bipolar disorder type I; S.D., standard deviation; HAMD, Hamilton Depression Rating Scale; ADHD, attention deficit hyperactivity disorder; CGI-BP, Clinical Global Impression Scale for Bipolar Disorder; BZs, benzodiazepines.
stimulants (either methylphenidate or amphetamine) with primary target symptoms being residual depression and medication-induced sedation (Carlson et al. 2004). Subjects with ADHD comorbidity were excluded, although other comorbidities were allowed. Concomitant medications including antidepressants, mood stabilizers, atypical antipsychotics and benzodiazepines were permitted as well. Patients showed moderate improvement in target symptoms as well as robust (2.9 points) improvement of overall bipolar illness severity on the Clinical Global Impression Scale – Bipolar Patient Version (CGI-BP; Spearing et al. 1997) with adequate tolerability and no evidence of switching or abuse. Of note, mean duration of treatment was 18 months.

In 2006, Lydon and El-Mallakh conducted a retrospective chart review of 16 BD patients (including nine with bipolar I disorder) who received methylphenidate (Lydon & El-Mallakh, 2006). On average, the duration of treatment was 14 months (ranging from 1 to 60 months). Five patients had comorbid ADHD and the remainder had bipolar depression. The mean dose of methylphenidate was 16.3 mg/d (ranging from 5 to 40 mg/d). Side-effects were generally mild to moderate, with only two subjects (12.5% of the sample) discontinuing methylphenidate due to side-effects. Of note, the Global Assessment of Functioning (GAF; APA, 2000), which was available in the 44% of the sample, showed a significant improvement, leading the authors to conclude that naturalistic, extended methylphenidate administration appeared to be safe and effective.

Recently, Parker and Brotchie reported on an open case series of 10 consecutively recruited patients with treatment-resistant depression, including 27 bipolar subjects, treated with methylphenidate or dextroamphetamine, either as monotherapy or adjunctive therapy (in most of the patients) (Parker & Brotchie, 2010). At last visit, after 6 wk to 62 months (mean 57 wk), 52% of the sample was still receiving stimulant treatment. It was challenging to distinguish outcomes in bipolar as opposed to unipolar patients, but overall approximately 1/3 had one of the three possible following outcomes: distinct relief of depression, some improvement, and no improvement and/or side-effects. For subjects with distinct improvement or some improvement, the modal dose of methylphenidate was 20 mg/d. Significant side-effects were reported by 18% (including one manic response); and switching was rare and limited to bipolar subjects, and most side-effects were mild. Of clinical interest, positive responses seemed to occur rapidly and loss of efficacy was uncommon.

Modafinil and armodafinil

Modafinil is a novel stimulant-like medication with α₁ post-synaptic agonist and vigilance-promoting properties, while armodafinil is the longer half-life, R-enantiomer of racemic modafinil. Both of these medications are currently US FDA-approved for improving wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnoea and shift-work sleep disorder (Czeisler et al. 2005), although the European Medicines Agency (EMEA) has decided to limit modafinil-approved use to narcolepsy (EMEA, 2010) and has not to date approved armodafinil. Clinical reports on the use of modafinil and armodafinil in BD and adult bipolar depression are summarized in Table 2.

In 2000, Menza and colleagues, in a retrospective case series, described three patients with bipolar depression (along with four other cases of major depression) and partial/non-response to antidepressants, for whom modafinil was used as adjunctive agent (Menza et al. 2000). At doses of 100–200 mg/d, all patients achieved full or partial remission, generally within 1–2 wk. All subjects had residual tiredness or fatigue prior to starting treatment, and these symptoms appeared to be particularly responsive to modafinil augmentation. Side-effects were minimal and did not lead to modafinil discontinuation in any patient.

In 2003, Fernandes and Petty reported on two bipolar patients who had residual drowsiness after depressive episodes, despite taking mood stabilizers. They were treated by adding modafinil (100–400 mg/d) to their stable mood-stabilizing regimen for 8 wk, which yielded significant and rapid improvement in drowsiness [measured on the Epworth Sleepiness Scale (ESS; Johns, 1991)] and level of functioning. No hypomanic or manic switch or side-effects were observed (Fernandes & Petty, 2003).

Nasr reported in a retrospective chart review that openly adding modafinil to antidepressants in 78 outpatients, in a general psychiatric practice (including some bipolar subjects), yielded positive outcomes, particularly in those with problematic sleepiness or fatigue (Nasr, 2004).

Nasr and colleagues subsequently published a retrospective chart review of patients with mood disorders who received modafinil at some point during their treatment, which aimed to assess switching, dose stability and abuse liability (Nasr et al. 2006). This review included a subsample of 64 bipolar depressed subjects (including 31 BPI) who took modafinil (mean dosage ranging from 250 to 290 mg/d), usually as adjunctive medication – for <2 months in 25 (including...
<table>
<thead>
<tr>
<th>Citation</th>
<th>Study design</th>
<th>Sample and prior treatment</th>
<th>Treatment dose</th>
<th>Study length</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Menza et al.</td>
<td>Open, retrospective case series of mood disorder patients</td>
<td>Subgroup of 3 bipolars with depression with residual tiredness/fatigue despite antidepressants</td>
<td>Adjunctive modafinil 100–200 mg/d</td>
<td>10–12 wk</td>
<td>All had full/partial remission, mostly in 1–2 wk. Residual tiredness/fatigue particularly responsive. Side-effects minimal, did not cause discontinuation.</td>
<td>Adding modafinil to antidepressants may relieve depression, tiredness, and fatigue, and be relatively safe.</td>
</tr>
<tr>
<td>Fernandes &amp; Petty (2003)</td>
<td>Open, prospective case series</td>
<td>2 bipolars (1 BDI, 1 with prior comorbid substance abuse, 1 with current comorbid medical conditions) with excessive daytime sleepiness taking mood stabilizers</td>
<td>Adjunctive modafinil 100–400 mg/d</td>
<td>8 wk</td>
<td>Significant rapid improvement in drowsiness and functioning. No hypomanic/manic switch or side-effects</td>
<td>Adding modafinil to mood stabilizers for residual drowsiness may be effective and well-tolerated</td>
</tr>
<tr>
<td>Nasr (2004)</td>
<td>Open, retrospective chart review of mood disorder patients</td>
<td>Unspecified subgroup of depressed bipolars taking antidepressants</td>
<td>Adjunctive modafinil (unspecified doses)</td>
<td>Un-specified</td>
<td>Positive outcomes, particularly in those with problematic sleepiness or fatigue</td>
<td>Adding modafinil to antidepressants may yield benefit.</td>
</tr>
<tr>
<td>Nasr et al.</td>
<td>Open, retrospective chart review of mood disorder patients</td>
<td>Subgroup of 64 depressed bipolars (31 BDI) mostly taking other medication(s)</td>
<td>Adjunctive (most often) modafinil mean 230–287 mg/d</td>
<td>&lt;2 months to 2 yr</td>
<td>Modafinil persistence: &lt;2 months in 25 bipolars (13 BDI); 2 months in 39 bipolars (18 BDI); 1 yr in 27 bipolars (11 BDI); 2 years in 16 bipolars (BDI = 7). No manic/hypomanic switch, abuse. Modafinil dosage relatively stable</td>
<td>Adding modafinil to other medications may not induce manic/ hypomanic switches or tolerance/abuse independent of history of chemical abuse/dependence</td>
</tr>
<tr>
<td>Frye et al.</td>
<td>Randomized, double-blind placebo-controlled, multisite acute study</td>
<td>85 bipolars (64 BDI) with major depressive episode (IDS &gt; 16) despite treatment with mood stabilizer antidepressant</td>
<td>Adjunctive modafinil 200 mg/d (n = 41) vs. placebo (n = 44)</td>
<td>6 wk</td>
<td>Adjunctive modafinil compared to placebo yielded greater improvement on mean IDS, IDS 4-item fatigue and energy subset and CGI depression severity, as well as higher IDS response/remission rates, and similar incidence of treatment-emergent hypomania/mania, and blood pressure, heart rate, and weight effects. Headache was most common modafinil side-effect</td>
<td>Adding modafinil to mood stabilizer antidepressant may improve depressive symptoms with good tolerability</td>
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</table>
In 2007, Frye and colleagues conducted a multisite acute-phase, double-blind, placebo-controlled study in 85 patients with bipolar depression (including 64 BDI), inadequately responsive to a mood stabilizer with or without concomitant antidepressant therapy (Frye et al. 2007). Patients had moderate depression severity, with Inventory of Depressive Symptoms (IDS; Rush et al. 1986) scores of at least 16. Patients were randomized to adjunctive placebo (n = 44) or modafinil (n = 41), two tablets of 100 mg/d for 6 wk. The endpoint scores of the IDS, 4-item fatigue and energy subset of the IDS, and CGI depression severity item, showed a significant reduction in the modafinil group compared to placebo. Percentages of IDS responders and remitters were also significantly higher in the modafinil group compared to the placebo group (43.9% vs. 22.7% responded, and 39% vs. 18% remitted). Rates of treatment-emergent hypomania or mania, and mean blood pressure, heart rate and weight did not differ significantly between treatment groups. Headache was the most common side-effect with modafinil. The authors suggested that, taken together, the results supported adjunctive modafinil being an effective and safe treatment for bipolar depression, independent of the compound’s effect on sleepiness and fatigue.

Recently, Calabrese and co-workers conducted an 8-wk, multicentre, randomized, double-blind, placebo-controlled study in bipolar I patients with current major depressive episode despite treatment with lithium, olanzapine, or valproic acid. Patients were randomly assigned to adjunctive armodafinil or placebo (Calabrese et al. 2010). Armodafinil 150 mg/d (n = 128) and placebo (n = 129) were administered once daily in the morning. The primary outcome measure was change from baseline in the total 30-item IDS score. Secondary outcomes included changes from baseline in the total 30-item MADRS score and IDS and MADRS response rates. At endpoint, adjunctive armodafinil compared to placebo yielded significantly greater improvement in mean IDS scores, but failed to separate on any of the secondary outcomes. Adverse events, including headache and insomnia, were reported more frequently in the armodafinil group, compared to the placebo group. The authors concluded that adjunctive armodafinil may improve depressive symptoms, for some outcomes, with good tolerability.
insomnia. Of note, armodafinil was not associated with an increased incidence and/or severity of suicidality, depression, or mania or with changes in metabolic profile measurements.

Discussion

Taken together, the systematic evidence regarding the use of stimulants in adult bipolar depression consists of only one modafinil RCT and one armodafinil RCT (with no controlled study of methylphenidate or amphetamines) along with scattered, open case series for modafinil, methylphenidate, and amphetamines. Despite the limited systematic data, these reports seem to converge to offer at least some support for the use of adjunctive stimulants in at least some patients with bipolar depression, perhaps offering particular advantages in patients with prominent drowsiness or fatigue. However, the overall quality and quantity of published studies does not allow, at the current time, adjunctive stimulants to be considered as well-established, evidence-based options for bipolar depression with previous poor response to standard first-line treatments. Nevertheless, many interesting cues may be extrapolated to inform cautious off-label use of these agents in clinical practice as well as for encouraging and implementing further controlled trials in the field (see Table 3).

Table 3. Potential strengths, limitations, and areas for future research of stimulant use in adult bipolar depression as extrapolated from reviewed evidence and additional issues deserving further investigation

<table>
<thead>
<tr>
<th>Potential strengths</th>
<th>Potential limitations</th>
<th>Potential areas for future research</th>
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</thead>
<tbody>
<tr>
<td>May attenuate specific target symptoms (e.g. apathy, fatigue, hypersomnia, lethargy, sedation, excessive appetite, weight gain, and poor concentration)</td>
<td>Only two randomized clinical trials (for modafinil and armodafinil); possible selection bias in some studies</td>
<td>Potential beneficial effects upon cognitive impairment in bipolar disorder patients</td>
</tr>
<tr>
<td>Relatively rapid onset of action</td>
<td>Possible misuse/abuse in predisposed subjects; energy prior to mood improvement could have suicidality implications</td>
<td>Discontinuation effects; effects on suicidality</td>
</tr>
<tr>
<td>Favourable somatic safety/tolerability</td>
<td>Possible induction of tachycardia and hypertension in predisposed subjects</td>
<td>Effects in elderly and medically ill patients with bipolar disorder</td>
</tr>
<tr>
<td>Do not induce sedation, fatigue, weight gain, or metabolic problems</td>
<td>Insomnia, agitation, anxiety and excessive weight loss in predisposed subjects</td>
<td>Relationships between baseline anxiety and adverse effects.</td>
</tr>
<tr>
<td>Low potential for mood destabilization in patients already taking antimanic agents</td>
<td>Potential psychiatric safety/tolerability challenges (manic/hypomanic switches, rapid cycling, psychosis) in predisposed subjects</td>
<td>Drug-interaction potential with medications used in bipolar disorder (e.g. antimanic agents)</td>
</tr>
<tr>
<td>Sustained action over extended follow-up observation (i.e. methylphenidate)</td>
<td>Potential tolerance to mood and somatic benefits in predisposed subjects</td>
<td>Cost-benefit analysis, particularly for newer, more expensive agents</td>
</tr>
</tbody>
</table>

A first important issue that seems to characterize the majority of the reviewed reports concerns the nature of the samples. Besides a possible enthusiastic interpretation of the results in open-label case series, frequently, such studies enrolled patients from samples enriched for symptoms that could respond to stimulants (e.g. subjects with prominent sleepiness or fatigue) (Connolly & Thase, 2011), which may help in identifying a subpopulation that may benefit from these agents, but limits the generalizability of findings in patients lacking such clinical features. However, concerns are commonly raised (not necessarily specific to the therapeutic agent investigated) that clinical trial results may not be extendable to all bipolar-depressed patients, given the heterogeneity of BD and bipolar depression (Belmaker, 2007). Indeed, demonstration of the utility of stimulants in a subgroup of bipolar individuals with a particular clinical profile may provide clinicians with information needed to better craft personalized treatment (Belmaker, 2007; McIntyre, 2010). However, demonstration of utility in a subgroup of patients with certain clinical features in the absence of studies in patients without such features raises regulatory concerns regarding the potential for economically opportunistic ‘pseudospecificity’.

Moreover, in the interpretation of clinical results a possible influence of concomitant medications (e.g. mood stabilizers) needs to be taken into account across
different studies. This might somehow explain part of the discrepancy observed in some studies, such as the controlled trials of modafinil and armodafinil, along with a possible influence resulting from a different sample nature (BDI vs. BDII).

Another critical issue is safety/tolerability. Reviewed studies have, in general, reported favourable somatic tolerability and overall low rates of switch/mood destabilization with adjunctive stimulants in bipolar depression. This may have been due to the concomitant presence of antimanic agents in patients’ therapeutic regimens. However, reports have raised specific concerns about the possibility of mania being viewed in the reviewed studies which, although conducted openly, entailed observation periods of several months or years (Carlson et al. 2004; Lydon & El-Mallakh, 2006, Parker & Brotchie, 2010). It may be that the findings of published reports were confounded by the exclusion of patients at high risk of abusing stimulants.

With respect to induction of medical side-effects, the reviewed evidence reported that the majority of the patients lacked such adverse events. Controlled trials for modafinil and armodafinil did not find any specific significant difference vs. placebo with respect to blood pressure, heart rate or weight (Frye et al. 2007) as well as laboratory values, ECG parameters and physical examination findings (Calabrese et al. 2010). In addition, the widespread reported use of stimulants in depressive disorders associated with medical conditions (Lazarus et al. 1992; Masand et al. 1991; Rosenberg et al. 1991; Rothenhäusler et al. 2000; Roy & Bernier, 1999; Rozans et al. 2002; Thomas & Lipsky, 2000; White et al. 1992; Woods et al. 1986) as well as in the elderly (Katon & Raskind, 1980; Wallace et al. 1995) should somewhat mitigate somatic safety/tolerability concerns of these agents, which have been historically considered relatively medically safe in light of their low drug-interaction potential as well as presence of few absolute medical contraindications (Markowitz et al. 1999).

Other arguments of clinical interest for the use of stimulants in selected subgroups of adult bipolar depressed patients are related to the potential for cognitive benefits in view of their utility in ADHD and mechanisms of action. It has been documented, in fact, that these compounds – although having some variability in mechanisms of actions – can improve memory, attention and executive functions not only in selected populations of psychiatric patients with schizophrenia or ADHD (Morein-Zamir et al. 2007; Turner et al. 2004a,b), but also in healthy individuals (Baranski et al. 2004; Repantis et al. 2010; Turner et al. 2004a,b). Given the well-established cognitive impairment in BD (particularly during the depressive phase) as well as the substantial lack of therapies offering cognitive benefits, preliminary findings suggesting some potential value for adjunctive stimulants (Goldberg & Chengappa, 2009) should encourage further investigation in this field, as well as in the area of cognitive endophenotypes (Bora et al. 2009; Hayden & Nurnberger, 2006).

Speed of onset of action is another issue of great clinical interest for therapies used in BD (Candy et al. 2008; Nguyen & Tampi 2005; Satel & Nelson, 1989;
Tohen et al. (2000) and the majority of reviewed data found early (within the first 2 wk) onset improvement of target symptoms with stimulant augmentation, highlighting the need for further research in this area.

The safety/tolerability profiles of stimulants in adult bipolar depression need to be considered in view of those of other treatment options. From the perspective of somatic safety/tolerability, it could be argued that stimulants (which do not entail sedation, fatigue, weight gain or metabolic problems) are comparable to antidepressants and lamotrigine, and superior to lithium, valproate, carbamazepine, and antipsychotics (Ketter & Wang, 2010a, b). However, it is possible that the psychiatric safety/tolerability risks of stimulants – such as mood switching, cycle acceleration, psychosis, and abuse – are sufficient to preclude their use at least in some patients, such as those with histories of mood switching, rapid cycling, or psychosis.

Finally, clinical issues definitely deserving preliminary investigation are related to potential discontinuation effects of adjunctive stimulants in BD and bipolar depression as well as cost-benefit analysis and economic feasibility assessment, particularly for expensive proprietary agents.

After having reviewed the evidence on the adjunctive use of stimulants in BD and bipolar depression, caution for endorsing their use is still recommended, even though reconsideration of their overall potential usefulness as a class in specific subgroups of patients is probably indicated as a potential novel approach. Several lines of evidence suggest the need to reconsider the tendency to generally avoid stimulants in bipolar patients, including studies showing good tolerability of stimulants in ADHD comorbid bipolar patients, and stabilized bipolar patients as well as case reports even showing an acute antimanic effect of stimulants (Hensch et al. 2010). As with benzodiazepines in anxiety disorders (Dell’Osso & Lader, in press) and antidepressants in BD (Amsterdam & Shults, 2010a, b; Grunze, 2008; McIntyre, 2010), absoluetsit prohibitions ought to be avoided. It is likely that for carefully selected patients (i.e. with specific target symptoms and no previous history of treatment-induced switch, rapid cycling, psychosis, or substance abuse who are already taking antimanic agents) stimulants could offer a benefit/risk ratio favouring their judicious use.

Conclusions

Despite several reports suggesting the possible efficacy and safety/tolerability of adjunctive stimulants in adult bipolar depression, evidence from RCTs still remains limited and restricted to modafinil and armodafinil. Taken as a whole, however, the available evidence may suggest that cautious use of adjunctive stimulants in well-characterized subgroups of bipolar subjects (e.g. those with apathy, psychomotor retardation, fatigue and cognitive impairment, without history of treatment-induced switch, rapid cycling, psychosis, or substance abuse and who are already taking antimanic agents) may be a reasonable option compared to other available treatments.

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Statement of Interest

None.

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