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Assessing the Roles of Stimulants/Stimulant-like Drugs and Dopamine-agonists in the Treatment of Bipolar Depression

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Abstract Bipolar depression is considered the most difficult-to-treat phase of bipolar disorder, in relation to its pervasiveness and efficacy and/or tolerability limitations of available treatments. Indeed, most mood stabilizers and atypical antipsychotics are not as effective in ameliorating depressive compared with manic symptoms, and entail substantial tolerability limitations. However, the use of antidepressants is highly controversial, as their efficacy appears less robust in bipolar compared with unipolar depression. In addition, antidepressants, in spite of generally having adequate somatic tolerability, in BD may be associated with a higher risk of manic/hypomanic switch, suicidality and rapid cycling. Among alternative pharmacological strategies, compounds with stimulant and pro-dopaminergic effects, such as methylphenidate, modafinil, armodafinil and pramipexole, have showed potential antidepressant activity, even though their use in clinical practice has been limited by the paucity of controlled evidence. This article seeks to review available evidence about the use of the aforementioned compounds in the treatment of bipolar depression. Findings from reviewed studies suggested that pro-dopaminergic compounds, such as pramipexole and stimulants/stimulant-like agents, deserve consideration as adjunctive therapies in bipolar depressed patients, at least in some subgroups of patients. Nevertheless, caution regarding their use is recommended as further clinical trials with larger samples and longer follow-up periods are necessary to clarify the roles of these medications in bipolar depression.

Keywords Bipolar depression · Stimulants · Dopamine agonists · Pramipexole · Methylphenidate · Modafinil · Armodafinil · Mood disorders · Psychiatry

Introduction

Over the course of bipolar disorder (BD), patients experience depressive more often than manic symptoms [1], and the persistence of subsyndromal depressive symptoms during euthymia can increase the risk of relapse [2]. Over the last decade, in spite of the advent of new treatment options, the management of bipolar depression still represents a significant challenge, with limited treatments with proven efficacy. In fact, mood stabilizers and second-generation antipsychotics most often provide suboptimal relief of depressive symptoms, while entailing substantial somatic tolerability challenges. However, the use of antidepressants is highly controversial in bipolar depression in light of a reduced efficacy compared with unipolar depression, as well as in relation to significant risks of manic/hypomanic switch, rapid cycling and suicidality [3, 4, 5••, 6••]. Therefore, additional treatment strategies with evidence-based efficacy and safety/tolerability are under investigation in bipolar depression.

Currently available international treatment guidelines for bipolar depression indicate compounds targeting the dopaminergic system as useful augmentative strategies, in case of poor response. In particular, dopamine agonists (i.e., pramipexole) and stimulants/stimulant-like agents (i.e., methylphenidate, modafinil and armodafinil) have received increasing interest for their potential antidepressant effects in bipolar depression [7•]. Pramipexole and ropinirole are non-ergot dopamine agonists. Pramipexole is a full agonist of the dopamine D_3 receptor, with very low affinity for dopamine D_1 receptors and serotonin

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5-HT_{2A} and 5-HT_{2B} receptors. Dopamine D_3 receptors are diffusely distributed in the mesolimbic system [8], and appear involved in the pathogenesis of motoric and anhedonic symptoms. Pramipexole is approved for the treatment of Parkinson's disease and restless leg syndrome, and has shown antidepressant activity in patients with major depressive disorder [9], BD [10••, 11••] and depressed patients with Parkinson's disease [12–14].

Stimulants and stimulant-like drugs include several compounds (i.e., amphetamines, methylphenidate, modafinil and armodafinil), widely used to reduce fatigue, and to promote alertness and wakefulness. In spite of having a similar structure to amphetamine, methylphenidate is not a dopamine transport substrate, whereas it increases synaptic concentrations of norepinephrine, serotonin and dopamine [15]. Methylphenidate has been approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) and narcolepsy [16, 17], and, moreover, may be effective in the treatment of depression secondary to medical illness [18, 19]. Modafinil, (2-(benzhydrylsulfinyl) acetamide) is a stimulant-like agent, previously thought to primarily enhance dopaminergic and noradrenergic neurotransmission, secondarily enhance serotonergic, glutamatergic and histaminergic neurotransmission, and influence orexinergic neurotransmission [20]. Modafinil's current putative chief mechanism is low-affinity dopamine transporter inhibition [21], likely associated to its lower abuse liability [22]. Armodafinil is the R-enantiomer of racemic modafinil [23]. Both compounds have been approved by the United States Food and Drug Administration to promote wakefulness, in case of excessive sleepiness associated with narcolepsy, obstructive sleep apnea and shift-work sleep disorder [24]. However, the European Medicines Agency limited modafinil-approved use to narcolepsy [25], without having approved armodafinil yet.

Taken as a whole, dopamine-agonists and stimulants/stimulant-like drugs may be worth considering in bipolar depression in light of their ability to improve wakefulness and reduce fatigue and appetite. In fact, their use has been assessed in a variety of mood disorders (e.g., treatment-resistant depression, psychotic unipolar depression, depression associated with medical disorders, geriatric depression, etc.). In order to advance the understanding of the efficacy and safety of dopamine agonists and stimulants/stimulant-like drugs in bipolar depression, the present article aims to review current evidence in the field.

Methods

A systematic literature search was conducted in two steps, through MEDLINE and Cochrane Library databases. First, we identified articles published in English and focused on the use of stimulants/stimulant-like drugs and dopamine agonists in BD, using the following keywords: 'stimulant', 'psychostimulant', 'amphetamine', 'methylphenidate', 'modafinil', 'armodafinil', 'pramipexole' and 'dopamine agonists' variably combined with 'bipolar depression' and 'major depression'. A second search was conducted in the area of safety and tolerability, combining the keywords 'stimulant', 'psychostimulant', 'methylphenidate', 'modafinil', 'armodafinil', 'pramipexole' and 'dopamine agonists' with the terms 'tolerability', 'safety', 'side-effects', 'adverse events', 'discontinuation', 'drop out', 'mania', 'suicide' and 'cycle acceleration'. Additionally, reference lists of retrieved articles and proceeding of recent scientific meetings were searched manually for relevant publications.

The main purpose of the research was to specifically identify efficacy and safety/tolerability studies on the use of stimulants/stimulant-like drugs and dopamine-agonists in bipolar depression. Both controlled [e.g., meta-analyses and randomized clinical trials (RCTs)] and open observational studies were taken into consideration, whereas one- and two-patient case reports were not considered in order to enhance the focus of the review. Further information in the field was obtained reviewing current international guidelines on BD treatment and conference proceedings [5••, 6••, 26••, 27].

Results

Once studies not specifically focused on bipolar depression, as well as one-/two-patient case reports [28–31] were excluded, 18 reports met the inclusion criteria and were reviewed in detail. Nine reports dealt with pramipexole in adult bipolar depression, including two double-blind RCTs assessing depressive symptoms, one double-blind RCT targeting cognitive dysfunction and six open observational reports. Ten reports focused on the use of adjunctive stimulant-like agents and stimulants, including one double-blind RCT with armodafinil and one double-blind RCT with modafinil targeting depressive symptoms, four open observational modafinil studies and four open observational methylphenidate reports.

Herein, in chronological order, studies on pramipexole in bipolar depression are described, followed by reports on stimulants, listed by compound type (i.e., methylphenidate, modafinil and armodafinil).

Pramipexole

Published studies with adjunctive dopamine agonists in bipolar depression have been conducted mainly with pramipexole, with only one report partially focused on ropirinole. Table 1 briefly summarizes such studies.

In 2000, Sporn and colleagues [32], through a retrospective chart review, identified 32 treatment-resistant patients (20 with unipolar and 12 with bipolar depression), who received

Table 1 Published studies with adjunctive dopamine agonists (i.e., pramipexole) in bipolar depression

Reference	Study design	Sample characteristics	Study length	Group dosage	Outcome
Sporn et al. [32]	Open, retrospective chart review	32 treatment resistant patients (20 unipolar, 12 bipolar); 33.3 % had rapid cycling features	Mean 24.4 weeks	Adjunctive pramipexole (0.7 mg/day)	Pramipexole effective in 50 % of the sample (moderate-to-marked improvement on CGI-I). No discontinuation owing to lack of efficacy; 3 patients interrupted it owing to side-effects, mostly in the first 4 weeks of augmentation (tremor, sedation, irritability, dry mouth, nausea, tics, urinary hesitancy, decreased appetite, vivid dreams, insomnia, transient word-finding difficulty, dizziness). One case of transient hypomania observed while no patient reported psychosis or sleep attacks
Perugi et al. [34]	Open, retrospective chart review	18 treatment resistant, bipolar II depressed patients; 10 treated with pramipexole and 8 with ropinirole	Mean 17.6 weeks	Adjunctive pramipexole (0.75–1.5 mg/day), adjunctive ropinirole (1.5–5 mg/day)	Four patients (40 %) pramipexole responders (CGI ratings of 1 or 2). Overall favorable tolerability. Discontinuation of pramipexole in one patient because of nausea, irritability and agitation
Lattanzi et al. [35•]	Open, prospective, naturalistic study	37 patients (16 unipolar, 21 bipolar; 17 included in the analyses: 11 BD II and 6 BD I)	16 weeks	Adjunctive pramipexole (mean maximal dose 0.95 mg/day)	Significant decrease of MADRS and CGI-S scores, with no difference in response rate between BD I and II patients. The exact number of drop-outs in bipolar patients was not reported (within the original sample of 37 patients, 10 patients discontinued pramipexole for adverse events). Most common side-effects among completers: tremor and excitement/psychomotor retardation. Mixed tolerability along with a low rate of hypomanic switches
Goldberg et al. [10••]	Double-blind, randomized, placebo-controlled trial	22 treatment-resistant, bipolar depressed patients (15 BD I and 7 BD II), randomized to pramipexole (n=12) or placebo (n=10)	6 weeks	Adjunctive pramipexole, (2.5 mg/day) or placebo	67 % of responders on pramipexole vs 20 % of placebo patients. One patient on pramipexole dropped out prematurely because of manic switch. Discontinuation rates for any cause: 17 % for pramipexole vs 40 % for placebo. Discontinuation rates owing to lack of efficacy: 8 % for pramipexole vs 30 % for placebo. Nausea reported more frequently in patients with pramipexole vs placebo. Overall favorable tolerability
Zarate et al. [11••]	Double-blind, randomized, placebo-controlled trial	21 bipolar II depressed patients, with drug-resistance features, randomized to pramipexole (n=10) or placebo (n=11)	6 weeks	Adjunctive pramipexole, (0.375–3.000 mg/day) or placebo	Significant treatment effect reported. Treatment response (≥50 % decrease on MADRS) in 60 % of patients on pramipexole vs 9 % of those on placebo. Discontinuation rates for any cause: 10 % for pramipexole vs 9.1 % on placebo owing to lack of efficacy. One patient on pramipexole and 2 patients on placebo developed hypomanic symptoms. Tremor

Table 1 (continued)

Reference	Study design	Sample characteristics	Study length	Group dosage	Outcome
					more frequently observed in pramipexole patients. Overall favorable tolerability.
Cassano et al. [39•]	Open, long-term follow-up extension of previous study (Lattanzi et al. [35•], 2002)	11, treatment-resistant, bipolar, depressed patients (9 BD II, 2 BD I)	6–12 months (median 28 weeks)	Adjunctive pramipexole (0.75–1.5 mg/day)	Efficacy and safety data for bipolar subgroup were not separately reported. In the overall sample, 60.9 % of remitters. 2 bipolar patients developed hypomania and psychotic mania. Five adverse events reported (21.7 %): psychomotor agitation, ataxia, impulse dyscontrol, vomiting and hypomania. Overall mixed safety/tolerability and presumably positive effectiveness for pramipexole in the mid-/long-term follow-up
El-Mallakh et al. [40]	Retrospective chart review	16 bipolar depressed patients (13 BD I)	Average 6.7±-9 months	Adjunctive pramipexole (average dose 1.03±0.65 mg/day)	62.5 % of the sample benefited from treatment and 50 % of patients remained on pramipexole for >3 months. Severity of depressive symptoms dropped significantly within 4 weeks. Discontinuation of pramipexole in half of the patients, an average of 2 months after starting it. Common adverse events: insomnia (41.2 %), irritability (31.5 %), nausea (25 %), anxiety (25 %) and sleepiness, lethargy and dizziness (12.5 % of the sample each). No changes in mania ratings at any time. Overall favorable effectiveness data, mixed results in terms of safety/tolerability
Burdick et al. [41••]	Double-blind, randomized, placebo-controlled trial	50 bipolar patients (subtype not specified)	8 weeks	Adjunctive pramipexole (0.25–1.50 mg/day)	Significant overall effect for treatment on neurocognitive functioning in the euthymic subgroup of patients. Higher levels of baseline cognitive impairment associated with greater cognitive improvement after treatment. No discontinuation owing to adverse event. Restlessness was the only mentioned side-effect
Dell'Osso et al. [42•]	Retrospective chart review	39 bipolar patients (15 BD I, 17 BD II, 7 BP NOS)	Median 7 months	Adjunctive pramipexole (average dose 1.0±0.7 mg/day)	Somatic/psychiatric intolerability discontinuation rate for first 12 weeks was low (12.8 %) and statistically similar to adjunctive modafinil, but for entire 7 months increased to 38.5 %, significantly higher than for chronic (median 9 months) adjunctive modafinil

BD I bipolar disorder type I, *BD II* bipolar disorder type II, *BD NOS* bipolar disorder not otherwise specified, *MADRS* Montgomery-Åsberg Depression Rating Scale, *CGI-S* Clinical Global Impression Scale

adjunctive pramipexole. The Clinical Global Impression-Improvement (CGI-I) [33] scale was used to assess effectiveness, and response was defined as moderate-to-marked improvement. Pramipexole (mean dose: 0.7 mg/day, average duration: 24.4-weeks) was found to be effective in 50 % of bipolar patients and in 40 % of unipolar patients. No bipolar patient discontinued

pramipexole for lack of efficacy, even though three patients stopped it because of side effects (see Table 1). On the basis of such findings, pramipexole seemed to be adequately tolerated and potentially useful in the adjunctive treatment of drug-resistant bipolar depression.

In 2001, Perugi and co-workers [34] conducted a retrospective chart review of 18 bipolar II, treatment-resistant depressed patients treated with augmentative dopamine agonists, i.e., pramipexole (10 patients, 0.75–1.5 mg/day, mean duration of 17.6 weeks) and ropinirole (eight patients), added to ongoing treatment with antidepressants and mood stabilizers. Four patients (40 %) responded to pramipexole (CGI-S [33] ratings of 1 or 2), and two other patients showed mild response, considered as a CGI-S [33] score of 3. Pramipexole did not cause major side effects or negative interactions with concomitant psychotropic medications. One patient had to interrupt it owing to nausea, increased agitation and irritability.

In 2002, Lattanzi et al. [35•] conducted a 16-week naturalistic study assessing the efficacy and tolerability of adjunctive pramipexole (0.375–1.000 mg/day) in patients with drug-resistant depression. Thirty-seven patients (16 with unipolar and 21 with bipolar depression) were enrolled, and 31 patients were included in the analyses, while 19 patients completed the 16-week follow-up. Response was defined as a >50 % reduction on Montgomery-Åsberg Depression Rating Scale (MADRS) [36] total score or a CGI-S [33] score of 1 or 2. At the endpoint, 67.7 % were considered MADRS [36] responders and 74.2 % met CGI-S [33] response criteria, with no significant difference between BD I and BD II patients. Authors reported a relatively adequate tolerability: the most commonly observed side effects included excitement/psychomotor retardation and tremor. Hypomanic switch was observed in two cases.

In 2004, Goldberg and colleagues [10••] conducted a randomized, double-blind, placebo-controlled trial with 22 patients (15 BD I and 7 BD II), with inadequate response to at least two trials of antidepressants, associated with mood stabilizers. Patients were randomized to receive placebo (n=10) or pramipexole (n=12, 1–2.5 mg/day) for 6 weeks. At the endpoint, pramipexole was found to be superior to placebo in terms of efficacy, with 67 % of patients being responders (Hamilton Depression Rating Scale [37] score reduction >50 %) versus only 20 % of patients on placebo. Of note, discontinuation rate for any cause was 40 % for placebo versus 17 % for pramipexole. Although one patient on pramipexole dropped out for a manic switch, mean Young Mania Rating Scale [38] scores did not significantly differ between the two groups at the endpoint. Nausea was more commonly reported by patients on pramipexole compared with placebo.

In the same year, Zarate et al. [11••] conducted another randomized, double blind, placebo-controlled trial, assessing antidepressant effect of augmentative pramipexole, in 21 BD II patients experiencing a major depressive episode, despite pharmacological treatment with lithium or valproate. Patients were randomly assigned to adjunctive placebo (n=11) or pramipexole (n=10, 0.375–3 mg/day) for 6 weeks. All patients, except one taking placebo and one taking pramipexole, completed the study. Treatment response (>50 % decrease in MADRS [36] score), was observed in the 60 % of patients on pramipexole versus 9 % of those on placebo. Hypomania occurred in two patients on placebo and one on pramipexole. Tremor was the most common side effect in patients on pramipexole.

In 2004, Cassano and co-workers [39•] extended previous acute evaluation [35•] of pramipexole (0.75–1.5 mg/day) effects to mid-/long-term (6–12 months), after recruiting 23 adults with treatment-resistant depression, including 11 bipolar patients. At the endpoint, 60.9 % of patients experienced remission, while 21.7 % of the overall sample discontinued pramipexole owing to side effects (Table 1).

In 2010, El-Mallakh and co-workers [40] conducted a naturalistic retrospective chart review of 16 bipolar depressed patients, treated with augmentative pramipexole (average dose: 1 mg/day, mean duration: 6.7 months). Even though half of the sample did not remain on pramipexole for more than 3 months, 10 patients (62.5 %) showed an early and sustained improvement of depressive symptoms. However, adverse events were quite frequent with half of patients discontinuing pramipexole after an average of 2-months from the beginning of treatment because of poor tolerability (Table 1). No changes in mania ratings were reported for 36 months.

Recently, Burdick and co-workers [41••] assessed the effects of adjunctive pramipexole on cognition, by recruiting 50 stable outpatients in an 8-week, double-blind, randomized, placebo-controlled trial, including neurocognitive assessment at baseline and 8 weeks later. Forty-five patients (24 on placebo and 21 on pramipexole 0.25–1.5 mg/day) completed the study. At the endpoint, no relevant effect of treatment group on measures of depression and mania was observed, as well as no manic switch or discontinuation owing to adverse events. Among patients on pramipexole, the only mentioned side-effect was represented by restlessness. Even though primary cognitive analyses highlighted no significant cognitive benefit from pramipexole, secondary data identified a subgroup of patients who might more rapidly take advantages from cognitive enhancement strategies. In fact, the euthymic subgroup of patients showed a significant benefit on neurocognitive functioning. In addition, higher levels of cognitive deficits were associated with a more pronounced improvement in cognitive performances, after pramipexole treatment.

Even more recently, Dell'Osso et al. [42•] reported a naturalistic retrospective chart review of 39 bipolar disorder patients (most of whom were depressed), treated with

augmentative pramipexole (average dose: 1 mg/day, median duration: 7 months). The somatic/psychiatric intolerability discontinuation rate for adjunctive pramipexole for the first 12-weeks was low (12.8 %), and statistically similar to that seen with adjunctive modafinil, but for the entire 7 months increased to 38.5 %, which was significantly higher than for chronic (median 9 months) adjunctive modafinil. Pramipexole discontinuations were most often owing to intolerability (in 15 trials: five owing to nausea/vomiting, five owing to sedation, three owing to hypomania, one due to mania and one due to Internet poker addiction), followed by inefficacy (in 8 trials) and other reasons (in 3 trials). These data suggested that during longer-term treatment, adjunctive pramipexole compared with adjunctive modafinil may have poorer somatic/psychiatric tolerability.

Stimulant-like Agents and Stimulants

Clinical reports on the use of adjunctive methylphenidate, modafinil and armodafinil in bipolar depression are reported in Table 2.

Methylphenidate

In 2000, El-Mallakh [43] conducted a 12-week, open study with 14 mildly-depressed bipolar patients (including 10 with BD I), treated with 10–20 mg/day of methylphenidate in augmentation to mood stabilizers. Three patients withdrew from the trial because of increased agitation, anxiety and hypomania. Results showed a relevant improvement in both depressive and global psychiatric symptoms, supporting the use of methylphenidate as effective and relatively safe compound for the treatment of bipolar depression.

In 2004, Carlson and co-workers retrospectively reported on eight bipolar patients (five with BD I and three with BD II), treated with adjunctive stimulants (either methylphenidate or amphetamines) for a mean treatment duration of 18 months, in order to improve residual depression and medication-induced sedation [44]. A moderate clinical relief from target symptoms was associated with a consistent improvement of overall bipolar illness. The adequate tolerability and the absence of induced hypomania/mania, increased cycling or abuse supported the use of such compounds as a reasonable therapeutic option in patients with poor response to standard treatment.

In 2006, Lydon and El-Mallakh [45] conducted a retrospective chart review of 16 bipolar patients (nine with BD I), treated, on average, with methylphenidate (mean dose 16.3-mg/day) for 14 months. The compound was generally well tolerated, leading to a significant symptomatic relief. Several mild-to-moderate side effects were reported as well, responsible for drug discontinuation in two patients (Table 2).

In 2010, Parker and Brotchie [46] reported a case series of 50 patients with treatment-resistant depression (including 27 bipolar patients), treated with methylphenidate (20 mg/day) or dexamphetamine, either as monotherapy or augmentative agents. After a mean duration of 14 months of follow-up, 34 % of patients reported a significant improvement in target symptoms, 30 % some degree of improvement, while 36 % did not show any substantial difference. Switching was rare and limited to bipolar patients. Most adverse effects, reported by 18 % of the sample, were mild. Furthermore, positive response seemed to occur rapidly and loss of efficacy was unusual.

Modafinil and Armodafinil

In 2000, Menza and colleagues [47] reported a retrospective case series of seven depressed patients (including three bipolar patients), treated with augmentative modafinil (100–200 mg/day), in order to improve partial or non-response to antidepressants. The total sample fully or partially remitted, after 1–2 weeks of treatment, being residual tiredness or fatigue, observed prior to starting modafinil, particularly responsive to augmentation. Side effects were limited and caused no treatment discontinuation.

In 2004, Nasr [48] conducted a retrospective chart review in a general psychiatric practice of 78 depressed outpatients, including bipolar patients, receiving adjunctive modafinil to antidepressant treatment. Patients showed a significant improvement in wakefulness, fatigue and everyday functioning, along with overall favorable tolerability.

In 2006, Nasr and co-workers [49] performed a retrospective chart review of 191 patients with mood disorders (including 64 depressed bipolar patients), treated with adjunctive modafinil (250–290 mg/day), in order to assess switching, dose stability and abuse liability. Twenty-five patients received modafinil for <2 months, 39 for ≥2 months, 27 for ≥1 year and 16 for ≥2 years. Reasons leading to modafinil discontinuation included lack of efficacy, cost or adverse events, mostly sleep-related. No manic/hypomanic switch did not occur, supporting the overall safety and tolerability of modafinil over long-term treatment.

In 2007, Frye et al. [50••] conducted a 6-week, randomized, double-blind, placebo-controlled study with 85 bipolar depressed patients (including 64 BD I) inadequately responsive to mood stabilizers with or without antidepressants, and randomized to receive adjunctive modafinil or placebo. Improvement in outcome measures, particularly in relation to fatigue and energy, was significantly greater with modafinil (mean dose of 174.2 mg/day) compared with placebo. Headache was the most frequent side-effect, likely related to modafinil use, whereas no significant differences in treatment-induced mania, blood pressure, heart rate or weight gain were observed between the two groups. In conclusion, adjunctive modafinil

Table 2 Published studies with adjunctive methylphenidate, modafinil and armodafinil in bipolar depression

Reference	Design	Sample characteristic	Study lengths	Group dosage	Outcome
El-Mallakh [43]	Open, prospective study	14 mildly-depressed bipolar patients (10 BD I)	12 weeks	Adjunctive methylphenidate (10–20 mg/day)	44 % decrease in mean HAMD score. Discontinuation in 3 patients owing to anxiety, agitation, hypomania. Adjunctive methylphenidate to mood stabilizers effective and relatively safe
Menza et al. [47]	Open, retrospective case series of depressed (including bipolar) patients	Subgroup of 3 bipolar depressed patients	10–12 weeks	Adjunctive modafinil 100–200 mg/day	Full/partial remission in all patients, mostly in 1–2 weeks. Residual tiredness/fatigue particularly responsive. Side-effects minimal, no discontinuation. Adjunctive modafinil to antidepressants relatively safe
Carlson et al. [44]	Open, retrospective case series	8 depressed bipolar patients (5 BD I, 3 BD II)	Mean 18 months (range 11–24)	Adjunctive methylphenidate (10–20 mg/day) or amphetamines (unspecified dose)	Moderate clinical relief from target symptoms and consistent improvement of overall bipolar illness. No switch reported. Adjunctive methylphenidate/amphetamines to various medications effective and relatively safe
Nasr [48]	Open, retrospective chart review of mood (including bipolar) patients	Unspecified subgroup of depressed bipolar patients taking antidepressants	Unspecified	Adjunctive modafinil (unspecified doses)	Positive outcome, particularly in those with problematic sleepiness or fatigue. Adjunctive modafinil to antidepressants yielded benefit
Lydon and El-Mallakh [45]	Open, retrospective chart review	16 depressed bipolar patients (9 BD I, 7 BD II)	Mean 14 months (range 1–60)	Adjunctive methylphenidate (range 5–40 mg/day)	Mostly attenuation of depression. (Generally mild) adverse events in 62 % (irritability in 19 %, agitation in 13 %). No mania/hypomania, cycling exacerbation, nor substance abuse induction. Adjunctive methylphenidate to mood stabilizers and BZs effective in most patients and relatively safe
Nasr et al. [49]	Open, retrospective chart review of mood patients (including bipolar)	Subgroup of 64 depressed bipolar patients (31 BD I, 33 BD II) mostly taking other medication(s)	<2 months to 2 years	Adjunctive (most often) modafinil (250–290 mg/day)	Modafinil maintenance: <2 months in 25 bipolars (13 BD I); 2 months in 39 bipolar patients (18 BD I); 1 year in 27 bipolar patients (11 BD I); 2 years in 16 bipolar patients (7 BD I). No manic/hypomanic switch, tolerance/abuse. Modafinil dosage relatively stable
Frye et al. [50••]	Randomized, double blind, placebo-controlled, multisite acute study	85 depressed bipolar patients (64 BD I), despite treatment with mood stabilizers or antidepressant	6 weeks	Adjunctive modafinil (mean dose 174.2 mg/day, n=41) vs placebo (n=44)	Greater improvement in outcome measures, particularly in relation to fatigue and energy, compared to placebo. Similar incidence of treatment-emergent hypomania/mania, and blood pressure, heart rate or weight effects. Headache most common modafinil side-effect. Good tolerability of adjunctive modafinil to mood stabilizer or antidepressants
Calabrese et al. [51••]	Randomized, double blind, placebo-controlled multisite acute study	258 bipolar I depressed patients, despite treatment with lithium, olanzapine or valproic acid	8 weeks	Adjunctive armodafinil (mean dose 150 mg/day, n=128) vs placebo (n=129)	Greater improvement in depressive symptoms according to primary outcome measures (but not on secondary outcomes), compared with

Table 2 (continued)

Reference	Design	Sample characteristic	Study lengths	Group dosage	Outcome
					placebo. Similar incidence of medical and psychiatric adverse events (but more insomnia, restlessness, anxiety and hypomania). Good tolerability
Parker and Brotchie [46]	Open, prospective case series of 50 patients with depressive disorders (including bipolar)	27 depressed bipolar patients (5 BD I), despite (in most cases) psychotropic medications	Mean 57 weeks (range 6–250)	Adjunctive (mostly) methylphenidate (10–60 mg/day, modal 20 mg/day) or dextroamphetamine (few cases)	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. Mild side-effects, reported by 18 % of the sample. Switching rare and limited to bipolar patients. Adjunctive methylphenidate to other psychotropics variably effective and relatively safe
Dell'Osso et al. [42•]	Retrospective chart review	24 bipolar patients (12 BD I, 11 BD II, 1 BP NOS)	Median 9 months	Adjunctive modafinil (average dose 167±70 mg/day)	Somatic/psychiatric intolerability discontinuation rate for first 12 weeks was low (8.3 %) and statistically similar to adjunctive pramipexole, and for the entire 9 remained low (12.5 %), significantly lower than for chronic (median 7 months) adjunctive pramipexole

BD I bipolar disorder type I, *BD II* bipolar disorder type II, *BD NOS* bipolar disorder not otherwise specified, *HAMD* Hamilton Depression Rating Scale, *BZs* benzodiazepines

was found to be efficacious and well tolerated in patients with bipolar depression, without inducing mood destabilization.

In 2010, Calabrese and co-workers [51••], in an 8-week, multicenter, randomized, double-blind, placebo-controlled study, evaluated safety and efficacy of adjunctive armodafinil (mean dose 150 mg/day), in bipolar I depressed patients on mood stabilizers. A greater symptom improvement was observed in patients on armodafinil, according to primary outcome measures, whereas no differences were reported in secondary outcomes, including MADRS [36]. In terms of side effects, headache, diarrhoea and insomnia were the most frequently reported ones. No increased incidence or severity of suicidality, depression or mania, or changes in metabolic profile was observed.

Finally, Dell'Osso et al. [42•] recently reported a naturalistic retrospective chart review of 24 bipolar disorder patients (most of whom were depressed), treated with augmentative modafinil (average dose: 167 mg/day, median duration: 9 months). The somatic/psychiatric intolerability discontinuation rate for adjunctive modafinil for the first 12 weeks was low (8.4 %), and statistically similar to that seen with adjunctive pramipexole, and for the entire 9 months remained low (12.5 %), which was significantly lower than for chronic (median 7 months) adjunctive pramipexole. Modafinil discontinuations were most often due to inefficacy (in six trials), followed by intolerability (in three trials: one owing to non-serious rash and two owing to hypomania) and other reasons (in one trial). These data suggested that during longer-term treatment, adjunctive modafinil compared with adjunctive pramipexole may have better somatic/psychiatric tolerability.

Conclusion

The present review sought to summarize available evidence on the use of augmentative pramipexole and stimulants in the treatment of bipolar depression.

On the basis of double-blind and open studies, the short-term efficacy and tolerability/safety of augmentative pramipexole seem to be adequately supported by controlled data. However, even though open reports support the mid-/long-term effectiveness of the compound as well, other follow-up studies [35•, 39•, 40•, 42•] raise mid/long term safety and tolerability concerns.

With respect to the use of stimulants in bipolar depression, despite quite limited systematic evidence (no RCTs and four open reports), available data support their cautious use in at least some bipolar depressed patients, in particular when significant drowsiness or fatigue are present. In contrast, the use of the

stimulant-like agents modafinil and armodafinil is more robust, supported by three RCTs and four open reports. In contrast to pramipexole, modafinil may have better mid-/long-term safety and tolerability [42•].

Taking into account the quality and quantity of published studies to date, adjunctive pramipexole and stimulants/stimulant-like drugs cannot be, actually, included among well-established, evidence-based strategies for treatment of bipolar depressed patients who fail to respond to first-line interventions. Such a perspective is consistent with recommendations of recently published international guidelines for the treatment of BD [5••, 6••, 26••, 27].

With regard to pramipexole efficacy, Aiken [52] supported its efficacy in augmentation for treatment-resistant bipolar depression by reporting a large effect size (0.77–1.1) [52] on the basis of two previous, small RCTs [10••, 11••]. Subsequent reports seemed to be consistent with such assessment.

In terms of mechanism of action, it is well-established that dopaminergic enhancement may promote the action of antidepressants, particularly in patients complaining of lack of energy and motivation [53, 54]. Such effect may depend on a re-sensitization and potentiation of mesolimbic dopamine D_2/D_3 receptors, indicated as the final common pathway of the long-term use of antidepressants [55, 56]. Also neurotrophic, neuroprotective and antioxidant activity, shown by pramipexole in cell cultures [57–60] may, at least partially, account for its antidepressant properties, on the basis of preclinical investigation [61].

With respect to stimulant/stimulant-like drug efficacy, it needs to be taken into account that positive results of reviewed studies could depend on the recruitment of patients experiencing symptoms effectively treated by stimulants/stimulant-like drugs, such as sleepiness or fatigue [62]. Although the presence of such symptoms in studies may help, on one hand, to identify patients who may benefit from a more personalized treatment [63], on the other hand, the presence of such symptoms in studies could limit the generalizability of findings of such studies. Furthermore, the possible influence of concurrent medications (such as mood stabilizers) on clinical results, potentially leading to discrepancy observed in some studies, should be considered.

In terms of safety/tolerability, combined data from eight studies, up to 2004, indicated a discontinuation rate of 9 % among patients with mood disorders on pramipexole [52]. Nevertheless, such encouraging findings of positive short-term tolerability has been questioned by subsequent open follow-up reports, documenting higher drop-out rates with longer-term treatment, including the above-mentioned recent report showing a worse chronic tolerability of adjunctive pramipexole versus modafinil, as well as versus acute pramipexole tolerability in a sample of primarily depressed treatment-resistant bipolar disorder patients [42•].

In the short-term, favorable somatic tolerability and low risk of mood destabilization have been generally documented with both adjunctive pramipexole and stimulant/stimulant-like drugs. This may be related to the concomitant presence of anti-manic agents in patients' treatment and, with respect to pramipexole, to the use of lower dosage for a shorter duration compared with patients with Parkinson's disease [52, 64]. However, it is worth noting that evidence on the tolerability of dopamine agonists in the long-term treatment of bipolar patients is quite limited and further investigation may reveal higher rates of switch [11••] and psychiatric/somatic intolerability [42•].

Likewise, specific concerns about the possibility of mania induced by stimulants/stimulant-like drugs [65–67] may have been related to the absence of adequate concomitant anti-manic therapy [44] and further risks, including earlier onset and more severe course, have been reported for bipolar adolescents, with previous exposure to stimulants [68, 69]. However, low abuse potential has been reported for modafinil and armodafinil compared with stimulants [70]. Reviewed studies, moreover, reported low rates of misuse for methylphenidate, over several months or years of observation [44–46], even though such a result may be owing to the exclusion of patients at high risk of abuse. Certainly, it should be further investigated whether the above-mentioned risks (mood switching, cycle acceleration, psychosis and abuse) should preclude use of pramipexole and/or stimulants/stimulant-like drugs in patients with history of mood switching, rapid cycling or psychosis.

A gradual pramipexole titration has been recommended in order to limit the occurrence of side effects, whereas significant drug-interactions [71], weight gain potential or sexual side effects have not been reported in clinical studies. Similarly, acute controlled trials for modafinil and armodafinil have not documented any significant difference versus placebo with regard to side effects [50••, 51••]. In fact, the safety of stimulants/stimulant-like drugs, also supported by their low drug-interaction potential and limited absolute medical contraindication [72], seems to be confirmed by their widespread use in depressive disorders, associated with medical conditions [73–75] and in the elderly [76].

In the assessment of adjunctive pramipexole and stimulants/stimulant-like drugs in bipolar depression, another meaningful issue to consider is their potential for cognitive benefit, given that neurocognitive impairment represents one of the most characteristic features of depressive phases [77]. The only RCT targeting cognition with pramipexole conducted to date [41••] showed mixed results, with the low affinity of pramipexole for dopamine D_1 receptors, traditionally involved in working memory circuits [78] possibly accounting for the lack of advantage in cognitive performance [52]. In addition, even though stimulant/stimulant-like treatment can yield significant improvements in memory, attention and executive functions, in selected subgroups

of patients with schizophrenia, ADHD [79] or healthy patients [80], further investigations in large clinical populations of patients with affective disorders are needed.

Taken as a whole, findings from reviewed studies seem to suggest that pro-dopaminergic compounds, such as pramipexole and stimulants/stimulant-like agents, deserve consideration as adjunctive therapeutic agents in bipolar depressed patients, at least in some subgroups of patients. Nevertheless, caution for supporting their use is still recommended and further clinical trials with larger samples and longer follow-up periods are necessary to extend available evidence and better clarify the real role of these medications in bipolar depression.

Compliance with Ethics Guidelines

Conflict of Interest Bernardo Dell'Osso has served on speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Eli Lilly, Pfizer, GlaxoSmithKline, Lundbeck, Cyberonics and Italfarmaco.

Terence A. Ketter has received grant/research support from AstraZeneca, Cephalon, Eli Lilly and Company, Pfizer and Sunovion Pharmaceuticals; has served as a consultant for Allergan, Avanir Pharmaceuticals, Bristol-Myers Squibb, Cephalon, Forest Pharmaceuticals, Janssen Pharmaceutica Products, Merck & Co., Sunovion Pharmaceuticals and Teva Pharmaceuticals; has received lecture honoraria from Abbott Laboratories, AstraZeneca, GlaxoSmithKline and Otsuka Pharmaceuticals; and has received royalties from American Psychiatric Publishing. In addition, Dr. Ketter's spouse is an employee of and holds stock in Janssen Pharmaceuticals.

Laura Cremaschi and Gregorio Spagnolin declare that they have no conflict of interest.

A. Carlo Altamura has served as a consultant for Roche, Merck, AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lundbeck, Sanofi, Eli Lilly and Pfizer.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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