Augmentative dopaminergic interventions for treatment-resistant bipolar depression: a focus on dopamine agonists and stimulants

Interventi farmacologici dopaminergici in associazione per il trattamento della depressione bipolare farmaco-resistente: focus su dopamino-agonisti e stimolanti

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Summary

Objectives

Bipolar depression is the most difficult-to-treat phase of bipolar disorder, in relation to its significant disruption of every-day life functioning and high suicidality risk. Despite the availability of several treatment options, the management of bipolar depression is still particularly challenging, with limited approved therapies. Mood stabilizers and second-generation antipsychotics may not be as effective in ameliorating depressive compared to mood elevation symptoms, and entail substantial somatic tolerability limitations. In contrast, antidepressants are widely used off-label in bipolar depression (perhaps in part due to their better somatic tolerability), but such use is controversial, as they may be associated with a higher risk of manic/hypomanic switch and rapid cycling. Among pharmacological augmentation strategies, compounds with pro-dopaminergic activity such as stimulants and stimulant-like agents (e.g., methylphenidate, modafinil and armodafinil) and dopamine agonists (e.g., pramipexole and ropinirole), have shown potential antidepressant effects, even though their use in clinical practice is still limited by the paucity of systematic evidence of efficacy and safety. The present review sought to summarize available evidence about such augmentative dopaminergic interventions for treatment-resistant bipolar depression, considering results of recent randomized controlled trials, as well as open studies, systematic reviews and guidelines indications.

Methods

A systematic review of the literature was conducted. We first identified articles published in English and focused on the use of stimulants and dopamine agonists in bipolar disorder, using the keywords 'stimulant', 'psychostimulant', 'amphetamine', 'methylphenidate', 'modafinil', 'armodafinil', 'pramipexole', 'ropinirole', 'dopamine agonists', variably combined with 'bipolar disorder', 'bipolar depression', 'major depression' and 'treatment-resistant depression'. A second search was conducted about safety and tolerability, combining the keywords 'stimulant', 'psychostimulant', 'methylphenidate', 'modafinil', 'armodafinil', 'pramipexole', 'ropinirole', 'dopamine agonists' with 'tolerability', 'safety', 'side-effects', 'adverse events', 'discontinuation', 'drop out', 'mania', 'suicide', 'cycle acceleration'. Additionally, reference lists of retrieved articles and proceeding of recent scientific meetings were manually searched for relevant publications.

Results

21 reports met the inclusion criteria and were herein reviewed in detail. 11 reports described of pramipexole in adult bipolar depression, including 2 double-blind RCTs targeting depressive symptoms, 1 double-blind RCT targeting cognitive dysfunction, and 8 open reports, and one report on the use of ropinirole in bipolar depression was identified. 10 reports focused on the use of adjunctive stimulant-like agents and stimulants, including 1 double-blind armodafinil RCTs, and 1 double-blind modafinil RCT targeting depressive symptoms, 4 open uncontrolled modafinil studies, and 4 open uncontrolled methylphenidate studies. With respect to the use of stimulants in adult bipolar depression, although systematic evidence is quite limited, available data seems to support their use in at least some bipolar depressed patients, especially when they show significant drowsiness or fatigue. In contrast, the use of the stimulant-like agents modafinil and armodafinil seems to be more robust, supported by 2 RCTs as well as 4 open reports.

Conclusions

Taken as a whole, findings from reviewed studies seem to suggest that pro-dopaminergic compounds agonists, such as pramipexole and stimulant-like agents, deserve consideration as potential adjunct therapeutic agents in adult bipolar depression, at least in specific subgroups of patients, although caution for supporting their use is still recommended. Future research and clinical trials on larger samples and greater follow-up periods are encouraged to extend available evidence and better clarify the potential role of these medications in bipolar depression.

Key words

Bipolar disorder • Bipolar depression • Dopamine agonists • Stimulants • Pramipexole • Ropinirole • Methylphenidate • Modafinil • Armodafinil

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Introduction

Bipolar disorder (BD) is a lifelong psychiatric illness that is responsible for severe impact on quality of life and causes substantial psychosocial and functional burden [1]. Over the course of the illness, bipolar patients experience depression more often than mania [2] and the persistence of subsyndromal depressive symptoms, during euthymia, can increase the risk of relapse [3].

In spite of the advent of several alternative and adjunctive treatment options during last decades, the management of bipolar depression remains significantly challenging, with a limited number of established treatments. In fact, mood stabilizers and atypical antipsychotics may provide suboptimal relief of depressive symptoms while entailing substantial somatic tolerability challenges. Furthermore, even if antidepressants have superior somatic tolerability compared to mood stabilizers and atypical antipsychotics, they are substantially limited in terms of their controversial efficacy in bipolar compared to unipolar depression. In addition, antidepressants in bipolar patients have been associated with substantial psychiatric tolerability challenges, including risks of manic/hypomanic switch, rapid cycling and suicidality [4-7].

For these reasons, additional treatment strategies with evidence-based efficacy and safety/tolerability support are under investigation in bipolar depression. In this perspective, according to recent international treatment guidelines for BD and bipolar depression, adjunctive treatment options targeting the dopaminergic system appear to be an attractive strategy in case of poor response. Among such strategies, dopamine agonists (i.e. pramipexole and ropinirole) and stimulants and stimulant-like agents (i.e. methylphenidate, modafinil and armodafinil) have gained growing interest for their potential antidepressant effects in bipolar depression.

Pramipexole and ropinirole are non-ergot dopamine agonists. Pramipexole is a full agonist of the D3 subtype receptors, with very low affinity for D1 receptors and serotoninergic 5HT-2A and 2B receptors. Ropinirole acts as a D2, D3 and D4 dopamine receptor agonist, showing highest affinity for D2 [8 9]. Pramipexole and ropinirole are approved for the treatment of Parkinson's disease and restless leg syndrome. D3 receptors are diffusely distributed in the mesolimbic system [10] and appear to be involved in the pathogenesis of motoric and anhedonic symptoms. In contrast to the ergot dopamine agonists, such as bromocriptine and pergolide, typically used for the treatment of Parkinson disease, pramipexole seems to fully activate dopamine receptors. After first evidence of its antidepressant effect in animal models [11-13], pramipexole has shown similar activity in different trials involving patients with major depressive disorder [14], BD [15 16] and depressed patients with Parkinson's disease [17-19].

Stimulants include several compounds with various chemical structures and biological functions (i.e. amphetamines, methylphenidate, modafinil and armodafinil), which are widely used to reduce fatigue and promote alertness and wakefulness. Although having a similar structure to amphetamine, methylphenidate is not a dopamine transport substrate, whereas it increases the synaptic concentration of norepinephrine, serotonin and dopamine [20]. Actually, it is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy [21 22], although it may be effective in the treatment of depression secondary to medical illness [23 24]. 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 [25]. Modafinil's current putative chief mechanism is low-affinity dopamine transporter inhibition [26]. Modafinil's low affinity for the dopamine transporter compared to other agents could contribute to its lower abuse potential [27]. Armodafinil is the R-enantiomer of racemic modafinil. Both have been approved by the United States Food and Drug Administration (US FDA) to promote wakefulness, in case of excessive sleepiness associated with narcolepsy, obstructive sleep apnoea and shift-work sleep disorder [28]. The European Medicines Agency (EMEA) limited the approved use of modafinil to narcolepsy [29] and has not approved armodafinil. Taken as a whole, stimulants and stimulant-like agents medications may be worth considering, since their use has been associated with significant improvement in wakefulness, attenuation of fatigue and appetite. In addition, the use of stimulants 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.). Moreover, these agents tend to be associated with somatic tolerability challenges comparable to antidepressants and less problematic than mood stabilizers or atypical antipsychotics. Results from clinical reports partially support their use in specific treatment-resistant depressive disorders, even though they highlight the possible risk of treatment-induced mood destabilization [30-32], particularly in bipolar depression [33]. In fact, although they are likely to enhance cognitive function, their use may be limited by the potential switch to manic and hypomanic phases.

In order to better understand the efficacy and safety of dopamine agonists and stimulants in treatment-resistant bipolar depression, we conducted the present study, aimed to review current evidence in the field.

Methods

A systematic search of the literature, using MEDLINE and Cochrane Library, was conducted in two steps. First, we identified articles published in English and focused on the use of stimulants and dopamine agonists in BD, using the following keywords: "stimulant", "psychostimulant", "amphetamine", "methylphenidate", "modafinil", "armodafinil", "pramipexole", "ropinirole", "dopamine agonists", variably combined with "bipolar disorder", "bipolar depression", "major depression" and "treatment-resistant depression".

A second search was conducted in the area of safety and tolerability, combining the keywords "stimulant", "psychostimulant", "methylphenidate", "modafinil", "armodafinil", "pramipexole", "ropinirole", "dopamine agonists" with the terms "tolerability", "safety", "side-effects", "adverse events", "discontinuation", "drop out", "mania", "suicide", "cycle acceleration". Additionally, reference lists of retrieved articles and proceeding of recent scientific meetings were manually searched for relevant publications.

Our main purpose was to specifically identify efficacy and safety studies on the adjunctive use of stimulants and dopamine-agonists in bipolar depression. Meta-analyses, randomized clinical trials (RCTs), naturalistic and retrospective studies, case series, case reports and clinical reviews were taken into consideration. On the other hand, single case-reports were not considered, in order to enhance the focus of the review. Further information regarding the use of these compounds in bipolar depression was obtained reviewing current international guidelines on BD treatment and conference proceedings [6 34 7 35].

Results

After excluding studies not specifically focusing on bipolar depression, 21 reports met the inclusion criteria and were reviewed in detail. Eleven reports described pramipexole in adult bipolar depression, including 2 double-blind RCTs targeting depressive symptoms, 1 double-blind RCT targeting cognitive dysfunction and 8 open reports. Only one report on the use of ropinirole in bipolar depression was identified. Ten reports focused on the use of adjunctive stimulant-like agents and stimulants, including 1 double-blind armodafinil RCTs, 1 double-blind modafinil RCT targeting depressive symptoms, 4 open uncontrolled modafinil studies, and 4 open uncontrolled methylphenidate studies.

We first review studies on dopamine agonists (i.e. pramipexole, ropinirole) in bipolar depression, followed by reports on stimulants and stimulant-like agents, listed by compound type (i.e. methylphenidate, modafinil and armodafinil) and in chronological order.

Dopamine agonists

Published studies with adjunctive dopamine agonists (i.e. pramipexole and ropinirole) in bipolar depressed patients are summarized in Table I.

Pramipexole

In 1999, Goldberg and co-workers first described a positive effect for augmentation therapy of pramipexole in two patients affected by treatment-resistant BD I depression [36]. The first patient had a 23-year history of BD type I, with multiple hospitalizations and a relevant family history of bipolar illness. On the basis of clinical judgement, marked improvement in mood and overall functioning was reported within one week of treatment with pramipexole started at a dose of 0.25 mg/day and then increased to 0.75 mg/day. Euthymia persisted and no side effects were observed at 8-week follow up. The second patient, affected by BD type I with comorbid alcohol abuse (in remission) was on pharmacological treatment with olanzapine, topiramate and lamotrigine, which seemed to control mania and cycling, until a severe depressive episode occurred. He was then started on 1 mg/day of pramipexole and, within 6 weeks, the depressive phase remitted. Improvement continued over the 6-month follow-up. The drug was well tolerated in this case, except for transient dose-related nausea.

In 2000, Sporn and colleagues evaluated the effectiveness and safety of pramipexole as adjunctive medication in refractory unipolar and bipolar depression [37]. Through retrospective chart review, they identified 20 patients with unipolar depression and 12 with bipolar depression who received pramipexole. In the bipolar depressed group, 4 patients were rapid cyclers and the 78% of the entire sample was treated with antidepressants. The Clinical Global Impression-Improvement (CGI-I) [38] scale was used to assess effectiveness, being response defined as moderate to marked improvement at the CGI-I. Pramipexole, administered at a mean dose of 0.7 mg/day for an average duration of 24.4 weeks, was found to be effective in 50% of patients with bipolar depression (6/12) and in 40% of patients with unipolar depression (8/20). In the bipolar group, there were no discontinuations of pramipexole for lack of efficacy, even though 3 subjects stopped because of side effects, whereas 8 unipolar patients dropped out for lack of efficacy and only 1 subject for side effects. These included: tremor, sedation, irritability, dry mouth, nausea, tics, urinary hesitancy, decreased appetite, vivid dreams, insomnia, transient word-finding difficulty and dizziness. On the basis of such findings, pramipexole seemed to be adequately tolerated and potentially useful in the adjunctive treatment of drug-resistant bipolar and unipolar depression.

A retrospective chart review of 18 bipolar II, treatment-

TABLE I.
Published studies with adjunctive dopamine agonists (i.e. pramipexole, ropinirole) in bipolar depression.
Studi pubblicati riguardo l'utilizzo di dopamino-agonisti (pramipexolo, ropinirolo) in associazione nella depressione bipolare.

Citation	Study design	Sample characteristics	Study length
Goldberg et al. (1999)	Open, case-series	2 bipolar I patients with treatment-resistant depression	8 weeks and 6 months, respectively
Sporn et al. (2000)	Open, retrospective chart review	32 subjects, including 12 treatment refractory, bipolar patients (subtype not specified); 33.3% had rapid cycling features	Mean 24.4 weeks
Perugi et al. (2001)	Open, retrospective chart review	18 treatment resistant, bipolar II depressed subjects; 10 treated with pramipexole and 8 with ropinirole	Mean 17.6 weeks (range 4-34)
Lattanzi et al. (2002)	Open, prospective, naturalistic study	37 subjects, including 21 bipolar subjects (17 included in the analyses: 11 BD II and 6 BD I)	16 weeks
Goldberg et al. (2004)	Double-blind, randomized, placebo controlled trial	22 treatment-resistant, bipolar depressed patients (15 BD I and 7 BD II), with baseline HAMD score > 18 and YMRS score < 12, randomized to pramipexole (n = 12) or placebo (n = 10)	6 weeks
Zarate et al. (2004)	Double-blind, randomized, placebo controlled trial	21 bipolar II depressed patients, with drug-resistance features and baseline MADRS score > 20, randomized to pramipexole (n = 10) or placebo (n = 11)	6 weeks
Cassano et al. (2004)	Open, long-term follow-up extension of previous study (Lattanzi et al., 2002)	11 bipolar, treatment-resistant, subjects (9 BD II and 2 BD I)	6 to 12 months, median 28 weeks
Gupta et al. (2006)	Retrospective case series	2 bipolar I, treatment-resistant depressed, subjects	8 to 18 weeks
Akdeniz et al. (2009)	Retrospective case series	2 bipolar, treatment-depressed, subjects (1 BD I)	6 to 8 months
El Mallakh et al. (2010)	Retrospective chart review	16 bipolar patients (13 BD I)	Average 6.7 ± 9 months
Burdick et al. (2012)	Double-blind, randomized, placebo controlled trial	50 bipolar patients (subtype not specified)	8 weeks

BDI: Bipolar disorder type I; SD: Standard deviation; HAMD: Hamilton Depression Rating Scale; ADHD: Attention Deficit Hyperactivity Disorder; CGI-BP: Clinical Global Impression Scale for Bipolar Disorder; BZs: Benzodiazepines.

	Group dosage	Outcome
	Adjunctive pramipexole (0.75 and 1 mg/day)	Marked improvement in both cases, though standardized outcome measures were not used. Overall well tolerated, transient dose-related nausea in one patient
	Adjunctive pramipexole (0.7 mg/day)	Pramipexole effective in 50% of the sample, based on moderate to marked improvement on the CGI. No patient in the bipolar group stopped pramipexole due to lack of efficacy; 3 subjects interrupted pramipexole due 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
	Adjunctive pramipexole (0.75 -1.5 mg/day), adjunctive ropinirole (1.5-5 mg/day)	Four patients (40%) were found to be pramipexole responders, based on CGI ratings of 1 or 2. Four patients (50%) were found to be ropinirole responders. Overall favourable tolerability. One patient had to stop pramipexole because of nausea, irritability and agitation
	Adjunctive pramipexole (mean maximal dose 0.95 mg/day)	Significant decrease of MADRS and CGI-S scores observed; no difference in response rate between BD I (83.3%) and BD II (63.6%) subjects. The exact number of drop-outs in bipolar patients was not reported (within the original sample of 37 patients, 10 subjects discontinued pramipexole for adverse events). Most common side effects among completers were tremor and excitement/psychomotor retardation. Mixed tolerability along with a low rate of hypomanic switches
	Adjunctive pramipexole, (dose range 1-2.5 mg/day) or placebo	67% of responders on pramipexole (≥ 50% reduction on the HAMD) *vs*. 20% of placebo patients. Mean HAMD change from baseline: 48% for pramipexole *vs*. 21.4% for placebo. 1 patient on pramipexole dropped out prematurely because of manic switch. Discontinuation rates for any cause were 17% for pramipexole (2/12) *vs*. 40% for placebo (4/10). Discontinuation rates due to lack of efficacy were 8% for pramipexole (1/12) *vs*. 30% for placebo (3/10). Nausea was reported more frequently in patients with pramipexole compared to placebo. Overall favourable tolerability
	Adjunctive pramipexole, (dose range 1-3 mg/day) or placebo	Significant treatment effect reported. Treatment response (≥ 50% decrease on the MADRS) occurred in 60% of patients on pramipexole *vs*. 9% of those on placebo. Discontinuation rates for any cause were 10% for pramipexole (1/10) *vs*. 9.1% on placebo (1/11) and were due to lack of efficacy. One patient on pramipexole and 2 patients on placebo developed hypomanic symptoms (YMRS ≥ 12). Most of the reported side effects were similar for the treatment groups, except tremor, more frequently observed in pramipexole patients. Overall favourable tolerability
	Adjunctive pramipexole (dose range 0.75-1.5 mg/day)	Efficacy and safety data for bipolar sub-group were not separately reported. In the overall sample, 60.9% were remitters. 2 bipolar subjects developed hypomania and psychotic mania. In the overall sample, 5 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
	Adjunctive pramipexole (dose range 0.75-1.5 mg/day)	Significant improvement in HAMD total scores, from the second week of augmentation onward. No significant side effects noted
	Adjunctive pramipexole (dose range 0.5-0.75 mg/day)	Assessment, based exclusively on clinical impressions, showed a decrease in severity and duration of depressive episodes in the mid-term observation. Sleep and gastrointestinal side-effects were reported exclusively in the short-term, whereas no serious adverse event was observed during the maintenance treatment
	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. The severity of depressive symptoms dropped significantly within 4 weeks. CGI and GAF scores showed a consistent improvement. Half of the patients stopped pramipexole an average of 2 months after starting it. Common adverse events were: insomnia (41.2%), irritability (31.5%), nausea (25%), anxiety (25%) and sleepiness, lethargy and dizziness (12.5% of the sample each). Six patients (37.5%) stopped pramipexole due to adverse effects. Manic symptoms did not worsen at any time during study. Overall favourable effectiveness data, mixed results in terms of safety and tolerability
	Adjunctive pramipexole (target dose 1.5 mg/day)	A significant overall effect for treatment on neurocognitive functioning was found in the euthymic subgroup of patients. Higher levels of baseline cognitive impairment were associated with greater cognitive improvement after pramipexole treatment. Pramipexole did not cause any discontinuation due to adverse event

resistant depressed patients was conduced by Perugi and colleagues in 2001 [39]. These subjects were treated with augmentative dopamine agonists, i.e. pramipexole (10 subjects) and ropinirole (8 subjects), added to on-going treatment with antidepressants and mood stabilizers. Patients treated with pramipexole received a mean dose of 0.75-1.5 mg/day for a mean duration of 17.6 weeks. Four patients (40%) were found to be pramipexole responders (Clinical Global Impression Scale CGI-S[38] ratings of 1 or 2), and two other patients showed mild response, considered as a CGI-S score of 3. Pramipexole did not cause major side effects, being well tolerated, with no negative interactions with concomitant psychotropic medications. One patient had to interrupt it due to nausea, increased agitation and irritability.

In 2002, Lattanzi and co-workers conducted a 16-week naturalistic study, aimed to assess the efficacy and tolerability of adjunctive pramipexole in subjects with drug-resistant depression [40]. Thirty-seven patients were enrolled: 16 with unipolar depression and 21 with bipolar depression; 31 subjects were included in the analyses and 19 patients completed the 16-week follow-up. Pramipexole was added to antidepressant treatment (SSRIs or TCAs) and was initiated at a dose of 0.375 mg/day, increased to a maximum of 1 mg/day in the third week. Patients were defined responders if they had a > 50%-reduction on Montgomery-Åsberg Depression Rating Scale (MADRS) [41] total score or a CGI-S score of 1 or 2. At the endpoint, 67.7% were considered MADRS responders and 74.2% met response criteria on the basis of CGI-S. BD I patients did not significantly differ from BD II ones in terms of response rate. The authors reported relatively adequate tolerability: most commonly observed side effects included excitement/psychomotor retardation and tremor. Two cases of hypomanic switch were reported.

In 2004, Goldberg and colleagues conducted a randomized, double-blind, placebo controlled trial, recruiting 22 patients: 15 affected by BD I and 7 by BD II, with a baseline Hamilton Depression Rating Scale (HAMD) [42] score > 18 and Young Mania Rating Scale (YMRS) [43] score < 12 [15]. All patients had an inadequate response to at least two trials of antidepressants, used in association with mood stabilizers. Subjects were randomly assigned to receive, in addition to mood stabilizers such as lithium or anticonvulsants, placebo (n = 10) or pramipexole (n = 12), administered in a range of 1-2.5 mg/day for 6 weeks. At the end of the study, pramipexole was found to be superior to placebo in terms of efficacy: 67% of patients on pramipexole were responders (HAMD score reduction > 50%), whereas only 20% of subjects on placebo were considered responders. Of note, the discontinuation rate for any cause was 40% for placebo *vs*. 17% for pramipexole. Although one patient taking pramipexole dropped out for a manic switch, mean YMRS scores did not significantly differ between the two groups at endpoint. Nausea was more common in subjects on pramipexole compared to placebo.

In the same year, another randomized, double blind, placebo-controlled trial, assessing the antidepressant effect of augmentative pramipexole was conducted by Zarate and colleagues [16]. In this study, 21 patients affected by BD II were enrolled. Patients were experiencing a major depressive episode despite pharmacological treatment with lithium or valproate, and were randomly assigned to adjunctive placebo (n = 11) or pramipexole (n = 10) for 6 weeks. Pramipexole was initiated at 0.375 mg/day and gradually increased to a range of 1-3 mg/day. All patients, except one taking placebo and one taking pramipexole, completed the study. Treatment response (> 50% decrease in MADRS score) was reported in 60% of subjects taking pramipexole *vs*. 9% of subjects taking placebo. Hypomania was experienced by 2 patients taking placebo and one patient taking pramipexole, and the most common side effect in patients treated with pramipexole was tremor.

In 2004, Cassano and colleagues extended acute evaluation of pramipexole effects to the mid/long term, after recruiting 23 adults with treatment-resistant major depressive episodes, 11 of which had bipolar depression [44]. Patients were followed up for additional 6 to 12 months, after a 16-week pramipexole add-on trial, with doses ranging from 0.75 to 1.5 mg/day. Baseline assessment of depression with MADRS and CGI-S was followed by a 16-, 32-, and 48-week assessment. At the endpoint, pramipexole was found to be efficacious: 14 of 23 patients (60.9%) experienced remission, defined as at least 8 weeks of no depressive symptoms or just residual symptoms, with a mean time of 10 weeks. The authors reported 5 adverse events (21.7%) in the entire sample resulting in pramipexole discontinuation (psychomotor agitation, ataxia, impulse dyscontrol, vomiting and hypomania).

In 2006, Gupta and co-workers reported a retrospective case series of 3 patients treated with augmentative pramipexole [45]. Two subjects had BD I, and were taking antidepressants and atypical antipsychotics. Depressive symptoms were assessed with the HAMD, at baseline, and at 2 and 8 weeks after the beginning of the treatment with pramipexole, which was started and maintained at doses of 0.75-1.5 mg/day. The improvement of depressive symptoms was documented by HAMD score reductions from 24 to 7 and from 21 to 6, for the 2 patients, respectively, at the follow-up visit, 2 weeks later. As no significant side effects were noted, the authors gave support to tolerability and effectiveness of pramipexole in refractory depression.

In 2009, Akdeniz and colleagues reported on two bipolar patients with recurrent long-term and severe depression treated with augmentative pramipexole [46]. Although based

only on clinical impressions, patients benefited from low dose of augmentative pramipexole (0.5-0.75 mg/day): the duration and the severity of the depressive episode was markedly decreased in the mid-term observation after 6 to 8 months of follow-up. No serious adverse events were observed during follow-up, with the exception of sleep and gastrointestinal side-effects, both reported only during short-term treatment.

In 2010, a naturalistic retrospective chart review of 16 bipolar depressed patients treated with augmentative pramipexole was conducted by El Mallakh and co-workers [47]. In order to assess the safety and efficacy of pramipexole, it was administered at an average dose of 1 mg/day for a mean duration of 6.7 months. Even though half of patients did not remain on pramipexole for more than 3 months, 10 subjects (62.5%) benefited from treatment: depressive symptoms improved within 4 weeks and their severity remained low for up to 9 months. CGI-S and Global Assessment of Functioning (GAF) [48] scores both improved with pramipexole. However, adverse events were quite common: half of patients stopped pramipexole after an average of 2 months from the beginning of treatment because of insomnia (41.2%), irritability (31.5%), nausea (25%), anxiety (25%) and sleepiness, lethargy and dizziness (12.5% each). No changes in mania ratings were reported at 36 months.

Recently, Burdick and colleagues aimed to assess 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 [49]. Forty-five patients completed the study: 24 received placebo, whereas 21 subjects were treated with pramipexole, starting from 0.25 mg/day to a target dose of 1.5 mg/day. At study endpoint, no relevant effect of treatment group on measures of depression and mania was reported, as well as no switching to mania/psychosis or discontinuation due to adverse events. Among subjects on pramipexole, the only side effect was restlessness. Although primary cognitive analyses did not highlight significant cognitive benefit from pramipexole, secondary data identified a subgroup of patients who might rapidly experience advantages from cognitive enhancement strategies. In particular, the euthymic subgroup of patients appeared to show a significant overall effect of treatment on neurocognitive functioning. Furthermore, higher levels of cognitive deficits were related to a more pronounced improvement in cognitive performance after pramipexole treatment.

Ropinirole

In one of the aforementioned studies, Perugi and coworkers, in 2001, conducted a retrospective chart review on 18 bipolar depressed treatment-resistant patients on therapy with dopamine agonists to assess their effectiveness and safety as add-on medications in refractory bipolar depression [39]. Patients were defined responders on the base of CGI-S, with ratings of 1 or 2. In particular, 8 subjects were treated with ropinirole, receiving a mean dose of 2.97 mg/day (range: 1.5-5 mg/day); 4 patients (50%) showed response on the basis of CGI-S. Ropinirole was well tolerated and did not show any negative interaction with concomitant psychiatric medications.

Stimulant-like agents and stimulants

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

Methylphenidate

In 2000, El-Mallakh conducted an open, 12-week, trial with 14 mildly-depressed bipolar patients (including 10 with BD type I) with HAMD score ≥ 15, and treated with 10-20 mg/day of methylphenidate in addition to a stable mood stabilizing regimen [50]. Three patients withdrew from the trial, because of increased agitation, anxiety and hypomania. The results showed a relevant improvement in both depressive and global psychiatric symptoms, as confirmed by a moderate decrease in mean HAMD scores from 16.9 ± 1.79 at baseline, to 9.4 ± 9.7 at endpoint, as well as a quite significant decrease in Psychiatric Symptom Assessment Scale (PSAS) [51] scores from 17.9 ± 5.63 to 4.8 ± 7.47. In conclusion, authors reported that the use of methylphenidate was effective and relatively safe for the treatment of bipolar depressed subjects.

In 2004, Carlson and colleagues retrospectively reported on 8 patients with BD (5 with BD type I and 3 with BD type II) who received adjunctive stimulants (either methylphenidate or amphetamine) for a mean duration of 18 months to improve residual depression and medication-induced sedation [52]. A moderate clinical relief from target symptoms was associated with consistent improvement of overall bipolar illness, as assessed by a mean improvement in CGI-S score of 2.9 points from baseline to the time of last visit. The adequate tolerability and the absence of induced hypomania, mania, increased cycling or abuse seemed to support the use of these compounds as reasonable therapeutic option in individuals who do not properly respond to standard treatment.

Two years later, Lydon and El-Mallakh conducted a retrospective chart review of 16 bipolar patients (9 with BD I, 7 with BD II, 1 with cyclothymia and 1 bipolar not otherwise specified) receiving methylphenidate for 14 months, on average, to assess its long-term tolerability, safety and efficacy [53]. The mean dose of methylphenidate

TABLE II.
Published studies with adjunctive methylphenidate, modafinil and armodafinil in bipolar depression.
Studi pubblicati riguardo l'utilizzo di metilfenidato, modafinil e armodafinil in associazione nella depressione bipolare.

Citation	Design	Sample characteristic	Study lengths
El-Mallakh (2000)	Open, prospective study	14 bipolar (10 BDI, 3 with prior alcohol abuse); depressed patients on mood stabilizing treatment	12 weeks
Menza et al. (2000)	Open, retrospective case series of depressed (including bipolar) patients	Subgroup of 3 bipolars with depression and residual tiredness/fatigue, despite antidepressants	10-12 weeks
Fernandes and Petty (2003)	Open, prospective case series	2 bipolars (1 BDI, 1 with prior comorbid substance abuse, 1 with current comorbid medical conditions) with excessive daytime sleepiness, taking mood stabilizers	8 weeks
Carlson et al. (2004)	Open, retrospective case series	8 depressed bipolars (5 BDI, comorbidities other than ADHD allowed); despite variable concomitant medications	Mean 18 months (range 11-24)
Nasr (2004)	Open, retrospective chart review of mood (including bipolars) patients	Unspecified subgroup of depressed bipolars taking antidepressants	Un-specified
Lydon and El Mallak (2006)	Open, retrospective chart review	16 bipolar (9 BDI, 5 also with ADHD); depressed subjects despite mood-stabilizing therapy	Mean 14 months (range 1-60)
Nasr et al. (2006)	Open, retrospective chart review of mood patients (including bipolars) receiving modafinil at some point	Subgroup of 64 depressed bipolars (31 BDI) mostly taking other medication(s)	< 2 months to 2 years
Frye et al. (2007)	Randomized, double blind, placebo controlled, multisite acute study	85 bipolars (64 BDI) with major depressive episode (IDS > 16) despite treatment with mood stabilizer or antidepressant	6 weeks
Calabrese et al. (2010)	Randomized, double blind placebo controlled multisite acute study	258 bipolar I with major depressive episode (HAMD ≥ 20) despite treatment with lithium, olanzapine or valproic acid	8 weeks
Parker and Brotchie (2010)	Open, prospective case series of 50 patients with depressive disorders (including bipolars)	27 bipolars (5 BDI) with history of persistent and/or recurrent treatment-resistant depression; depressed despite (in most cases) psychotropic medications	Mean 57 weeks (range 6-250) (among patients continuing stimulant drugs at final review)

BDI: Bipolar disorder type I; SD: Standard deviation; HAMD: Hamilton Depression Rating Scale; ADHD: Attention Deficit Hyperactivity Disorder; CGI-BP: Clinical Global Impression Scale for Bipolar Disorder; BZs: Benzodiazepines.

Group dosage	Outcomes	Conclusions
Adjunctive methylphenidate (10-20 mg/day)	44% decrease in mean HAMD score. 3 patients discontinued due to anxiety, agitation, hypomania	Adjunctive methylphenidate to mood stabilizers effective and relatively safe
Adjunctive modafinil 100-200 mg/day	All had full/partial remission, mostly in 1-2 weeks. Residual tiredness/fatigue were particularly responsive. Side-effects minimal, did not cause any discontinuation	Adjunctive modafinil to antidepressants relieved depression, tiredness and fatigue, and was relatively safe
Adjunctive modafinil 100-400 mg/day	Significant rapid improvement in drowsiness and functioning. No hypomanic/manic switch or side-effects	Adjunctive modafinil to mood stabilizers for residual drowsiness was effective and well-tolerated
Adjunctive methylphenidate (10-20 mg/day) or amphetamines (unspecified dose)	Robust mean CGI-BP improvement 2.9) with prolonged treatment. No switch reported	Adjunctive methylphenidate/amphetamines to various medications were effective and relatively safe
Adjunctive modafinil (un-specified doses)	Positive outcome, particularly in those with problematic sleepiness or fatigue	Adjunctive modafinil to antidepressants yielded benefit
Adjunctive methylphenidate mean dose 16.3 mg/day (range 5.40 mg/day)	Most had attenuation of depression and inattention. (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 was effective in most patients and relatively safe
Adjunctive (most often) modafinil mean 230-287 mg/day	Modafinil maintenance: < 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	Adjunctive modafinil to other medications did not induce manic/hypomanic switches or tolerance/abuse independent of history of chemical abuse/dependence
Adjunctive modafinil 200 mg/day (n = 41) *vs.* placebo (n = 44)	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	Adjunctive modafinil to mood stabilizer or antidepressant improved depressive symptoms with good tolerability
Adjunctive armodafinil 150 mg/day (n = 128) *vs.* Placebo (n = 129)	Adjunctive armodafinil compared to placebo yielded greater improvement in depressive symptoms on mean IDS (but not on secondary outcomes), and similar incidence of medical and psychiatric adverse events (but more insomnia, restlessness, anxiety and hypomania)	Adjunctive armodafinil to lithium, olanzapine, or valproic acid improved depressive symptoms, for some outcomes, with good tolerability
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. Significant side effects in 18% – mostly minor, but 1 mania; switching rare and limited to bipolars	Adjunctive methylphenidate to other psychotropics was variably effective and relatively safe

was 16.3 mg/d ± 8.7 mg/day, ranging from 5 to 40 mg/day, and it appeared to be generally well tolerated, leading to a significant symptomatic relief (GAF score). Several mild to moderate side effects were reported, mainly represented by increased irritability and agitation, which were responsible for discontinuation of methylphenidate in two patients.

In 2010, Parker and Brotchie reported a case series of 50 subjects with treatment-resistant depression, including 27 bipolar patients, treated with methylphenidate or dexamphetamine, either as monotherapy or augmentative drugs [54]. After a mean duration of 57 weeks of follow-up, with a modal dose of 20 mg/day, 34% of patients reported a significant improvement in target symptoms, 30% some level of amelioration, while 36% revealed no substantial differences. Switching was rare and limited to bipolars, and 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 reported a retrospective case series of 7 depressed patients (including 3 subjects with bipolar depression) treated with augmentative modafinil to improve partial or nonresponse to antidepressants [55]. The entire sample fully or partially remitted after 1-2 weeks of treatment with 100-200 mg/day of modafinil. Residual tiredness or fatigue, observed in all individuals prior to starting modafinil, were particularly responsive to augmentation. Side effects were limited and did not lead to treatment discontinuation in any patient.

In 2003, Fernandes and Petty described two bipolar patients with recent depressive episodes in remission with prominent residual hypersomnia [56]. In spite of adequate pharmacological treatment with mood stabilizers and antidepressants, patients continued to experience excessive daytime sleepiness that significantly improved with the addition of modafinil at a dose of 100-400 mg/day for 8 weeks, as confirmed by Epworth Sleepiness Scale score (ESS) [57]. No side effects or mood changes were reported.

In 2004, Nasr conducted a retrospective chart review of 78 depressed outpatients, including bipolar subjects, in a general psychiatric practice, receiving adjunctive modafinil to antidepressant therapy [58]. Significant improvement in wakefulness, fatigue and everyday functioning was observed, along with overall favourable tolerability.

Two years later, Nasr and co-workers performed a retrospective chart review of 191 patients with mood disorders (including 64 depressed bipolar subjects, 31 BP I and 33 BP II), who were given modafinil at some point during their treatment to assess switching, dose stability and abuse liability [59]. Modafinil was generally administered at a dose ranging from 250 to 290 mg/day, for < 2 months in 25 patients (including 13 BP I), for ≥ 2 months in 39 (including 18 BP I), for ≥ 1 year in 27 (including 11 BP I) and for ≥ 2 years in 16 (including 7 BP I). Reasons leading to discontinuation of modafinil were lack of efficacy, cost or adverse events, which were mostly sleep-related. No manic/hypomanic switch was observed, reinforcing the overall safety and tolerability of the compound in long-term treatment.

In 2007, Frye and colleagues conducted an acute phase, 6-week, randomized, double-blind placebo-controlled study of 85 bipolar depressed patients (including 64 BD I), inadequately responsive to mood stabilizers with or without antidepressant treatment and randomly assigned to receive adjunctive modafinil or placebo [60]. Improvement in Inventory Depressive Symptoms-Clinician Rated score (IDS) [61] was significantly greater with modafinil (mean dose of 174.2 mg/day) compared to placebo. Scores on the IDS, the four-item fatigue-and-energy subset of the IDS, and the CGI-BP depression severity item significantly improved with modafinil compared to placebo. Headache was the most common side effect apparently induced by modafinil, whereas no significant differences in treatment-induced mania, blood pressure, heart rate or weight gain were observed between the two groups. Taken together, these data support the role of adjunctive modafinil in improving symptoms of bipolar depression, without inducing mood destabilization.

In 2010, Calabrese and co-workers evaluated safety and efficacy of armodafinil as adjunctive compound in bipolar depression [62]. In an 8-week, multicenter, randomized, double-blind, placebo-controlled study, bipolar I depressed patients on treatment with lithium, olanzapine or valproate were randomly assigned to adjunctive armodafinil (mean dose 150 mg/day) or placebo. Greater improvement was seen in patients receiving armodafinil as confirmed by a significant decrease in the Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C30) used as a primary outcome measure. No differences were reported in secondary outcomes, including MADRS. Among induced side effects, headache, diarrhoea and insomnia were the most frequently reported. No increased incidence and/or severity of suicidality, depression, or mania or changes in metabolic profile occurred.

Discussion

Herein, the available evidence on the use of augmentative pro-dopaminergic agents, including stimulants and dopamine agonists, in the treatment of bipolar depression has been overviewed. Examining results on the use of pramipexole from either double-blind or open studies, the short-term efficacy and tolerability/safety of the compound, when used in augmentation, is adequately supported by controlled data. On the other hand, even though some open observations seem to support the mid/

long term effectiveness of the compound, other reports (i.e. Lattanzi [40], Cassano [44] and El-Mallakh [47]) have reaised safety and tolerability concerns.

The open case series reported by Perugi et al. in 2001 seems, in turn, to provide evidence for the efficacy of augmentative ropinirole in treatment-resistant bipolar II depression. Nevertheless, evidence on the use of ropinirole as add-on, in the treatment of treatment-resistant bipolar depression, relies upon this single report. Accordingly, at present, the compound cannot be recommended as augmentative intervention, due to the limited number of treated cases.

Considering the use of stimulants in adult bipolar depression, although the systematic evidence is quite limited (no RCTs and 4 open reports), the available data seems to advocate their use in at least some bipolar depressed patients, especially when significant drowsiness or fatigue is present. In contrast, the evidence to support the use of the stimulant-like agents modafinil and armodafinil is more robust, supported by 2RCTs as well as 4 open reports.

Taking into account the quality and quantity of published studies to date, adjunctive dopamine agonists and stimulants cannot be, at present, included among well-established, evidence-based strategies for treatment of bipolar depressed patients who fail to respond to first-line interventions. Such perspective is consistent with recommendations of recent international guidelines for treatment of BD [6 34 7 35].

However, the emerging evidence regarding the stimulant-like agent armodafinil indicates that in the not too distant future there may be sufficient support to recommend its use in bipolar depressed patients who fail to respond to first-line interventions.

Regarding the efficacy of pramipexole, Aiken and colleagues suggested that augmentative pramipexoleis a valid therapeutic option for treatment-resistant bipolar depression, and reported a large effect size (0.77-1.1) [63] on the basis of two very small previous RCTs [15 16]. Subsequent reports appear to be consistent with this perspective, allowing researchers to speculate about the mechanism of action of these compounds in bipolar depression. Dopaminergic enhancement, for instance, may promote the action of antidepressant medications, particularly in patients complaining of a lack of energy and motivation [64 65]. Furthermore, it has been suggested that a resensitization and potentiation of mesolimbic D2/D3 receptors, indicated as the final common pathway of the long-term use of antidepressants [66 67], may represent one of the key antidepressant effects of pramipexole and ropinirole. In addition, the neurotrophic, neuroprotective and antioxidant activity shown by pramipexole in cell cultures [68 8 69 70] may, at least partially, account for its antidepressant properties, even though evidence is mainly based on preclinical level investigation [71].

Focusing on the efficacy of stimulants, it is worth nothing that the recruitment of patients experiencing symptoms effectively treated by stimulants, such as sleepiness or fatigue [32], may be partially responsible for the positive results. Although this may help in identifying a subgroup of subjects who may benefit from a more personalized treatment [72], on the other hand, it could limit the generalizability of findings. In addition to sample heterogeneity, another issue that should be considered is the possible influence of concurrent medications (such as mood stabilizers) on clinical results, potentially leading to discrepancy observed in some studies.

In terms of safety/tolerability, combined data from 8 studies, up to 2004, had previously shown a discontinuation rate of 9% among patients with mood disorders taking pramipexole [63]. Nonetheless, this encouraging finding of adequate short-term tolerability has not been confirmed in the mid- to long-term by subsequent open reports, documenting higher drop-out rates for a total of 33 patients. In the short-term, favourable somatic tolerability and low risk of switch or mood destabilization have been generally documented with both adjunctive pramipexole and stimulants. This may be related to the concomitant presence of antimanic agents in the patients' pharmacological treatment and, compared to pramipexole, to the administration of a lower dosage for a shorter duration compared to patients with Parkinson's disease. In fact, the potential switch to mania or psychosis induced by dopaminergic compounds such as pramipexole, along with other psychiatric and somatic adverse effects, may occur less frequently in psychiatric patients than those with Parkinson's disease[55], being likely related to the absence of ongoing antimanic therapy and the degeneration of extrastriatal dopaminergic pathways [73 63]. However, it is worth noting that investigations on dopamine agonists in the long-term treatment of bipolar patients are scanty and further investigations may reveal higher rates of switching into mania [16].

Likewise, specific concerns about the possibility of mania induced by stimulants [74-76] may have been related to the absence of concomitant antimanic therapy [52] and further risks, including earlier onset and more severe course, have been reported for BD adolescents, with previous exposure to stimulants [77 78]. On the other hand, low abuse potential has been reported for the stimulant-like agents modafinil or armodafinil compared to stimulants [79]. The reviewed studies did not highlight the risk for potential stimulant misuse/abuse, and documented low rates of misuse for methylphenidate over several months or even years of observation [52-54]. This may be due to the exclusion of subjects at high risk of stimulant abuse.

With regard to induced side effects, gradual pramipexole titration has been recommended to limit the occurrence of orthostatic hypotension, tremors, somnolence, insomnia, dizziness and nausea. No significant drug-interac-

tions [31], weight gain potential or sexual side effects have been described in clinical studies. Similarly, controlled trials for modafinil and armodafinil have not documented any significant difference versus placebo with regards to blood pressure, heart rate or weight [60], laboratory values, ECG parameters and physical examination findings [62]. The safety of stimulants, also sustained by their low drug-interaction potential and the limited absolute medical contraindications [80], seems to be confirmed by their widespread use in depressive disorders associated with medical conditions [81-83] and in the elderly [84].

While assessing the role of adjunctive dopaminergic compounds in bipolar depression, another meaningful issue to consider is their potential for cognitive benefit, as neurocognitive impairment is one of the most characteristic feature of depressive phases [85]. The only RCT targeting cognition with pramipexole conducted to date [49] reported mixed results, with the low affinity of pramipexole for D1 receptors, traditionally involved in working memory circuits [86], perhaps accounting for the lack of advantage in cognitive performance [63]. Stimulant drug treatment frequently leads to a significant improvement in memory, attention and executive functions, both in selected subgroups of patients with schizophrenia, ADHD [87] and in healthy subjects [88]. However, further investigations in large clinical populations of patients with affective disorders are needed to extend this data to mood disorder populations.

In terms of psychiatric safety/tolerability, it should be further clarified whether the above-mentioned risks (mood switching, cycle acceleration, psychosis and abuse) should preclude their use in patients with a history of mood switching, rapid cycling or psychosis.

Taken together, the findings from the studies reviewed seem to suggest that pro-dopaminergic compounds agonists, such as pramipexole and stimulant-like agents, deserve consideration as potential adjunct therapeutic agents in adult bipolar depression, at least in specific subgroups of patients, although caution for is still recommended. Future research and clinical trials on larger samples and greater follow-up periods are encouraged to extend the available evidence and better clarify the potential role of these medications in bipolar depression.

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