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Use of Stimulants in Bipolar Disorder

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Abstract Several international guidelines indicate stimulants, including methylphenidate (MPH), amphetamines and derivatives, modafinil, and armodafinil among the second-third-line choices for bipolar depression. Efficacy of stimulants has been also reported for the management of residual depressive symptoms such as fatigue and sleepiness and for the management of affective, cognitive, and behavioral symptoms in children and adult bipolar patients with comorbid ADHD. Few case reports show positive results with MPH in the treatment of resistant mania. Finally, MPH might be an option in some bipolar forms observed in psychiatric presentations of frontotemporal dementia and traumatic brain injury. In spite of these preliminary observations, the use of stimulants in bipolar patients is still controversial. Potential of misuse and abuse and mood destabilization with induction of (hypo)manic switches, mixed states, and rapid cycling are the concerns most frequently reported. Our aims are to summarize available literature on this topic and discuss practical management implications.

This article is part of the Topical Collection on *Bipolar Disorders*

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Introduction

Methylphenidate (MPH), amphetamines and derivatives (i.e., the prodrug lisdexamphetamine (LDX)), modafinil, and armodafinil are the stimulant drugs most commonly utilized in the treatment of bipolar disorder. Both MPH and amphetamines have the FDA approval for the treatment of ADHD and narcolepsy, whether LDX is approved only for ADHD. Modafinil and armodafinil are considered wakefulness-promoting agents indicated for narcolepsy, obstructive sleep apnea syndrome, and shift work sleep disorder.

All those compounds via different mechanisms of actions share the property to enhance dopaminergic prefrontal transmission. Amphetamines, which are considered *releasers* in the psychostimulant class on the basis of the interaction with the DAT, enhance central nervous system via not only blocking the reuptake of both dopamine and norepinephrine but also promoting catecholamine release. Indeed, amphetamines occupy the substrate site of catecholamine transporters (DAT and NET) which are K+-Na+ pump channels: they inhibit the reuptake of dopamine and norepinephrine, and the pump may run in reverse actively diffusing neurotransmitters in the synaptic cleft. Moreover, intracellular amphetamines also reduce the metabolism of dopamine via inhibiting the vesicular monoamine transporter (namely VMAT-2) with a mechanism similar to that involving DAT: dopamine is pumped into the cytoplasm also favoring its passive diffusion out of the cell. MPH, classified among the *blockers* [1], shows a similar mechanism of action with subtle but important differences: MPH sits mostly at allosteric site of the protonic pump almost only inhibiting the reuptake of dopamine and norepinephrine. The intracellular effects

(for example the inhibition of VMAT2) are probably lower than amphetamines, although different comparing to other blockers and not completely understood. Both MPH and amphetamines share the property to enhance dopaminergic transmission not only in the reticular activating system and prefrontal cortex but also in the nucleus accumbens, probably responsible for addictive potential of these drugs and worsening/appearance of tics. It is also debated whether the stimulation of nucleus accumbens is involved in the induction of (hypo)manic switches, cycle acceleration, and psychosis.

Modafinil and its R-enantiomer armodafinil are stimulant-like agents promoting dopamine- and norepinephrine-related transmission. The differences with stimulants are the low affinity for the DAT [2], the interaction with neurotransmission of different mediators as GABA, glutamate, serotonin, histamine, and hypocretin with less interactions with monoamines comparing to other stimulants [3]. Moreover, these compounds seem to show a certain selectivity for the brain regions, mostly acting in suprachiasmatic nucleus, anterior hypothalamus, and amygdale, all regions primarily involved in wakefulness. So, the interaction with nucleus accumbens would be less relevant with reduced addictive potential [4].

Bipolar depression is considered difficult-to-treat with standard antidepressant drugs, and its pharmacological treatment still represents a clinical challenge [5, 6]. Several reasons could be identified to explain the failure of standard antidepressant treatments in bipolar depression: resistance per se, antidepressants induced cycle changes, mixed features, and/or "wear-off" phenomenon [6], frequent alterations of daily rhythms as in delayed phase sleep disorder and unrecognized concomitant neurodevelopmental disorders such as ASD and ADHD.

Some randomized-controlled studies and open clinical reports documented the use of stimulants as augmentation treatment for resistant major depressive disorder [7]. The use of these medications in bipolar depression is understudied, and it is debated whether they should be considered safe, especially regarding their potential induction of mood switches, affective instability, mixed features, and rapid cycling [8]. The use of stimulants is controversial also in the subpopulation of BD patients with comorbid ADHD [9], since available evidence is very sparse and controlled studies virtually absent [8]. Stimulants may also have some role in several neuropsychiatric conditions related to BD or with a bipolar-like presentation. This might be the case of the management of some specific neuropsychiatric symptoms in frontotemporal dementia (FTD) and traumatic brain injury (TBI).

Although all these are poorly explored fields, some of the current international guidelines (the World Federation of Societies of Biological Psychiatry (WFSBP) [10] and the Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (CANMAT–ISBD)) [11] support the adjunctive use of stimulants, namely modafinil, as the second-line choice for bipolar depression.

We systematically reviewed the available literature on the use of stimulant drugs in bipolar disorder.

Methods

A systematic PubMed search of the available literature was conducted to evaluate the possible efficacy and tolerability of stimulants in bipolar disorder. Combinations of the following search terms were used: bipolar disorder, treatment, stimulants, methylphenidate, amphetamine, modafinil, and armodafinil along with terms related to each of the areas of focus listed above. We found only five RCTs on the use of stimulant medications in bipolar depressive patients: three of them involved only bipolar patients (one regarding adjunctive modafinil [12], one adjunctive armodafinil [13], and one on the use of LDX [14] in bipolar depressive patients) and two had mixed samples of both bipolar and unipolar probands [15, 16]. Given the paucity of controlled data, we decided also to include information from open-label studies and case reports. Ten open-label, both prospectively and retrospectively designed, studies are available as well as five case reports. Furthermore, reference lists from each article were assessed for additional citations of interest. We excluded articles in languages other than English. Two reviewers (G.V. and G.P.) evaluated the results of the search on the basis of title and/or abstract and assessed them for the suitability for inclusion on the basis of full publications.

Results and Comments

Randomized Controlled Trials on Stimulants in BD

Randomized controlled trials regarding the use of stimulants in bipolar depression are very few, and the results are not conclusive (Table 1). In interpreting the results, several limitations have to be considered. All the studies suffer from selection biases: in fact, included patients have all a treatment-resistant depression and the stimulants are added to various combinations of other medications. Secondly, samples are usually small and heterogeneous. Finally, the follow-up period is too short to evaluate both medium and long-term efficacy and tolerability of these medications. For example, the induction of mood destabilization and cycle acceleration are not easily evaluable in a study of few weeks. In this sense, the data have to be cautiously interpreted and cannot be easily generalized to other clinical populations.

Frye and colleagues [12] evaluated the efficacy and safety of modafinil in add-on for the treatment of depression in a sample of 85 BD patients in whom mood stabilizers and eventually antidepressants had failed. Patients were randomly

Table 1 Randomized controlled and open-label studies on the use of stimulants in bipolar disorder

Study	Patients	Drug(s)	Follow-up period	Response/remission rates
RCTs				
Silberman et al. 1981 [15]	7 depressive BD patients	Amphetamine vs. placebo (crossover)	4 days	*Response of depressive symptoms not significant
Frye et al. 2007 [12]	85 depressive BD patients	Add-on modafinil vs. placebo (+ mood stabilizer and/or antidepressant)	6 weeks	*Response 43.9 vs. 22.7% Remission 39% vs. 18%
Calabrese et al. 2010 [13]	257 depressive BD I patients	Add-on armodafinil vs. placebo	8 weeks	*Response 37 vs. 38%
Calabrese et al.2014 [17]	400 depressive BD I patients	Add-on armodafinil vs. placebo	8 weeks	*Response 46 vs. 34% Remission 21% vs. 17%
McElroy et al. 2015 [14]	25 depressive BD patients	Lisdexamphetamine vs. placebo	8 weeks	*Response 55 vs. 29% Remission 55 vs. 29%
Scheffer et al. 2005 [21]	40 ADHD patients with mania (pediatric sample)	Divalproex ± D-amphetamine vs. placebo	8 + 4 weeks	§Response 80% °Response 89.6 vs. 10%
Findling et al. 2007 [20]	16 ADHD-BD patients (pediatric sample)	(Lithium or divalproex) + - methylphenidate vs. placebo	4 weeks	°Methylphenidate > placebo ES = 0.90
Open-label trials				
El-Mallakh et al. 2000 [19]	14 moderatly depressed BD patients	Add-on methylphenidate (+ mood stabilizer or antipsychotic)	12 weeks	*Moderate response of depressive symptoms, good response for overall psychiatric picture
Nasr et al. 2004 [26]	78 depressive patients	Add-on modafinil	Chart review	*Significant improvement
Nasr et al. 2006 [27]	191 depressive patients (64 BD)	Add-on modafinil	Chart review	*Significant improvement
Carlson et al. 2004 [23]	8 BD patients (residual depression, sedation, weight gain, anergia)	Add-on metylphenidate or amphetamines	Chart review	*Improvement
Lydon and El-Mallakh 2006 [29]	16 (5 with ADHD too) BD patients	Add-on methylphenidate	Chart review	*(°) Significant improvement
Wingo et al. 2008 [30]	34 BD patients (depressive and/or ADHD)	Previous treatment with stimulants	Chart review	40% rate of (hypo)mania switch
Parker et al. 2010 [24]	27 BD treatment-resistant depressive patients	Monotherapy or add-on methylphenidate	Prospective	*66.6%: mild/moderate improvement 14.%: no improvement 22.2%: adverse psychiatric events
Parker et al.2013 [31]	51 BD treatment-resistant melancholic depressive patients	Stimulants	Prospective	*50%: mild/moderate improvement 12%: adverse events requiring suspension
McIntyre et al. 2013 [25]	40 BD-ADHD patients	Add-on lisdexamphetamine	4 weeks	(*)° Improvement in residual depression (ES = 0.26), ADHD (ES = 0.74/0.76), global impression (ES = 0.75)

RCT= Randomized Controlled Trial; *BD*= Bipolar Disorder; *ADHD*= Attention Deficit/Hyperactivity Disorder; *ES*= Effect Size
* The outcome measures were related to variations of depressive symptoms
§ The outcome measures were related to variations of manic symptoms
° The outcome measures were related to variations of ADHD symptoms

assigned to placebo or modafinil and assessed for the following 6 weeks. Modafinil demonstrated to be significantly superior than placebo (response—defined as the reduction >50% in IDS scores—43.9 vs. 22.7%; remission 39 vs. 18%). Modafinil-treated patients showed progressive improvement not only in depressive symptoms but also in the overall clinical picture (as demonstrated by the improvement in CGI-BP).

Add-on armodafinil was also evaluated in an 8-week double-blind placebo-controlled trial in 257 BD type I patients [13]. Armodafinil seemed to improve depressive symptoms

measured with IDS-30 more than placebo. However, the active drug did not differ from placebo in the rates of clinical response and remission. Armodafinil resulted safe, not increasing the incidence and the severity of suicidality, depression, and mania. The same research group published in 2014 the results of the same 8-week RCT relative to add-on armodafinil in BD, enlarging the sample to 400 patients (201 treated with armodafinil at a dosage of 150 mg/day). The armodafinil group showed greater response rates comparing to placebo (46 vs. 34%, respectively; $p = .015$), whether no statistically significant differences were found in remission rates. Armodafinil also showed to be sufficiently tolerable at this dosage [17].

More recently, the efficacy and safety of adjunctive lisdexamphetamine (LDX) was tested in an 8-week, prospective, randomized, double-blind, placebo-controlled, flexible-dose study in 25 bipolar depressive patients [14]. Although LDX did not differ from placebo in reducing MADRAS scores, the authors found LDX to be superior to placebo in reducing self-reported depressive symptoms, daytime sleepiness, fatigue, and binge eating behavior and in ameliorating blood lipid profile; they also detected statistically significant tendency of LDX to globally improve the severity of overall depressive and bipolar symptoms. The active drug resulted well tolerated, not inducing/worsening suicidality or hypomania/mania. Only one out of 25 patients was ruled out from the study for misuse of the drug.

Finally, one old, double-blind, crossover RCT that tested the use of intravenous D-amphetamine in a mixed sample of 18 unipolar and bipolar depressive patients should be mentioned [15]. As the aim of the study was to examine behavioral response to intravenous D-amphetamine in a very short-term period (4 days), the symptomatological changes were not easily interpretable.

An important clinical area needing further research concerns the employ of stimulant drugs in adults with comorbid ADHD and BD. Although controlled data on this issue are substantially lacking, the CANMAT group [18] identified MPH and mixed amphetamine salts as the first- and second-line medications, respectively, for the treatment of ADHD in bipolar adults. This evidence was based on two controlled studies in pediatric samples and one in adults [19–21]. Some case reports [22–24] also support efficacy and safety of stimulants in this specific population, especially highlighting the absence of negative effects on the symptoms and course of the comorbid mood disorder [9].

Open-Label Trials and Case Reports on Stimulants in Bipolar Disorder

Several open-label trials focused on the use of stimulants in bipolar patients (Table 1). In a 4-week open-label trial, positive results were reported for adjunctive LDX in BD patients with comorbid ADHD [25]. The trial showed that adjunctive flexible doses of LDX in stabilized ADHD-BD patients determined significant reduction both in ADHD and residual depressive symptoms, improved the global quality of life, and were not associated with (hypo)manic switches and/or BD destabilization, at least in a short-term period.

Another 12-week open-label study explored the use of adjunctive MPH in 14 moderately depressed bipolar patients (both BD I and II), non-responding to mood stabilizers and/or antipsychotics. MPH demonstrated to ameliorate both depression and overall symptom severity. As expected, an early response, with significant reduction of depressive symptoms during the first week, predicted a positive response during the overall follow-up period. No (hypo)manic switches were reported as well as other psychiatric adverse reactions, such as activation or anxiety. Non-response was associated with BD type II, organic condition related to BD, and previous adverse reactions to antidepressants [19].

Two retrospective chart reviews (the second is the enlargement of the former sample) reported the use of adjunctive modafinil in depressive patients (both unipolar and bipolar) with unsatisfying response to antidepressants [26, 27]. In both papers, the authors found modafinil to be effective in a proportion of depressive patients (almost one fourth of the sample), improving wakefulness, fatigue, and global functioning besides depressive symptoms. No patients showed mood switches during modafinil treatment. Modafinil appears to be more tolerable of some dopaminergic agents currently used as adjunctive treatment in resistant depression, just like pramipexole, as showed in a recent STEP-BD-derived report [28]. This is especially true in the long term (7–9 months), and the low discontinuation rate is mostly due to the lack of physical/somatic adverse effects of modafinil, whereas efficacy and psychiatric adverse effects are similar for the two compounds.

Similarly, two other retrospective chart reviews [23, 29], considering 16 and 8 BD patients, respectively, reported that adjunctive MPH or other amphetamine derivatives were generally well tolerated in a long-term period and effective for the treatment of depressive symptoms and relapses of bipolar depression not completely respondent to usual pharmacotherapy. Sedation, weight gain, low energy, and fatigue represented the symptoms that showed the best response.

Less encouraging results were reported in a retrospective chart review of 137 adult bipolar patients previously receiving stimulants for the treatment of comorbid ADHD or as add-on during depressive episodes [30]. The authors noted that only the 43% were currently treated with a mood stabilizer and that the estimated rate of stimulant-associated (hypo)mania was 40%.

In a prospective open study [24], 50 treatment-resistant depressive patients were treated with monotherapy or add-on stimulants, mostly MPH. Twenty-seven of them were bipolar (5 BD I and 22 BD II): the 66.6% ($n = 18$) of them reported from moderate to mild improvement in depression severity and 14.8% ($n = 4$) did not experience any improvement, whereas the 22.2% ($n = 6$) reported psychiatric adverse events as transient mood elevation and excitement phenomena that in only one case

turned into a manic episode. In 2013, the same research group [31•] published the results of the extension of the abovementioned study, finally enrolling 112 (51 BD) patients with treatment-resistant melancholic depression, followed up for a mean time of 69 weeks. Both unipolar and bipolar patients in the 70% of the cases reported to be from "very" to "somewhat" ameliorated (respectively, 20 and 50%). Although the 40% of the sample reported significant side effects, only the 12% required the interruption of the medication (the most common were irritability/agitation, increased anxiety, impaired concentration, feeling "jazzed up," "jittery" and "buzzy," tachycardia, sedation or fatigue, and worsening of mood). It is important that the 20% of bipolar patients experienced an excitation phase or the worsening in terms of frequency and/or amplitude of the highs.

In addition to the above reported open observations, some information for clinical or research purposes can be derived from case reports. For example, the efficacy of adjunctive stimulants was described in melancholic bipolar depression [32], in catatonia [33], and in the treatment of residual depressive symptoms, such as fatigue, tiredness [34], and hypersomnia [35] in BD.

An interesting case report described the use of methylphenidate in a patient with comorbid ADHD, BD, panic disorder, and substance and alcohol abuse [36]. The patient had been stabilized with her mood and anxiety symptoms with lamotrigine and quetiapine, but she continued reporting attention deficits and severe bulimia. After the addition on MPH, concentration improved and binging purging symptoms completely remitted. Most importantly, in a 1-year follow-up period, no adverse events or recurrences regarding mood symptoms, addiction, and eating disorders emerged.

Stimulants in Bipolar Patients with Comorbid ADHD

BD and ADHD have a tangled relationship; high rates of comorbidity between the two disorders have been shown both in children and adult clinical populations [8, 18, 37–43]. The two disorders shared a wide overlap in symptoms, diagnostic criteria, clinical presentation, and common developmental trajectories and comorbidities (i.e., substance use disorders, borderline, and antisocial personality). All these overlaps contribute to the complexity of the clinical presentations and create difficulties in differential diagnosis and treatment approach.

Systematic data regarding the treatment of ADHD with stimulants in adult bipolar patients are substantially lacking, but some recommendations can be derived from open trials and case reports. The CANMAT group recently drew a "ranking" based on levels of evidence and MPH and amphetamine mixed salts received, respectively, levels 1 and 2 of evidence for the treatment of ADHD in adults with comorbid BD. Level 3 was attributed to bupropion and atomoxetine and level 4 to cognitive behavioral therapy, modafinil, venlafaxine, desipramine, nortriptyline, and LDX [18]. Beyond the relative value of these recommendations, it is important to underline that available data on the safety of these medications in bipolar patients are encouraging. In fact, as illustrated in a recent meta-analysis based on RCTs, the cumulative incidence of psychosis and mania in treated ADHD adults was 1.48 per 100 person/years, with a very high number needed to harm of 526 [44]. Recently, 2307 bipolar patients who initiated a therapy with MPH were found in the Swedish National Registry and grouped on the basis of concomitant mood-stabilizing treatment. In a 12-month follow-up period, the risk of developing an excitatory phase, as severe as it would require the initiation of an antipsychotic, was increased in those patients assuming MPH monotherapy (with a hazard ratio (HR) of 7.0 in the first 3 months). The risk of mania was increased too, during the first 3 months (HR 3.0), but at a non-significant level, and then was unchanged. By the contrary, in those patients assuming both MPH and mood stabilizers, the risk of excitation resulted reduced and unchanged in the first 3 months and in the successive period, respectively (HR = 0.6 and 1.1). Similar results regard the emergency of full-blown mania [45].

Nonetheless, concerns regarding the use of stimulants in ADHD-BD subjects are still present [8]. Many reports have shown manic switches or psychosis in ADHD-BD patients treated with stimulants [8, 46–50], and most importantly, there are no systematic data regarding the long-term use and safety of these drugs in ADHD-BD subjects. Stimulants should be avoided or considered as a second-line treatment for ADHD-BD patients in presence of an active substance use disorder, active eating disorders (especially anorexia nervosa), and pervasive cluster B personality with pronounced malingering features. Usually, a hierarchical approach is the best management strategy. ADHD should be treated only after a sustained stabilization of the mood disorder [8, 51].

Stimulants in Mania

A new interesting research area is focused on the "vigilance regulation model of mania." In this model, mania as well as other psychomotor excitatory phenomena (for example hyperactivity in ADHD) may be related, at least in some vulnerable individuals, to a vicious circle involving the override of the autoregulatory control of the brain arousal. The hypothesis started from the biunivocal relationship between vigilance and behavior: as vigilance influences behavior, so behavior influences vigilance. According to the hypothesis, in excited individuals, the increase of stimulating experiences and behaviors might be interpreted as an attempt to stabilize arousal via intense external stimulations [52–54]. In this perspective, in some patients, stimulant medications, counterintuitively, may represent a concrete option for the treatment of manic episodes. The evidence supporting this hypothesis is mainly derived from case reports of bipolar patients rapidly improved from a manic episode after the administration of stimulants [54–58]. Two reports also associated improvement of manic symptoms to stabilization of

vigilance assessed by means of EEG [59, 60]. Few years ago, a multicenter international study (MEMAP_Methylphenidate in Mania Project) has been constituted in order to systematically verify the utility of stimulants in the treatment of mania [61].

Stimulants in Other Neuropsychiatric Conditions with Bipolar Presentation: the Case of Late Onset Bipolarity, Frontotemporal Dementia and Traumatic Brain Injury

Bipolar diathesis can be elicited by medical conditions (i.e., vitamin B12 deficiency, hyperthyroidism, Cushing's syndrome, and corticosteroid administration) or by many neurologic conditions such as Alzheimer disease, frontotemporal dementia [62], vascular dementia, silent cerebral infarcts and stroke, normal pressure hydrocephalus, brain tumors, brain injury, epilepsy, infections of the central nervous system, Huntington disease, and prion diseases [63–66]. Interestingly, some authors defined a clinical variant of late onset bipolarity elicited by neurodegenerative dementia as bipolar type VI, which is characterized by mixed-labile mood symptoms and cognitive dysfunction associated with hyperthymic/cyclothymic/irritable temperament, family history of bipolarity, refractoriness to antidepressants and acetylcholinesterase inhibitors, response to mood stabilizers, and/or atypical antipsychotics [62].

One of the best example of late onset bipolarity can be associated to the prodromal phases of frontotemporal dementia (FTD) in its frontal variant (fvFTD). The onset of this neurodegenerative condition is usually earlier than that of other types of dementia, and often, it begins with severe changes of personality and mood episodes of both polarities and behavioral disorders [67]. In the prodromal phase of the illness, when frank neurological signs are absent or subclinical, fvFTD may mimic BD in various aspects. Similar mood disturbances can be observed in some traumatic brain injured (TBI) patients.

Clinical reports for both these conditions suggested positive response to psychostimulants in the management of specific symptoms such as depression, fatigue, tiredness, distractibility, and other cognitive dysfunctions. An interesting double-blind, placebo-controlled, crossover RCT showed a significant reduction in impulsive risk-taking behavior (namely gambling) in eight FTD patients treated with MPH. In this sample, the improvement was independent from the effect on cognitive functioning, which remained unchanged [68]. The authors hypothesized that this effect could be related to a possible normalization of frontal electroencephalographic rhythms as found in FTD [69]. MPH is supposed to ameliorate frontal circuitry transmission with a normalization of signal-to-noise ratio [70].

An example of the use of stimulants in TBI with bipolar-like manifestations is a case report showing the "paradoxical" antimanic effect of dextroamphetamine in a brain-injured manic adolescent, previously treated without effect with standard medications (e.g., divalproex, lithium, haloperidol, and carbamazepine) [58, 71, 72]. In a "personalized"-"stratified" medicine perspective [73], this is an area of great interest for clinical practice that deserves closer attention and further study.

Potential Limitations

A specific concern on the use of stimulants in BD patients regards their potential destabilizing effects on the course of the illness. The major problem of the available literature is the short duration of the studies, ranging from a minimum of 4 to a maximum of 12 weeks. This is insufficient period to evaluate the potential destabilization of the illness. It has been advocated that the induction of (hypo)manic switches linked to stimulants/stimulant-like drugs [74–76] may have been related to the absence of adequate concomitant antimanic or mood-stabilizing therapy [23]. High risks of BD destabilization, including earlier onset and more severe course, have been reported for bipolar adolescents, with previous exposure to stimulants [77, 78], and for adults with ADHD-BD comorbidity treated with MPH [8]. Other reports indicated that psychostimulants did not worsen symptoms of mania in most stabilized BD patients [19–21, 23, 29, 79, 80]. In our experience, at least in stabilized BD patients, the risk of precipitating mania or mixed states is reduced, when stimulant medications are used in combination with mood stabilizers.

Misuse and abuse of MPH or amphetamines may be another problem, in particular in BD patients with comorbid ADHD or substance use disorder. Although several of the reviewed studies showed low rates of misuse for MPH over several months or years of observation [23, 24, 29], other reports suggested high risk of abuse and addiction mainly not only for amphetamines but also for MPH. Such different conclusions may be influenced by the exclusion or inclusion of high-risk patients. In BD patients with a past or current substance use disorder, a conservative approach should be preferred, considering if necessary the use of less addictive drugs such as modafinil and armodafinil [81]. The same strategy can be suggested for ADHD-BD patients with a personal history of treatment misuse and malingering.

Conclusions

Although several international guidelines support the adjunctive use of stimulant drugs as the second-third-line choice for bipolar depression [10, 11], their efficacy and safety in bipolar disorder is still poorly explored. Few short-term controlled studies and some open clinical reports documented the potential efficacy of MPH and modafinil as augmentation treatment for resistant bipolar depression. Available data did not sufficiently clarify whether the use of stimulant in depression (not only bipolar) should be considered an effective therapeutic option for specific depressive phenotypes or a sort of palliative, symptomatic medication with

limited indication for the management of residual or specific symptoms such as fatigue and somnolence.

The employ of MPH in adult BD patients with comorbid ADHD is supported by several preliminary observations, although available evidence is very sparse and long-term studies are virtually absent. Clinical reports supporting that MPH may also have some benefit in several neuropsychiatric conditions with a bipolar-like presentation are also anecdotal. This might be the case of the management of some specific neuropsychiatric bipolar presentations in FTD and TBI.

Data on the use of stimulants in BD are still few and sometimes contradictory. Based on the current level of information, we do not recommend stimulants in BD patients in the absence of mood stabilizers. If stimulants are used, patients should be frequently and regularly assessed for possible manic or mixed symptoms, as these symptoms may occur acutely or after several months. If manic or mixed symptoms arise, it is necessary to discontinue stimulants and use mood stabilizers or other antimanic drugs [82••, 83].

Bipolar disorder is probably a heterogeneous condition with many different clinical presentations mostly qualified by the current symptomatology, longitudinal course, and physical and psychiatric comorbidity. The stratification of patients, in both clinical practice and research, may lead to specific treatment strategies. We should expect that specific BD subpopulations such as patients with a history of ADHD or TBI may respond more favorably to a combination of mood stabilizers and stimulants than to other possible treatments. An appropriate "stratification" process should be considered the basis for more refined treatment approaches and the starting point for future research in this field.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Sonders MS et al. Multiple ionic conductances of the human dopamine transporter: the actions of dopamine and psychostimulants. J Neurosci. 1997;17(3):960–74.
2. Schmitt KC, Reith ME. The atypical stimulant and nootropic modafinil interacts with the dopamine transporter in a different manner than classical cocaine-like inhibitors. PLoS One. 2011;6(10):e25790.
3. Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology. 2008;33(7):1477–502.
4. Vosburg SK et al. Modafinil does not serve as a reinforcer in cocaine abusers. Drug Alcohol Depend. 2010;106(2-3):233–6.
5. Neubauer H, Bermingham P. A depressive syndrome responsive to lithium. An analysis of 20 cases. J Nerv Ment Dis. 1976;163(4):276–81.
6. Sharma V, Khan M, Smith A. A closer look at treatment resistant depression: is it due to a bipolar diathesis? J Affect Disord. 2005;84(2-3):251–7.
7. Wharton RN et al. A potential clinical use for methylphenidate with tricyclic antidepressants. Am J Psychiatry. 1971;127(12):1619–25.
8. Wingo AP, Ghaemi SN. A systematic review of rates and diagnostic validity of comorbid adult attention-deficit/hyperactivity disorder and bipolar disorder. J Clin Psychiatry. 2007;68(11):1776–84.
9. Perugi G, Vannucchi G. The use of stimulants and atomoxetine in adults with comorbid ADHD and bipolar disorder. Expert Opin Pharmacother. 2015;16(14):2193–204.
10. Grunze H et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry. 2010;11(2):81–109.
11. Yatham LN et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord. 2009;11(3):225–55.
12. Frye MA et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry. 2007;164(8):1242–9.
13. Calabrese JR et al. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. J Clin Psychiatry. 2010;71(10):1363–70.
14. McElroy SL et al. Adjunctive lisdexamfetamine in bipolar depression: a preliminary randomized, placebo-controlled trial. Int Clin Psychopharmacol. 2015;30(1):6–13.
15. Silberman EK et al. Heterogeneity of amphetamine response in depressed patients. Am J Psychiatry. 1981;138(10):1302–7.
16. Reus VI et al. d-Amphetamine: effects on memory in a depressed population. Biol Psychiatry. 1979;14(2):345–56.
17. Calabrese JR et al. Efficacy and safety of adjunctive armodafinil in adults with major depressive episodes associated with bipolar I disorder: a randomized, double-blind, placebo-controlled, multicenter trial. J Clin Psychiatry. 2014;75(10):1054–61.
18. Bond DJ et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid attention-deficit/hyperactivity disorder. Ann Clin Psychiatry. 2012;24(1):23–37.
19. El-Mallakh RS. An open study of methylphenidate in bipolar depression. Bipolar Disord. 2000;2(1):56–9.
20. Findling RL et al. Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(11):1445–53.
21. Scheffer RE et al. Randomized, placebo-controlled trial of mixed amphetamine salts for symptoms of comorbid ADHD in pediatric bipolar disorder after mood stabilization with divalproex sodium. Am J Psychiatry. 2005;162(1):58–64.
22. Biederman J et al. Longitudinal course of deficient emotional self-regulation CBCL profile in youth with ADHD: prospective controlled study. Neuropsychiatr Dis Treat. 2012;8:267–76.
23. Carlson PJ, Merlock MC, Suppes T. Adjunctive stimulant use in patients with bipolar disorder: treatment of residual depression and sedation. Bipolar Disord. 2004;6(5):416–20.

24. Parker G, Brotchie H. Do the old psychostimulant drugs have a role in managing treatment-resistant depression? Acta Psychiatr Scand. 2010;121(4):308–14.
25. McIntyre RS et al. The effect of lisdexamfetamine dimesylate on body weight, metabolic parameters, and attention deficit hyperactivity disorder symptomatology in adults with bipolar I/II disorder. Hum Psychopharmacol. 2013;28(5):421–7.
26. Nasr S. Modafinil as adjunctive therapy in depressed outpatients. Ann Clin Psychiatry. 2004;16(3):133–8.
27. Nasr S, Wendt B, Steiner K. Absence of mood switch with and tolerance to modafinil: a replication study from a large private practice. J Affect Disord. 2006;95(1-3):111–4.
28. Dell'osso B et al. Superior chronic tolerability of adjunctive modafinil compared to pramipexole in treatment-resistant bipolar disorder. J Affect Disord. 2013;150(1):130–5.
29. Lydon E, El-Mallakh RS. Naturalistic long-term use of methylphenidate in bipolar disorder. J Clin Psychopharmacol. 2006;26(5):516–8.
30. Wingo AP, Ghaemi SN. Frequency of stimulant treatment and of stimulant-associated mania/hypomania in bipolar disorder patients. Psychopharmacol Bull. 2008;41(4):37–47.
31.• Parker G et al. Psychostimulants for managing unipolar and bipolar treatment-resistant melancholic depression: a medium-term evaluation of cost benefits. J Affect Disord. 2013;151(1):360–4. **A systematic report on the effectiveness of stimulant drugs in a large sample of bipolar patients**.
32. Adida M, Azorin JM. Effectiveness of methylphenidate as augmentation therapy after failure of adjunctive neuromodulation for patients with treatment-refractory bipolar depression: a case report. Neuropsychiatr Dis Treat. 2014;10:559–62.
33. Bajwa WK et al. The management of catatonia in bipolar disorder with stimulants. Case Rep Psychiatry. 2015;2015:423025.
34. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. J Clin Psychiatry. 2000;61(5):378–81.
35. Fernandes PP, Petty F. Modafinil for remitted bipolar depression with hypersomnia. Ann Pharmacother. 2003;37(12):1807–9.
36. Guerdjikova AI, McElroy SL. Adjunctive methylphenidate in the treatment of bulimia nervosa co-occurring with bipolar disorder and substance dependence. Innov Clin Neurosci. 2013;10(2):30–3.
37. Halmoy A et al. Bipolar symptoms in adult attention-deficit/hyperactivity disorder: a cross-sectional study of 510 clinically diagnosed patients and 417 population-based controls. J Clin Psychiatry. 2010;71(1):48–57.
38. McIntyre, R.S., et al., Attention-deficit/hyperactivity disorder in adults with bipolar disorder or major depressive disorder: results from the international mood disorders collaborative project. Prim Care Companion J Clin Psychiatry, 2010. **12**(3).
39. Nierenberg AA et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. Biol Psychiatry. 2005;57(11):1467–73.
40. Ryden E et al. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. Acta Psychiatr Scand. 2009;120(3):239–46.
41. Skirrow C et al. An update on the debated association between ADHD and bipolar disorder across the lifespan. J Affect Disord. 2012;141(2-3):143–59.
42. Tamam L, Karakus G, Ozpoyraz N. Comorbidity of adult attention-deficit hyperactivity disorder and bipolar disorder: prevalence and clinical correlates. Eur Arch Psychiatry Clin Neurosci. 2008;258(7):385–93.
43. Wender PH, Wolf LE, Wasserstein J. Adults with ADHD. An overview. Ann N Y Acad Sci. 2001;931:1–16.
44. Mosholder AD et al. Hallucinations and other psychotic symptoms associated with the use of attention-deficit/hyperactivity disorder drugs in children. Pediatrics. 2009;123(2):611–6.
45. Viktorin, A., et al., The risk of treatment-emergent mania with methylphenidate in bipolar disorder. AJP, 2016. in press.
46. Kraemer M et al. Methylphenidate-induced psychosis in adult attention-deficit/hyperactivity disorder: report of 3 new cases and review of the literature. Clin Neuropharmacol. 2010;33(4):204–6.
47. Ross RG. Psychotic and manic-like symptoms during stimulant treatment of attention deficit hyperactivity disorder. Am J Psychiatry. 2006;163(7):1149–52.
48. Spensley J. Folie a deux with methylphenidate psychosis. J Nerv Ment Dis. 1972;155(4):288–90.
49. Spensley J, Rockwell DA. Psychosis during methylphenidate abuse. N Engl J Med. 1972;286(16):880–1.
50. Young JG. Methylphenidate-induced hallucinosis: case histories and possible mechanisms of action. J Dev Behav Pediatr. 1981;2(2):35–8.
51. Schneider BN, Enenbach M. Managing the risks of ADHD treatments. Curr Psychiatry Rep. 2014;16(10):479.
52. Hegerl U, Hensch T. The vigilance regulation model of affective disorders and ADHD. Neurosci Biobehav Rev. 2014;44:45–57.
53. Hegerl U et al. Mania and attention-deficit/hyperactivity disorder: common symptomatology, common pathophysiology and common treatment? Curr Opin Psychiatry. 2010;23(1):1–7.
54. Hegerl U et al. Are psychostimulants a treatment option in mania? Pharmacopsychiatry. 2009;42(5):169–74.
55. Brown WA, Mueller B. Alleviation of manic symptoms with catecholamine agonists. Am J Psychiatry. 1979;136(2):230–1.
56. Clower CG. Treatment of mania with dextroamphetamine. J Clin Psychiatry. 1988;49(7):283.
57. Garvey MJ et al. Dextroamphetamine treatment of mania. J Clin Psychiatry. 1987;48(10):412–3.
58. Max JE, Richards L, Hamdan-Allen G. Case study: antimanic effectiveness of dextroamphetamine in a brain-injured adolescent. J Am Acad Child Adolesc Psychiatry. 1995;34(4):472–6.
59. Bschor T, Muller-Oerlinghausen B, Ulrich G. Decreased level of EEG-vigilance in acute mania as a possible predictor for a rapid effect of methylphenidate: a case study. Clin Electroencephalogr. 2001;32(1):36–9.
60. Schoenknecht P et al. Treatment of acute mania with modafinil monotherapy. Biol Psychiatry. 2010;67(11):e55–7.
61. Kluge M et al. Methylphenidate in mania project (MEMAP): study protocol of an international randomised double-blind placebo-controlled study on the initial treatment of acute mania with methylphenidate. BMC Psychiatry. 2013;13.
62. Ng B et al. A case series on the hypothesized connection between dementia and bipolar spectrum disorders: bipolar type VI? J Affect Disord. 2008;107(1-3):307–15.
63. Van Gerpen MW, Johnson JE, Winstead DK. Mania in the geriatric patient population: a review of the literature. Am J Geriatr Psychiatry. 1999;7(3):188–202.
64. Tohen M, Shulman KI, Satlin A. First-episode mania in late life. Am J Psychiatry. 1994;151(1):130–2.
65. Fujikawa T, Yamawaki S, Touhouda Y. Silent cerebral infarctions in patients with late-onset mania. Stroke. 1995;26(6):946–9.
66. Robinson RG et al. Comparison of mania and depression after brain injury: causal factors. Am J Psychiatry. 1988;145(2):172–8.
67. Graham, A. and J. Hodges, Pick's disease: its relationship to progressive aphasia, semantic dementia and frontotemporal dementia, in dementia, A. Burns, J. O'Brien, and J. Ames, Editors. 2005, Hodder Arnold: London. p. 678-688.
68. Rahman S et al. Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. Neuropsychopharmacology. 2006;31(3):651–8.

69. Goforth HW et al. Quantitative electroencephalography in frontotemporal dementia with methylphenidate response: a case study. Clin EEG Neurosci. 2004;35(2):108–11.
70. Seamans JK et al. Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons. J Neurosci. 2001;21(10):3628–38.
71. McAllister TW et al. Randomized placebo-controlled trial of methylphenidate or galantamine for persistent emotional and cognitive symptoms associated with PTSD and/or traumatic brain injury. Neuropsychopharmacology. 2016;41(5):1191–8.
72. Mooney GF, Haas LJ. Effect of methylphenidate on brain injury-related anger. Arch Phys Med Rehabil. 1993;74(2):153–60.
73. Schumann G et al. Stratified medicine for mental disorders. Eur Neuropsychopharmacol. 2014;24(1):5–50.
74. Fountoulakis KN et al. Ultra short manic-like episodes after antidepressant augmentation with modafinil. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(3):891–2.
75. Maremmani I et al. Mood stabilizers in the treatment of substance use disorders. CNS Spectr. 2010;15(2):95–109.
76. Plante DT. Treatment-emergent hypomania or mania with modafinil. Am J Psychiatry. 2008;165(1):134–5. author reply 135.
77. DelBello MP et al. Prior stimulant treatment in adolescents with bipolar disorder: association with age at onset. Bipolar Disord. 2001;3(2):53–7.
78. Soutullo CA et al. Severity of bipolarity in hospitalized manic adolescents with history of stimulant or antidepressant treatment. J Affect Disord. 2002;70(3):323–7.
79. Castaneda R et al. Treating adult attention deficit hyperactivity disorder in hospitalized psychiatric patients. Gen Hosp Psychiatry. 2008;30(6):572–7.
80. Hamrin V, Bailey K. Gabapentin and methylphenidate treatment of a preadolescent with attention deficit hyperactivity disorder and bipolar disorder. J Child Adolesc Psychopharmacol. 2001;11(3):301–9.
81. Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatry. 2006;67(4):554–66.
82.•• Asherson P et al. Differential diagnosis, comorbidity, and treatment of attention-deficit/hyperactivity disorder in relation to bipolar disorder or borderline personality disorder in adults. Curr Med Res Opin. 2014;30(8):1657–72. **A review that extensively explores diagnostic and treatment issues on the overlapping/comorbidity among bipolar disorder, borderline personality and ADHD**.
83. Scheffer RE. Concurrent ADHD and bipolar disorder. Curr Psychiatry Rep. 2007;9(5):415–9.