A Review of the Use of Stimulants and Stimulant Alternatives in Treating Bipolar Depression and Major Depressive Disorder

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ABSTRACT

Objective: Prescribers often consider the off-label use of stimulants or stimulant alternatives as adjunctive antidepressants. The authors reviewed the available literature on the efficacy of these agents for treatment of refractory unipolar and bipolar depression.

Data Sources: PubMed, MEDLINE, and relevant English-language literature from 1988–2013 were searched. Keywords were *dopaminergic, stimulant, augmentation, treatment refractory depression, dextroamphetamine, methylphenidate, modafinil, atomoxetine,* and *cardiovascular safety.*

Study Selection: All randomized controlled trials (RCTs) published during this time period were included. When RCTs were unavailable, open studies were summarized.

Data Extraction: Data on the efficacy of stimulants and stimulant alternatives as treatment augmentation for unipolar and bipolar depression were extracted.

Results: Three open studies showed positive findings for dopaminergic stimulants, and, although 2 RCTs showed negative findings, a recent RCT revealed positive results for lisdexamfetamine as an adjunctive agent. To date, dopaminergic stimulants have not been tested in bipolar depression RCTs. Four completed RCTs suggested that modafinil/armodafinil were beneficial as treatment adjuncts for unipolar and bipolar depression, with very low rates of mood switch in bipolar depression. One study was stopped prematurely due to safety concerns of increased suicidality.

Conclusions: Modafinil and armodafinil are recommended treatment adjuncts for refractory unipolar and bipolar depression. Until recently, RCT data on dopaminergic stimulants were too limited to warrant their use as first-line treatment adjuncts. However, the promising results of 1 recent lisdexamfetamine RCT, when considered in the context of the deleterious effect of subsyndromal depression, suggest consideration of dopaminergic medications in treatment-refractory unipolar or bipolar depression when modafinil is cost prohibitive or otherwise contraindicated.

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Stimulants are among the oldest medications used in psychiatry. Stimulants were introduced to the US clinical market in 1932 as Benzedrine, an asthma inhaler, and in 1935 as Dexedrine. In the 1940s, stimulants found popularity in the United States as diet pills. Realization of the abuse potential of stimulants first emerged in post–World War II Japan, where the government had been selling stimulants to the public without prescriptions. The Japanese government consequently began limiting availability of stimulants; this was followed by a similar series of restrictions enforced by the US government in the 1960s.[1]

Almost since their initial synthesis and release, stimulants have frequently been used off-label clinically for antidepressant purposes even though no systematic studies prior to the last 2 decades have provided evidence of their long-term efficacy or safety. In the last 25 years, first-line treatments of depression have shifted radically from the broader spectrum tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). Additionally, the stimulant alternatives modafinil and atomoxetine have presented new options as potential augmentation agents for refractory depression. To date, modafinil remains approved only to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder,[2] and atomoxetine is approved only for treatment of attention-deficit/hyperactivity disorder (ADHD).[3] However, some clinical trials have investigated the potential role of these agents as adjunctive medications in the treatment of depression. In this review, we will examine the existing evidence regarding the efficacy of dopaminergic stimulants, as well as that of the newer stimulant alternatives, modafinil and atomoxetine, for treatment-refractory unipolar and bipolar depression. We will also review the recent data regarding the long-term cardiac effects of stimulants.

Pharmacology of Stimulants and Stimulant Alternatives

Amphetamine and methylphenidate activate the central nervous system by simultaneously inhibiting the reuptake of dopamine, norepinephrine, and serotonin while also stimulating their release.[4] This increases dopamine in the reticular activating system and the prefrontal cortex, as well as in the nucleus accumbens. The mechanism of action of stimulants, unlike SSRIs, relies primarily on their catecholaminergic effects. Stimulants cause the intracellular release of dopamine within the postsynaptic nerve terminal so that dopamine is released into the synapse by reversal of a vesicular transporter, rather than by exocytosis. Additionally, amphetamines inhibit the intracellular monoamine oxidase metabolism of dopamine, which also leads to increased dopamine concentration in the synaptic cleft. Thus, amphetamines both promote catecholamine release and inhibit their reuptake.[4]

Clinical Points

- There is increasing evidence that subsyndromal symptoms of depressive disorders can persist in partially treated or treatment-refractory depression and can lead to significant impairment in daily function and greatly increased risk of suicidality.
- While dopaminergic stimulants have proven themselves clinically in over 80 years of successful antidepressant application, the newer stimulant alternative modafinil, with its unique mechanism of action, may offer the benefits found in its older counterparts, but with fewer cardiovascular and abuse potential risks.
- This review found that the stimulant alternatives modafinil/armodafinil currently have the most supportive randomized controlled trial efficacy and safety data and that clinicians might therefore consider these medications as a preferable augmentation option for treatment-refractory depression.

In contrast to the classic dopaminergic stimulants, stimulant alternatives produce central nervous system changes without relying on a direct dopaminergic mechanism since, unlike the dopaminergic stimulants, their use does not result in increased dopamine in the nucleus accumbens.[4] Also in contrast to classic stimulants, modafinil is believed to act relatively locally in brain regions that control wakefulness: the suprachiasmatic nucleus, anterior hypothalamus, and amygdala. Modafinil is thought to act on glutamate, γ-aminobutyric acid, histamine, and hypocretin and to have less interaction with monoamines than do other stimulants.

Atomoxetine works as a selective norepinephrine reuptake inhibitor that acts primarily in the prefrontal cortex to increase norepinephrine levels in humans.[5] Unlike methylphenidate or dextroamphetamine, however, atomoxetine does not appear to alter dopamine levels in the nucleus accumbens or striatum. For this reason, atomoxetine, like modafinil, does not have significant abuse potential.[4]

METHOD

Data Sources

Searches of PubMed, MEDLINE, and relevant literature published from 1988–2013 and available in English were performed. Keywords searched were *dopaminergic, stimulant, augmentation, treatment refractory depression, dextroamphetamine, methylphenidate, modafinil, atomoxetine,* and *cardiovascular safety.*

Study Selection

Studies were selected on the basis of design, with preference given to double-blind randomized controlled trials (RCTs) examining the efficacy or safety of dopaminergic stimulants, modafinil or armodafinil, or atomoxetine on treatment-refractory unipolar or bipolar depression. Ten studies met these criteria. When RCTs were not available, open-label trials (9) and cohort studies (2) were summarized. Although this review did include 1 case series, individual case reports were not included.

Data Extraction

The review included results of augmentation trials of stimulant or stimulant alternatives on treatment-refractory unipolar or bipolar depression. These outcome measures included *DSM-IV* diagnostic criteria, Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impressions scale (CGI), Young Mania Rating Scale (YMRS), Global Assessment of Functioning (GAF), Inventory of Depressive Symptomatology (IDS), the Brief Fatigue Inventory (BFI), the Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR), and the Psychiatric Symptom Assessment Scale (PSAS).

REVIEW OF STIMULANT STUDIES

Overview

To our knowledge, 4 open-label studies[6–9] (Table 1) and 2 double-blind randomized, placebo-controlled studies[10,11] (Table 2) have investigated the efficacy of dopaminergic stimulant use in patients with mood disorders. Two open studies[6,9] included participants with bipolar or unipolar depression, and 2 open studies[7,8] included only subjects with bipolar depression. The RCTs investigated the efficacy of adjunctive dopaminergic stimulants for treatment-refractory unipolar depression only (Table 2) and yielded negative results. Although 3 open-label studies[6,8,9] demonstrated a positive effect of dopaminergic stimulant augmentation on patients with bipolar depression (Table 1), to our knowledge, there are no double-blind randomized, placebo-controlled studies to support these findings.

Dopaminergic Stimulants

As adjunctive treatment for unipolar depression. In 1991, Fawcett et al[6] reported an open-label examination of the safety and efficacy of adjunctive stimulant use in 32 patients, with either unipolar or bipolar depression, who had failed to respond to at least one 4- to 6-week TCA trial. Eleven of these subjects had also failed electroconvulsive therapy (ECT). One group (n = 15) was treated with MAOIs and adjunctive pemoline (doses starting at 18.75 mg), the second (n = 4) was given MAOIs and adjunctive dextroamphetamine (doses starting at 5 mg), and the third (n = 13) was given a trial of both combinations in a sequential fashion (MAOI plus pemoline, and later dextroamphetamine plus MAOI). Twenty-five (78%) of the 32 patients showed a sustained positive response at 6-month follow-up, as measured by their CGI score, to at least 1 stimulant plus MAOI. This effect was observed even in patients who had failed previous aggressive medication trials and ECT. Additionally, no adverse outcomes resulting from combined use of MAOIs and stimulants were reported, and no tolerance to long-term stimulant use was observed (Table 1).

The next study evaluating the efficacy of dopaminergic stimulants in treatment-refractory unipolar depression was a 1998 open case series[10] that found a significant decrease, based on clinical presentation, in the depressive symptoms of 7 partial responders when their stable SSRI regimens were

Table 1. Open Studies of Unipolar and Bipolar Depression

Author/Year	Stimulant/Stimulant Alternative	Design (N)	Population Studied	Treatment Comparisons	Results
Fawcett et al, 1991[6]	Pemoline and dextroamphetamine	Prospective (32)	Treatment-refractory unipolar or bipolar depression	Pemoline + MAOI (n = 15) Dextroamphetamine + MAOI (n = 4) Pemoline + MAOI followed by dextroamphetamine + MAOI (n = 13)	Significant improvement in CGI score at 6-mo follow-up (sustained improvement in 78% of patients)
Masand et al, 1998[10]	Methylphenidate or dextroamphetamine	Case series (7)	Treatment-refractory unipolar depression	Methylphenidate + preexisting multiagent antidepressant regimen (n = 4) Dextroamphetamine + preexisting multiagent antidepressant regimen (n = 3)	Marked improvement in clinical presentation was observed in each patient's case
El-Mallakh, 2000[7]	Methylphenidate	Prospective (14)	Bipolar I and II with acute depressive episode	Methylphenidate + mood stabilizer	Significant PSAS change ($P = .016$) HDRS changes nonsignificant ($P = .1$)
Carlson et al, 2004[8]	Methylphenidate and amphetamine	Retrospective (8)	Bipolar I and II with medication-induced sedation and treatment-resistant depression	Adjunctive methylphenidate or amphetamine	Mean baseline-to-endpoint CGI-BP score improvement of 2.9 points
Parker and Brotchie, 2010[9]	Methylphenidate and dextroamphetamine	Prospective (50)	Treatment-refractory unipolar or bipolar depression	Stimulant monotherapy (n = 14) Stimulant + 1 or more antidepressants (n = 36)	34% of patients reported distinct improvement in depression
Markovitz and Wagner, 2003[11]	Modafinil	Prospective (27)	Treatment-refractory unipolar or bipolar depression	Modafinil + antidepressant	Significant increase in baseline-to-endpoint GAF scores ($P < .0001$)
DeBattista et al, 2004[12]	Modafinil	Prospective (35)	Partial responders with unipolar depression	Modafinil + antidepressant	Significant improvement in HDRS baseline-to–2 wk scores ($P < .001$)
Fava et al, 2007[13]	Modafinil	Retrospective pooled analysis (348)	Pooled data from 2 previous RCTs[19,20] Treatment-resistant MDD partial responders to SSRI	Modafinil plus SSRI (n = 180) Placebo plus SSRI (n = 168)	Significant improvement in baseline-to-endpoint CGI ($P = .035$), ESS ($P = .04$), and HDRS ($P = .02$) scores
Carpenter et al, 2005[14]	Atomoxetine	Prospective (15)	Partial responders and nonresponders with depressive disorders	Atomoxetine + antidepressant	Significant reduction in mean baseline-to-endpoint IDS-SR score ($P = .001$)
Papakostas et al, 2006[15]	Atomoxetine	Chart review (12)	Partial responders and remitters to antidepressant with residual fatigue	Atomoxetine + antidepressant	Significant decrease in BFI ($P = .0015$) and HDRS-17 ($P = .0466$) scores

Abbreviations: BFI = Brief Fatigue Inventory; CGI = Clinical Global Impressions scale; CGI-BP = Clinical Global Impressions scale, Bipolar Version; ESS = Epworth Sleepiness Scale; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; IDS-SR = Inventory of Depressive Symptomatology—Self Report; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; PSAS = Psychiatric Symptom Assessment Scale; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor.

augmented with a dopaminergic stimulant. All of the patients experienced improvement in their depression, with particular relief from the symptoms of fatigue and apathy. Furthermore, the positive antidepressant effect of the stimulant was found to be sustained over time, well tolerated, and free from any evidence of tolerance or drug-seeking behavior.

More recently, a 2010 open-label study[9] examined the efficacy of stimulants both as augmentation and as monotherapy for treatment-refractory unipolar (n = 23) or bipolar (n = 27) depression. All patients had experienced frequent side effects to previous or current antidepressant drugs; unipolar participants were selected for an acute episode of melancholic depression characterized by anhedonia, psychomotor retardation/agitation, sleep and appetite disturbance, and guilt. Forty-four participants were treated with methylphenidate, and 6, with amphetamine. Thirty-six of these individuals were given the stimulant in conjunction with an antidepressant (non-MAOI), and 14 used the stimulant as monotherapy. Patients monitored their own titration with suggested starting doses of 5 mg (maximum 60 mg/d) for amphetamine and 10 mg (maximum 30 mg/d) for methylphenidate. At endpoint (mean duration = 57 weeks), 17 patients (34%) reported a distinct improvement, and 30% reported some improvement (Table 1). Of those reporting distinct improvement, 7 received the stimulant as monotherapy, and 10 received the stimulant as an adjunct to 1 or more antidepressants. The category of patients who were the best responders contained twice as many patients with melancholic depression.

Two separate randomized, placebo-controlled trials[16,17] examined the efficacy of long-acting, osmotic release methylphenidate as augmentation to antidepressant monotherapy (Table 2). The first[16] was an RCT in which osmotic release methylphenidate was given in doses ranging from 18 to 54 mg/d for 4 weeks as antidepressant augmentation for treatment-refractory depression. The primary outcome measure was change from baseline to endpoint in HDRS scores, with positive response defined

Table 2. Randomized, Double-Blind, Placebo Controlled Studies of Unipolar and Bipolar Depression

Author/Year	Stimulant/Stimulant Alternative	Population Studied	N	Treatment Comparisons	Results
Patkar et al, 2006[16]	OROS methylphenidate	Treatment-refractory unipolar depression	60	OROS methylphenidate + antidepressant (n = 30) Placebo + antidepressant (n = 30)	No significant between-group difference ($P = .22$)
Ravindran et al, 2008[17]	OROS methylphenidate	Treatment-refractory unipolar depression	145	OROS methylphenidate + antidepressant (n = 73) Placebo + antidepressant (n = 72)	No significant between-group difference ($P = .74$)
Trivedi et al, 2013[18]	Lisdexamfetamine	MDD with partial response to escitalopram	129	Escitalopram + lisdexamfetamine (n = 65) Placebo + lisdexamfetamine (n = 64)	Significant between-group difference in baseline-to-endpoint MADRS score decrease ($P = .0902$)
DeBattista et al, 2003[19]	Modafinil	Residual unipolar depression: subjects with only partial response to at least 6 wk of treatment with SSRI	136	Modafinil + SSRI Placebo + SSRI	No significant difference between modafinil and placebo in baseline-to-endpoint change in HDRS, ESS, CGI, FSS scores
Fava et al, 2005[20]	Modafinil	Residual unipolar depression: subjects with only partial response to at least 8 wk of treatment with SSRI	311	Modafinil + SSRI Placebo + SSRI	Significant difference between modafinil and placebo in baseline-to-endpoint CGI ($P = .02$) and BFI ($P = .05$) scores
Frye et al, 2007[21]	Modafinil	Treatment-resistant bipolar depression	85	Modafinil + mood stabilizer (n = 41) Placebo + mood stabilizer (n = 44)	Significant between-group difference in percentage of patients with 50% baseline-to-endpoint improvement in IDS scores ($P = .038$)
Dunlop et al, 2007[22]	Modafinil	Unipolar depression, single episode or recurrent Off antidepressant treatment for 14 d prior to first visit	73	Modafinil + fixed-dose SSRI (n = 37) Placebo + fixed-dose SSRI (n = 36)	Study halted due to reports of suicidal ideation in 2 modafinil patients
Calabrese et al, 2010[23]	Armodafinil	Treatment-resistant bipolar I depression	257	Armodafinil + mood stabilizer (n = 128) Placebo + mood stabilizer (n = 129)	Significant between-group difference in baseline-to-endpoint improvement in IDS scores ($P = .08$)
Abolfazli et al, 2011[24]	Modafinil	Unipolar depression Subjects must be free of psychotropics for 4 wk prior to study	46	Modafinil 200 mg bid + fluoxetine 40 mg/d (n = 23) Placebo + fluoxetine 40 mg/d (n = 23)	Significant between-group difference in baseline-to-endpoint HDRS scores ($P = .001$)
Michelson et al, 2007[5]	Atomoxetine	Residual unipolar depression symptoms following 8 wk of treatment with sertraline	146	Atomoxetine + sertraline (n = 72) Placebo + sertraline (n = 74)	No significant between-group difference in primary outcome measures ($P = .865$)

Abbreviations: BFI = Brief Fatigue Inventory; CGI = Clinical Global Impressions scale; CGI-BP = Clinical Global Impressions scale, Bipolar Version; ESS = Epworth Sleepiness Scale; FSS = Fatigue Severity Scale; HDRS = Hamilton Depression Rating Scale; IDS = Inventory of Depressive Symptomatology; MADRS = Montgomery-Asberg Depression Rating Scale; OROS = osmotic release oral system; SSRI = selective serotonin reuptake inhibitor.

as a 50% score reduction. The CGI and the Beck Depression Inventory-II were secondary outcome measures. Fifty patients (83%) completed the study, and, although more people responded positively in the methylphenidate group (n = 12; 40%) compared with the placebo group (n = 7; 23.3%) ($P = .22$; Table 2), there were no significant differences between treatment groups on any outcome measures. The second study[17] was a 145-subject multicenter study of participants meeting *DSM-IV* criteria for major depressive disorder, each having failed 1 to 3 previous monotherapies. All participants were taking an adequate dose of either a single- or dual-action antidepressant and were randomly assigned placebo or 18–54 mg of methylphenidate as augmentation. Treatment efficacy was measured on the MADRS and several other mood and apathy rating scales. The study found no statistically significant difference on the MADRS between the 2 treatment groups ($P = .74$; Table 2). Significantly positive results were limited to stimulant effects on fatigue and apathy. In summary, while both open studies[6,9] appeared promising for the efficacy of stimulants as adjunctive agents for treatment of bipolar or unipolar depression, the 2 double-blind studies[16,17] of unipolar depression were negative.

Despite the negative findings for previous trials with dopaminergic stimulants, a 2013 RCT[18] found that, when compared to placebo, augmentation with the longer acting dopaminergic stimulant lisdexamfetamine led to significant improvement in depressive symptoms for patients who had experienced only partial response to escitalopram. The study population, adults aged 18–55 years who met criteria for acute, non-psychotic unipolar depression, were given an 8-week course of escitalopram. At the end of 8 weeks, the population of nonremitters, as defined by HDRS-17 scores of 4 or greater, was given an additional 6 weeks of escitalopram with blinded augmentation with either placebo (n = 64) or lisdexamfetamine (n = 65) at 20 mg/d, titrated to 50 mg/d. The primary outcome measure was the mean difference in MADRS scores

between weeks 8 (end of escitalopram alone) and 14 (end of the additional 6-week course of either placebo or lisdexamfetamine augmentation). The study found a mean decrease in baseline-to-endpoint MADRS score of −4.9 for the placebo group and −7.1 for the lisdexamfetamine group ($P = .0902$). This result was consistent with a predefined significant effect between the 2 groups (determined in advance by the study investigators to be $P = .1$). The study also found significant difference and improved effect of lisdexamfetamine over placebo on the secondary measure of mean baseline-to–14 weeks improvements on the QIDS-SR between the 2 groups ($P = .0203$). Measures of safety, which included comparisons of electrocardiographic changes, blood pressure, and heart rate changes, between the 2 groups were found to be nonsignificant, as were the numbers of emergent adverse reactions, the most common of which (experienced in both placebo and lisdexamfetamine group) were jitteriness, anxiety, insomnia, and irritability.

As adjunctive treatments for bipolar depression. Data regarding efficacy and safety of classic stimulants as adjunctive treatment in bipolar depression remain sparse. The theoretical risk of a stimulant precipitating mania has led most clinicians and researchers to opt for more traditional approaches for treating the depressed bipolar disorder patient. However, ongoing concern regarding the chronic and severe nature of depression in bipolar disorder, evidence regarding the effects of subsyndromal depression on long-term function,[25,26] and the lack of many large double-blind studies assessing the efficacy of antidepressants for treating bipolar depression, have sparked further investigation. In 2000, an open study[7] of 14 bipolar patients (12 bipolar I or II, and 2 with a history of secondary mania) indicated that doses of 5–10 mg of methylphenidate taken twice daily (total daily dosing up to 10–20 mg) may provide benefit for the bipolar depressed patient (Table 1). Methylphenidate was added to a therapeutic mood stabilizer regimen that had been unchanged for at least 1 month. The decrease in HDRS scores for the 5 patients who completed the study did not reach significance ($P = .1$) after 12 weeks. However, the mean decrease in PSAS scores for these patients was significant ($P = .016$). There was 1 reported case of mania during this trial.

A retrospective case review[8] of 8 bipolar patients who had been treated (open-label) with either methylphenidate or amphetamine as adjunctive antidepressant agents indicated that this treatment augmentation could lead to improvement in residual depression and medication-induced sedation (Table 1). These patients showed an overall improvement in the course of the bipolar disorder (mean treatment duration = 18 months), with no evidence of stimulant-induced mood state switching or stimulant abuse.

REVIEW OF STIMULANT ALTERNATIVE STUDIES

Modafinil

Overview. While dopaminergic stimulants appear to have equivocal antidepressant effects, more recent studies with stimulant alternatives appear promising. Two open-label studies of modafinil as augmentation for depression have been performed, 1 with only unipolar patients[12] and 1 with a combined unipolar and bipolar patient population.[11] Both studies yielded significantly positive results in their primary outcome measures. Additionally, 4 randomized, double-blind, placebo-controlled trials[19,20,22,24] investigating the efficacy of modafinil as treatment augmentation for unipolar depression and 2 trials[21,23] investigating modafinil/armodafinil as treatment for bipolar depression have been conducted to date. All studies, except for one[22] that was stopped due to safety concerns, revealed a significantly positive separation from placebo in their outcome measures, with possibly the most profound improvement found in patients with melancholic bipolar depression.

As adjunctive treatment for unipolar depression. Marketed for its efficacy and safety in decreasing fatigue and daytime sleepiness related to narcolepsy, obstructive sleep apnea, and shift work sleep disorder, modafinil became available clinically in 2002.

In 2004, an open-label study[12] explored the efficacy of modafinil on measures of depression and fatigue (Table 1). In addition to the therapeutic dose of the antidepressant to which the subjects had experienced a partial response, participants meeting *DSM-IV* criteria for major depressive disorder (unipolar) were given modafinil in doses ranging from 100 to 400 mg. Thirty-one of the 35 subjects completed the 4-week trial. The decrease in scores on the HDRS from baseline to 2 weeks was significant ($P < .001$; Table 1), whereas the decrease between weeks 2 and 4 was not. Performance on the Stroop Interference Test was also significantly improved at 4 weeks, indicating potential for modafinil to reduce cognitive impairment associated with depression.

The results of another open-label study[11] of adjunctive modafinil (200 mg for up to 38 weeks), which included patients with bipolar as well as unipolar depression, were consistent with the above findings (Table 1). All subjects (N = 27) had undergone 1 or more previous adequate antidepressant trials (totaling 60 trials) consisting of SSRIs and/or SNRIs and were taking an antidepressant (SSRI or SNRI) at the beginning of the study. Of note, all participants listed lethargy and fatigue as the most pervasive depressive symptoms, not remitting with antidepressants alone. Seven to 10 days after modafinil initiation, the modafinil dose was increased to 200 mg twice daily for patients who had no improvement on modafinil 200 mg/d alone. At the end of the study, baseline (mean GAF score = 52.3 ± 8.4) to endpoint (mean GAF score = 61.8 ± 7.5) GAF scores increased significantly ($P < .0001$; Table 1). Forty-one percent of the patients reported that their depressive symptoms had been reduced to either mild or nonexistent, and 81% of the patients had an improved GAF score. Investigators found no signs of tolerance or abuse throughout the population.

A 2007 retrospective analysis[13] pooled patients from 2 RCTs[19,20] including 348 subjects that had examined the efficacy of modafinil augmentation for patients with partial response to SSRIs. The retrospective study included patients who had been taking 1 of 3 SSRIs (fluoxetine, paroxetine,

and sertraline), had Epworth Sleepiness Scale (ESS) scores >10, Fatigue Severity Scale (FSS) scores of 4 or above, and HDRS (17 item) scores between 4 and 25. The primary outcome measures were baseline-to-endpoint changes in the above scales. The study also compared these scores at weeks 1 and 2, using a confidence interval of 95%. The percentage of responders as measured by CGI was significantly greater in the modafinil group at both week 1 (21% modafinil vs 10% placebo; $P = .003$) and endpoint (42% modafinil vs 31% placebo; $P = .035$). Reductions in ESS scores were significantly greater in the modafinil group at both week 1 (−2.5 modafinil vs −1.5 placebo; $P = .007$) and endpoint (−4.1 modafinil vs −3.1 placebo; $P = .04$). HDRS score reductions were also significantly greater in the modafinil group at week 1 (−3.1 modafinil vs −1.9 placebo; $P = .009$) and endpoint (−5.0 modafinil vs −3.6 placebo; $P = .02$). Surprisingly, however, significant reduction in overall fatigue (FSS) was achieved only at week 1 (−0.6 modafinil vs −0.3 placebo; $P = .007$), not at endpoint. However, the researchers postulated that because the reduction in fatigue at week 1 was slightly less than the reduction at endpoint, the lack of significant difference in baseline-to-endpoint FSS scores between modafinil and placebo was less likely due to development of a physiologic tolerance to the effects of modafinil than to other confounds that may have increased the patients' response to placebo.[13] The researchers concluded that the pooled analysis findings supported the use of modafinil as treatment augmentation in MDD patients who have a partial response to an SSRI, particularly when fatigue and sleepiness are persistent residual symptoms.[13]

In a more recent (2011) double-blind, placebo-controlled study,[24] modafinil 400 mg/d (200 mg bid) was added to a fixed regimen of fluoxetine 40 mg/d, resulting in a significant improvement of depressive symptoms that appeared to be independent of the known effect of modafinil on energy and alertness. Forty-six patients with unipolar depression were randomly assigned to either modafinil or placebo using the HDRS as the main outcome measure. The groups differed significantly in HDRS changes at endpoint compared to baseline (−14.04 ± 2.49 modafinil vs −10.04 ± 2.69 placebo; $P = .001$) (Table 2). Patients in the active treatment group showed improvement over the control group in all areas of depression, not just on measures of fatigue. No significant differences in side effects were reported. Although both groups showed a decrease in HDRS scores throughout the trial, 36% of the subjects in the modafinil group experienced full symptom remission after 6 weeks, as opposed to no patients in the control group ($P = .046$).

In contrast, 1 randomized placebo-controlled, double-blind investigation[22] of modafinil as augmentation for treatment of unipolar depression was stopped prematurely due to new-onset suicidal ideation in 2 modafinil patients (Table 2). This multisite study selected patients with unipolar depressive disorder between the ages of 18–65 years who had a MADRS score of at least 15 at both screening and baseline visits. Interestingly, this is the only study that listed treatment-refractory depression for the current depressive episode among its exclusion criteria. The study also excluded candidates with any Axis II diagnosis that might "interfere with the conduct of the study." Identical modafinil and placebo tablets were prescribed during the first week, then titrated to 200 mg the second week and added to an SSRI. During the course of the trial, 1 subject developed suicidality during an overlapping titration of sertraline from 50 to 100 mg and modafinil from 100 to 200 mg. A second modafinil subject, treated with fluoxetine 20 mg, also developed suicidal ideation when modafinil was increased from 100 to 200 mg. Although both patients recovered fully, the study was halted in order to complete a full safety evaluation. This finding has not, to our knowledge, been observed in other modafinil trials. Of note, a post hoc analysis of overall suicide item ratings on both the HDRS and the MADRS found that they did not differ significantly between the 2 groups.

As adjunctive treatment for bipolar depression. In 2007, a randomized, double-blind, placebo-controlled study[21] of adjunctive modafinil treatment in 85 patients with bipolar depression found significantly positive improvements in overall depressive symptoms, as measured by the IDS (Table 2). This study analyzed depressive scale outcomes for patients with bipolar depression who had a poor response to a mood stabilizer with or without an adjunctive antidepressant. The primary outcome measure was baseline-to-endpoint IDS score change. The 2 groups did not differ significantly in the overall number of psychotropic medications taken. The patients' current medication regimens were augmented with either modafinil (mean dose = 177 mg/d) or placebo for 6 weeks. The percentage of patients who showed a 50% improvement in IDS score was significantly higher in the modafinil group (43.9%) compared to the placebo group (22.7%; $P = .038$). Additionally, the remission rate (IDS score <12) was significantly higher in the modafinil (39%) versus the placebo group (18%; $P = .033$). Although modafinil showed a significant antidepressant effect, it did not show an effect on wakefulness (Epworth Sleepiness Scale) or fatigue (Fatigue Severity Scale). These results suggest a mood effect of modafinil that was seemingly independent of the known effects of modafinil on energy and wakefulness. Dropout rates did not differ significantly between the 2 groups, nor did endpoint blood pressure, heart rate, weight, or switch rate to mania or hypomania (modafinil: 12%; placebo: 16.7%).

To date, only 1 study[23] has evaluated armodafinil, the *R*-isomer of modafinil, as a treatment for bipolar depression (Table 2). This randomized, multicenter, double-blind, placebo-controlled study treated depressed bipolar patients with either a mood stabilizer plus armodafinil or a mood stabilizer and placebo. All 257 participants were adults aged 18–65 years who had been experiencing a major depressive episode that was inadequately responsive to monotherapy or combination therapy consisting of up to 2 of olanzapine, lithium (plasma level >0.6 mEq/L), or divalproex (plasma level >50 μg/mL) for at least 4 weeks prior to baseline screening. The main study outcome measure was mean change on the IDS-C from baseline to endpoint. The primary analysis showed a statistical trend ($P = .08$) toward the

benefit of armodafinil over placebo (Table 2). Patients in the armodafinil group showed similar incidence of depression and suicidal ideation as compared to the placebo group. The armodafinil group showed slightly higher rates of insomnia (10% vs 8%), restlessness (6% vs < 1%), and anxiety (4% vs 2%), but no differences in treatment-emergent mania.

Atomoxetine

As adjunctive treatment for unipolar depression. To our knowledge, only 1 randomized clinical trial[5] of patients with unipolar depression has evaluated atomoxetine as an adjunctive treatment for depression (Table 2). Subjects with a history of treatment-resistant depression were excluded from this study. Patients (N = 146) who experienced persistent depressive symptoms after an 8-week trial of sertraline up to 200 mg/d were randomly assigned to sertraline augmentation with either atomoxetine (40–120 mg/d) or placebo. At 8-week follow-up, no significant difference in the primary outcome measure (baseline-to-endpoint change in HDRS score) was found between the 2 groups ($P = .865$; Table 2).

While the RCT of atomoxetine failed to show efficacy as treatment augmentation for unipolar depression, positive responses were seen in 2 open studies. In a 2005 trial,[14] atomoxetine (begun at 40 mg/d and titrated to therapeutic response) was added to the preexisting treatment regimens of 15 adults with a known diagnosis of a depressive disorder who had experienced partial or no response to an 8-week trial of a standard antidepressant. Eleven participants completed at least 6 weeks of the study, 9 (60%) of whom met criteria for a significantly positive improvement on all outcome measures. Mean IDS baseline score was 33.4, and remission was defined as an endpoint IDS-SR score of < 15. A significant reduction in mean IDS-SR score from baseline to endpoint was seen ($P = .001$).

Similarly positive outcomes were reported in a 2006 chart review[15] of 12 patients who had experienced either partial recovery or remission from standard antidepressant therapies but who continued to experience residual fatigue. Atomoxetine was added to one of the following preexisting antidepressants: SSRI (n = 9), mirtazapine (n = 2), and amitriptyline (n = 1). Significant outcome measures of initial-to-endpoint (4-week) change in scores were found on the BFI ($P = .0015$) and HDRS ($P = .047$).

Both open studies had relatively low dropout rates in participants taking atomoxetine, with the most commonly reported side effects being nausea, dry mouth, and increased activation. No significant changes in blood pressure or heart rate were found.

The discrepant findings between the 1 negative atomoxetine RCT[5] and the 2 positive open studies[14,15] indicate that further RCTs may be helpful before definitive conclusions regarding the treatment efficacy of atomoxetine as antidepressant augmentation can be drawn.

For bipolar depression. No studies to date have assessed the safety or efficacy of atomoxetine for the treatment of bipolar depression.

SAFETY OF STIMULANT AND STIMULANT ALTERNATIVE MEDICATION IN ADULTS

The lack of long-term safety data on stimulants has contributed to the ongoing concern regarding the risk-benefit profile of these medications. However, results of a 4-site 2011 longitudinal retrospective cohort study[27] of cardiovascular events in persons averaging over a year of stimulant treatment for ADHD were reassuring. The study collected data from 150,359 adult stimulant users, ranging in age from 25 through 64 years, who had been dispensed prescriptions for methylphenidate, amphetamine, or atomoxetine. Each medication user was matched in study site, birth year, calendar year, and sex to 2 nonusers. Occurrences of serious cardiac events—myocardial infarction (MI), stroke, or cardiac death—were compared in current or new users to remote users or nonusers. No significant difference in risk of serious cardiovascular event was found between the 2 groups. Although the design of the study may have lent itself to some degree of healthy-user bias, the size and multisite nature of the study provide some reassurance of stimulant safety.

In a recent cohort study, 43,999 new methylphenidate users were matched and compared with (4 each) healthy nonuser counterparts.[28] New methylphenidate users were defined as adults (age 18 or over) who had at least 180 days of observation before the first methylphenidate prescription. The median follow-up for the methylphenidate group was 60 days. Events of primary interest were sudden death or ventricular arrhythmia, stroke, MI, and composite endpoint of stroke or MI. In this study, the second 180 days of methylphenidate therapy had a hazard ratio (rate of serious cardiovascular events and all-cause death in new methylphenidate users compared to nonusers) that was lower than that for the first 180 days (1.26 and 1.92, respectively). Initiation of methylphenidate was associated with an almost doubled rate of sudden death or ventricular arrhythmia. However, methylphenidate dosage was inversely associated with risk of all measured cardiovascular events (mean methylphenidate dose for patients with a cardiovascular events was 20 mg). Because of the inverse relationship between methylphenidate dose and cardiovascular events, the authors concluded that an unmeasured study confound, rather than a true causal influence of methylphenidate on cardiovascular events, was most likely responsible for these findings. This potential confound offers an opportunity for a similar investigation of methylphenidate in new users, with control for preexisting cardiac risks.

Modafinil Safety

To our knowledge, there is currently no literature regarding the long-term safety profile of modafinil. Modafinil has been marketed as a less addictive, and potentially safer, alternative to its traditional stimulant counterparts. This advantage is theorized to stem from the localized nature of modafinil's mechanism of action, which may preclude the systemic changes in heart rate and blood pressure that are observed in methylphenidate and dextroamphetamine use. Although the potential for modafinil abuse remains a topic of some debate,

modafinil maintains a schedule IV FDA classification, as opposed to the schedule II classification of the dopaminergic stimulants.

Regarding tolerability, modafinil and armodafinil are associated with few side effects. When compared to placebo, armodafinil had slightly higher rates of insomnia (10% vs 8%), diarrhea (10% vs 6%), and headache (11% vs 10%).[23] There were no significant changes in laboratory values, electrocardiographic parameters, or heart rate between the armodafinil and placebo groups. Four people in the armodafinil group reported weight loss of >7%, while no patients in the placebo group reported significant weight loss. Similarly, both of the positive, double-blind modafinil studies[21,24] found no significant baseline-to-endpoint differences in blood pressure, heart rate, or weight.

Atomoxetine Safety

To our knowledge, there is also no literature to date regarding the long-term safety profile of atomoxetine. Side effects of this drug that were significantly more frequent in patients taking atomoxetine versus those taking placebo were dry mouth, insomnia, and constipation. Neither group had clinically significant changes in laboratory outcomes or evidence of serious safety concerns.[5]

DISCUSSION

Outpatient clinicians have utilized dopaminergic stimulants and, more recently, stimulant alternatives (modafinil, armodafinil, atomoxetine) to aid in their approach to treatment-refractory unipolar and bipolar depression. This literature review found more supportive data for modafinil and armodafinil than for the dopaminergic stimulants. However, this conclusion may be limited both by the limited number of studies reviewed and by the weak statistical power due to the typically small number of subjects within each study. This offers the possibility that dopaminergic stimulants may have more efficacy than would be concluded from the negative RCTs. Additionally, this review was limited to published and peer-reviewed articles. Because unpublished data are not peer-reviewed and may not reflect final analyses, we did not include these studies in our review.

Our review found 3 RCTs[16–18] investigating the efficacy of dopaminergic stimulant augmentation for treatment-refractory unipolar depression. Two[16,17] of these found dopaminergic stimulants to be ineffective for this treatment purpose. However, the most recent study[18] compared the efficacy of lisdexamfetamine to placebo as treatment augmentation for escitalopram-refractory depression and yielded positive results in terms of both efficacy and safety.

Patients with refractory depression were also included in 3 open studies[6,9,10] of dopaminergic stimulants. Each of these studies examined patients with either bipolar or unipolar refractory depression and yielded positive findings. Clearly, more randomized clinical trials are needed to clarify these discrepant findings. Conversely, modafinil showed a significant effect in the 2 open trials,[11,12] 3 RCTs,[19,20,24] and 1 pooled analysis[13] that investigated it as an augmentation agent for unipolar depression. Another RCT[22] was halted due to the emergence of suicidality in 2 subjects. Clinicians have remained understandably reticent to add stimulants to the medication regimen of a depressed bipolar patient for fear of precipitating a hypomanic or manic episode. However, it would appear that this concern is largely unsubstantiated in the literature. Although safety data regarding stimulant augmentation in bipolar depression remain limited, destabilization of the depressed bipolar patient has so far not emerged in the few trials that have examined stimulants as adjuncts to mood stabilizing regimens. Moreover, the reviewed dopaminergic studies that included subjects with bipolar depression,[6–9] albeit all open trials, all reported positive outcomes on measures of overall depressive symptoms, not just the more expected relief of apathy and fatigue. As is the case with dopaminergic use in unipolar depression, more placebo-controlled blinded trials are needed to confirm these findings. Modafinil also shows promise as an effective augmentation agent for depressed bipolar patients. To date, modafinil and armodafinil are the only stimulants to have been investigated in randomized, placebo-controlled trials for the treatment of bipolar depression.[21,23] In these RCTs, modafinil augmentation produced a rapid improvement in treatment-refractory bipolar depression (14 days on average after the addition of modafinil[21]), as well as a seemingly sustained mood improvement (follow-up at 6 weeks[21] and 8 weeks,[23] respectively).

Dopaminergic stimulants and their alternatives could provide valuable options in the pharmacologic approach to partially recovered (subsyndromally depressed) or treatment-refractory depressed patients. Some studies have reported that suicide risk and occupational impairment are significantly associated with subsyndromal depression[25,26] and suggest that this population should be more aggressively treated. Yet, in both clinically and subclinically depressed patients, trials of currently available mood stabilizers and antidepressants are often unsuccessful. With depression being the dominant pole in bipolar disorder and with a relatively high incidence of unipolar depression in the general population, other approaches must be considered for these populations. To date, only quetiapine, lurasidone, and an olanzapine-fluoxetine combination have US Food and Drug Administration approval for treatment of major depressive episodes in bipolar patients. However, symptoms that contribute to functional impairment in clinical and subsyndromal depression, such as fatigue, hypersomnia, and poor concentration, have consistently been shown to be ameliorated by stimulants. This warrants the consideration of these medications as options for their effects on energy, wakefulness, and concentration and thus their potentially positive functional impact on this population.

Recently, data regarding the cardiac safety of dopaminergic stimulants have emerged. A recent, large cohort study[27] investigating adult cardiovascular outcomes in patients with long-term stimulant use presented reassuring data about potential cardiac risks in this population. Less reassuring were the findings of another recent study[28] that indicated a nearly doubled risk for cardiovascular events in new methylphenidate users. Conclusive assertions regarding the risk-benefit profile

of dopaminergic stimulants cannot be made without further RCT investigation; however, the most recent study of lisdexamfetamine revealed very reassuring safety data.[18]

As of this writing, it is the dopaminergic stimulants that have the most supportive longitudinal cardiovascular safety data. However, that study[27] did not include data about stimulant dosage. Therefore, it is not clear if higher stimulant doses correlate with a greater likelihood for adverse cardiovascular events. Similarly, conclusions about dopaminergic stimulant efficacy are likewise hindered by the relatively low doses of methylphenidate (18–54 mg) used in both negative RCTs,[16,17] as well as the low to moderate dosing of lisdexamfetamine in the positive RCT.[18] These conservative dosing regimens also call into question not only the issue of cardiovascular safety, but also the possibility that more positive efficacy outcomes may have been achieved with higher doses of stimulants.

The abuse potential of traditional stimulants along with the lack of a positive placebo-controlled efficacy trial would preclude these medications as first-line treatments for clinical depression. However, for patients with no history of substance abuse or preexisting cardiovascular conditions, the use of dopaminergic stimulants for the treatment of residual fatigue and apathy alone in the partially recovered depressed patient may provide enough improvement in functional outcome to justify their use. Of the stimulants currently available on the market, modafinil/armodafinil currently have the most double-blind, placebo-controlled trials to support their efficacy in both unipolar and bipolar depressions. This evidence, in conjunction with their tolerability and low cardiovascular risk, provides a rationale for consideration of modafinil/armodafinil as a potential treatment augmentation for both unipolar and bipolar depression.

Drug names: armodafinil (Nuvigil), atomoxetine (Strattera), divalproex (Depakote and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lisdexamfetamine (Vyvanse), lithium (Lithobid and others), lurasidone (Latuda), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), modafinil (Provigil), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), sertraline (Zoloft and others).

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