Unipolar major depression in adults: Augmentation of antidepressants with stimulants and stimulant-like drugs

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INTRODUCTION

Stimulants (eg, methylphenidate) are primarily used to treat attention deficit hyperactivity disorder (ADHD), and stimulant-like drugs such as modafinil are used for narcolepsy, obstructive sleep apnea, and sleep shift work disorder [1]. However, stimulants have also been used for decades as add-on treatment in patients with unipolar major depression who have not responded adequately to antidepressant monotherapy [2]. In a retrospective study of patients with unipolar major depression who were treated with an antidepressant and then received augmentation therapy (n >3200), stimulants were used in 5 percent of the patients [3].

This topic reviews the efficacy of stimulants and stimulant-like drugs for augmentation of antidepressants in treatment-resistant, unipolar major depression. Choosing a drug regimen for treatment-resistant depression is discussed separately. (See "Unipolar depression in adults: Choosing treatment for resistant depression".)

RATIONALE

Adjunctive therapy for unipolar major depression is often required because initial treatment with a single antidepressant leads to remission in only 30 to 50 percent of patients [4-6]. Options for add-on treatment include second-generation antipsychotics, lithium, triiodothyronine, a second antidepressant, and psychotherapy (eg, cognitive-behavioral

therapy). It is also thought that stimulants and stimulant-like drugs may be useful for patients with treatment-resistant depression because these drugs may ameliorate symptoms such as anergia, fatigue, hypersomnia, and impaired concentration, which are often initial or residual symptoms of major depression as well as side effects of some antidepressants [7,8].

In addition, it is biologically plausible that stimulants may be of value for treating depression when combined with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). The pathophysiology of major depression may involve insufficient monoaminergic neurotransmission, and SSRIs initially increase serotonergic activity and SNRIs increase serotonergic and noradrenergic activity. However, major depression may also be associated with diminished dopaminergic transmission, and stimulants, modafinil, and pramipexole increase dopaminergic activity [9-11].

INDICATIONS

Stimulants (eg, methylphenidate) are indicated for late-life, treatment-resistant unipolar major depression. In addition, stimulant-like drugs (eg, modafinil and pramipexole) have limited evidence for efficacy in the general population of patients with treatment-resistant major depression. The use of stimulants and stimulant-like drugs is consistent with multiple treatment guidelines [12-14]. Based upon our clinical experience, we are more inclined to use stimulants and stimulant-like drugs for patients who lack energy, drive, motivation, interest, optimism, pleasure, and the ability to initiate activities [15].

Contraindications — Stimulants are generally contraindicated in patients with psychosis, persistent symptoms of anxiety or insomnia, comorbid anxiety disorders, or a history of substance use disorder that would require close monitoring of dosing and vigilance against escalating doses and misuse. Stimulants may also be contraindicated in patients with preexisting cardiovascular conditions [1]. If treatment-emergent mania occurs during pharmacotherapy with stimulants, the drugs should be discontinued abruptly.

DRUG-DRUG INTERACTIONS

Drug-drug interactions may occur when stimulants or stimulant-like drugs are combined with antidepressants. Specific interactions may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

EFFICACY OF SPECIFIC DRUGS

The evidence supporting the use of modafinil as adjunctive treatment is more compelling than that for stimulants or other stimulant-like drugs [1]. In addition, the evidence for stimulants as augmentation may be stronger for late-life depression than the general population of patients with treatment-resistant depression.

Stimulants — For the general population of patients with treatment-resistant unipolar major depression, randomized trials generally indicate that the benefit of augmenting antidepressants with stimulants such as methylphenidate or lisdexamfetamine is limited at best, but can help alleviate some specific symptoms.

- **Methylphenidate** – Add-on methylphenidate may possibly be useful in the general population of patients with treatment-resistant depression:

  - In a five-week trial that compared adjunctive methylphenidate (extended release, 18 to 54 mg per day) with placebo in 145 patients who presented with treatment-resistant depression, improvement of the depressive syndrome (including apathy) was initially greater with methylphenidate than placebo [16]. However, at the end of treatment, improvement was comparable for the two groups.

  - A four-week trial compared extended release methylphenidate (18 to 54 mg per day) with placebo as adjunctive therapy in 60 patients who presented with treatment-resistant depression [17]. Symptomatic improvement was comparable for the two groups. However, response (reduction of baseline symptoms ≥50 percent) was larger with active drug than placebo (40 versus 23 percent). Although this difference was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful.

- **Lisdexamfetamine** – Add-on lisdexamfetamine does not improve treatment-resistant depression. A meta-analysis of four randomized trials compared add-on lisdexamfetamine with placebo in patients (n = 971) who did not respond to initial monotherapy with citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine [18]. Improvement with adjunctive lisdexamfetamine and placebo was comparable.

Other smaller studies provide only indirect evidence supporting the use of adjunctive stimulants for treatment-resistant depression. A meta-analysis of three randomized trials compared stimulants with placebo as monotherapy in 62 depressed patients [19]. The trials lasted one to three weeks, and the stimulants consisted of pemoline 50 mg per day, methylphenidate 20 mg per day, or dextroamphetamine with a maximum dose of 40 mg per day. The analysis found a significant and large clinical effect favoring stimulant monotherapy over placebo.

Studies of stimulants for unipolar major depression usually omit evaluation of comorbid adult attention deficit hyperactivity disorder (ADHD). This is relevant because emotional dysregulation may be associated with adult ADHD, and there is an increased risk of depression in patients with ADHD [20-22]. In addition, the risk of ADHD is elevated in patients with unipolar depression compared with the general population. The assessment and diagnosis of ADHD in adults is discussed separately. (See "Attention deficit hyperactivity disorder in adults: Epidemiology, clinical features, assessment, and diagnosis".)

Older patients — Adjunctive stimulants may be useful for late-life, treatment-resistant depression that is accompanied by apathy, fatigue, or general medical illnesses [23]:

- A 10-week randomized trial compared methylphenidate (mean daily dose 15 mg) plus citalopram with placebo plus citalopram in 16 patients (mean age 74 years) with major depression [24]. Most patients had chronic, recurrent, and treatment-resistant depression, and the study drug and citalopram were started concurrently. Improvement was greater with adjunctive methylphenidate than placebo.

- A subsequent 16-week randomized trial by the same principal investigator enrolled patients (n = 143; mean age 70 years) with unipolar major depression who were free of psychotropic medications for at least two weeks, and assigned them to receive citalopram plus methylphenidate, citalopram plus placebo, or methylphenidate plus placebo [25]. Treatment-resistant depression was present in 41 percent of the sample. Citalopram doses ranged from 20 to 60 mg/day and methylphenidate from 5 to 40 mg/day. Improvement was greater and occurred more quickly with combination treatment than either citalopram monotherapy or methylphenidate monotherapy. In addition, discontinuation of treatment due to side effects appeared to be comparable for the three groups. It is worth noting that stimulants can lead to adverse cardiac effects, and that the maximum dose of citalopram recommended by the US Food and Drug Administration for patients aged >60 years is 20 mg/day.

In addition, indirect evidence supporting the use of adjunctive stimulants includes a randomized trial that compared methylphenidate with placebo as monotherapy for major depression in older patients with general medical illnesses; methylphenidate was beneficial [26].

Modafinil and armodafinil — For patients with treatment-resistant depression, augmentation of antidepressants with modafinil can be useful, and modafinil lacks many of the undesirable effects of stimulants, including cardiovascular risks and the potential for abuse [11].

Evidence supporting the use of adjunctive modafinil includes randomized trials. As an example, a meta-analysis of three trials lasting six or eight weeks compared adjunctive modafinil (100 to 400 mg per day) with placebo in 522 patients with unipolar major depression [7]. The majority of patients were partial responders to initial treatment with antidepressant monotherapy (primarily SSRIs), and the remaining patients received augmentation from the beginning of treatment. The analysis found a significant, but clinically small effect favoring modafinil over placebo. In the largest study, nausea and feeling jittery were more common with modafinil than placebo [27].

In addition, augmentation with modafinil may perhaps be useful for patients who have recovered from an episode of depression but still have impaired memory. A proof-of-concept (pilot) randomized trial compared a single dose of add-on modafinil (200 mg) with placebo in 60 patients with remitted unipolar depression who still had some degree of residual depressive symptoms, including cognitive dysfunction [28]. Improvement of memory was greater with modafinil than placebo.

Longer treatment with modafinil may also be useful. A 12-week prospective observational study followed patients with treatment-resistant, unipolar major depression who responded to modafinil in a randomized trial (n = 57) [29]. Improvement of depression that accrued during the randomized trial persisted during the observational study.

Armodafinil is the R enantiomer of racemic modafinil, and the half-life of armodafinil is longer than that for modafinil. Although armodafinil has not been studied in unipolar major depression, it is probably effective for this indication, based upon the demonstrated efficacy of modafinil [7].

Pramipexole — Pramipexole may be beneficial as augmentation for unipolar major depression. An eight-week randomized trial compared pramipexole (mean daily dose 1.35 mg) with placebo as add-on treatment in 60 patients who remained depressed despite treatment with a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor [30]. Improvement was greater with pramipexole, and the frequency of specific adverse effects was generally comparable for the two groups.

Although a second trial found that the combination of pramipexole and an antidepressant was not effective for treatment-resistant depression, the negative results may have been attributable to the study methods. The six-week trial randomly assigned patients who had not responded to an antidepressant (n = 39) to receive pramipexole alone, escitalopram alone, or the combination of escitalopram and pramipexole [31]. Improvement was greater with pramipexole monotherapy than combination therapy. Most patients in the combination therapy

group could not tolerate the dose titration schedule for pramipexole, and discontinuation of treatment was greater with combination treatment (9/13, 69 percent) than pramipexole alone (2/13, 15 percent) or escitalopram alone (2/13, 15 percent). Concurrently starting pramipexole and escitalopram (rather than adding pramipexole to an established therapeutic dose) may have led to the high dropout rate. In addition, the small number of study patients makes it difficult to interpret the results.

Indirect evidence supporting the use of adjunctive pramipexole for treating depression includes an eight-week randomized trial that compared pramipexole (1 mg per day) with placebo as monotherapy for the initial treatment of 70 patients with unipolar major depression [32]. Improvement was greater with pramipexole than placebo.

Atomoxetine — Atomoxetine is a noradrenergic drug that is used to treat ADHD, but does not appear to be useful as add-on treatment for depression. An eight-week randomized trial compared atomoxetine (40 to 120 mg per day) with placebo as augmentation in 146 patients with unipolar major depression who did not respond satisfactorily to sertraline monotherapy [33]. Remission was comparable for adjunctive atomoxetine and placebo (40 and 38 percent of patients).

Other dopaminergic agents — Low-quality evidence suggests that amantadine, bromocriptine, pergolide, and ropinirole may possibly be useful as augmentation for treatment-resistant unipolar major depression [34-41].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

SUMMARY

- Stimulants and stimulant-like drugs may be useful for patients with treatment-resistant depression because these drugs may ameliorate symptoms such as anergia, fatigue, hypersomnia, executive dysfunction, impaired memory, and impaired concentration, which are often symptoms of major depression as well as side effects of some antidepressants. (See 'Rationale' above and 'Efficacy of specific drugs' above.)

- Stimulants (eg, methylphenidate) are indicated for late-life, treatment-resistant depression. In addition, stimulant-like drugs (eg, modafinil and pramipexole) have limited

evidence for efficacy in the general population of patients with treatment-resistant unipolar major depression. (See 'Indications' above.)

- Stimulants are generally contraindicated in patients with psychosis, persistent symptoms of anxiety or insomnia, comorbid anxiety disorders, or a history of substance use disorder. (See 'Contraindications' above.)

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