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Use of psychostimulants in the management of treatment-resistant major depressive disorder

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Introduction

Treatment-resistant depression (TRD) is diagnosed when symptom remission of major depressive disorder is not achieved after 2 or more adequate trials of antidepressants.[1] When TRD is present, treatment guidelines recommend either switching to an alternative antidepressant, including tricyclic antidepressants or monoamine oxidase inhibitors, or augmentation with a second-generation antipsychotic.[2-7] However, the use of these may be limited in clinical practice due to their side effect profiles and risk of drug–drug interactions. Thus, there is a need for additional treatment options for TRD. This manuscript will evaluate available literature and clinical pearls of psychostimulants in TRD through an illustrative case review.

Illustrative Case

Mr. M is a 50-year-old White male who is presenting for his outpatient mental health appointment for TRD. His current regimen includes bupropion XL 450 mg by mouth once daily in the morning, citalopram 40 mg by mouth once daily, and aripiprazole 30 mg by mouth once daily. He has tried and failed adequate trials of eleven alternative antidepressants and 3 augmenting antipsychotics. Patient Health Questionnaire-9 (PHQ-9) score upon presentation is 27 (severe depression). He is actively engaged in individual and couples psychotherapy. Within the past year, he has completed full courses of electroconvulsive therapy, transcranial magnetic stimulation (TMS), and ketamine. His lowest PHQ-9 score was 20 (severe depression) during his TMS course. His chief complaint at today's appointment is "still extremely depressed, no energy, can't get out of bed." His affect is flat, and fatigue has been a concern for more than 10 years. He has undergone extensive medical workups without any clearly identifiable cause of fatigue. He declines rereferral to TMS because of transportation difficulties to the facility multiple times per week.

Evidence-Based Discussion

Psychostimulants have been suggested as a potential augmentation agent for TRD, potentially because patients may report symptoms typically targeted by psychostimulants, including fatigue, apathy, and cognitive difficulties. Psychostimulants work by increasing the synaptic activity of dopamine, noradrenaline, and serotonin and are approved by the FDA for various conditions, the most common being attention-deficit/hyperactivity disorder and narcolepsy.[8] None of the psychostimulants are approved by the FDA for use in TRD.[9] However, some treatment guidelines do include them as augmentation options. The Canadian Network for Mood and Anxiety Treatment Guidelines list modafinil 100 to 400 mg as a second-line adjunctive agent with level 2 evidence, while other psychostimulants are third-line adjunctive agents with level 3 evidence at various doses.[3] The American Psychiatric Association treatment guidelines list psychostimulants as an additional augmentation strategy, with level III evidence.[4] There are multiple treatment guidelines that do not make recommendations regarding the use of psychostimulants.[2,5-7] Literature suggests that psychostimulants may have a role in the management of TRD. A systematic review of 37 randomized controlled trials evaluated dextroamphetamine, lisdexamfetamine, methylphenidate, and modafinil and found that all psychostimulants were associated with an overall improvement in depression.[10] However, there is limited guidance on picking an agent.

Dextroamphetamine and Lisdexamfetamine

Dextroamphetamine and its prodrug, lisdexamfetamine, have both been evaluated for TRD. Dextroamphetamine

Practice Points:

1. The literature is mixed regarding the efficacy of psychostimulants in TRD, and there is no guidance on which agent is preferred.
2. It is reasonable to trial a psychostimulant as an augmentation agent for TRD in patients with multiple antidepressant failures with consideration of the various agents and patient-specific factors.
3. Psychostimulants are not benign medications and have high rates of adverse effects in clinical trials. A risk versus benefit discussion with a patient is warranted before the initiation of a psychostimulant.

has a variety of preparations, including an extended-release capsule, a transdermal patch, and an oral solution. Lisdexamfetamine is limited to a capsule and a chewable tablet. Both agents are major substrates of cytochrome (CYP) 2D6, which may lead to interactions with other psychotropics, such as bupropion, fluoxetine, and paroxetine.[11,12] Literature for dextroamphetamine is limited to case series and a short, randomized, controlled trial. In these studies, some participants used dextroamphetamine as an augmentation agent to an antidepressant, and others used it as monotherapy. Doses of dextroamphetamine ranged from 5 to 40 mg divided twice daily, with an average dose of 22 mg/d, resulting in a notable reduction in Hamilton Depression Rating Scale (HAM-D) scores.[13,14] Lisdexamfetamine has been studied as an augmentation agent to SSRIs with larger sample sizes. In 2 double-blind, placebo-controlled trials, doses ranging from 20 to 70 mg/d showed an improvement in Montgomery-Åsberg Depression Rating Scale scores compared with placebo.[15,16] An important consideration for these medications is adverse effects. In the systematic review discussed above, dextroamphetamine and lisdexamfetamine had the highest rates of adverse effects compared with the other psychostimulants.[10] In the randomized controlled trials of lisdexamfetamine, treatment-emergent adverse effect rates were up to 78.9% in the treatment group. Common adverse effects of lisdexamfetamine included decreased appetite, headache, dry mouth, insomnia, and irritability. Adverse effects leading to lisdexamfetamine discontinuation included rash, worsening depression, loss of consciousness, and suicidal ideation.[15]

Methylphenidate

Similar to dextroamphetamine, methylphenidate has several preparations available, including an extended-release capsule, a transdermal patch, an oral solution, a chewable tablet, an osmotic-release oral system, and an oral-disintegrating tablet. Methylphenidate is not metabolized by a CYP450 enzyme, making it an appealing option for those on other psychotropic agents.[17] Methylphenidate has been extensively studied for depressive conditions in older adults, traumatic brain injury, and terminally ill patients.[8] Doses of methylphenidate studied range from 5 to 40 mg/d both as an augmentation agent to citalopram with a statistically significant difference in the HAM-D when compared with citalopram plus placebo.[18] The extended-release preparation has also been studied as an augmentation agent to an SSRI at doses of 18 to 54 mg/d in those with TRD. While there were no significant differences in the reduction of HAM-D scores between the treatment and placebo groups, there were numerically more responders with $\geq$ 50% reduction in HAM-D scores in the methylphenidate group. The most common adverse effects in the methylphenidate group were loss of appetite, nausea, headache, and insomnia.[19]

Modafinil

Modafinil has a different mechanism compared with the other psychostimulants. While not fully understood, it likely acts on gamma-aminobutyric acid and glutamate and increases dopamine by blocking dopamine transporters.[20] This stimulant-like agent is only available as a tablet and is typically dosed twice daily, which can be a barrier to adherence. It is a minor substrate of CYP3A4. While interactions with other psychotropics may not be as much of a concern when compared with dextroamphetamine and lisdexamfetamine, caution is still warranted in patients on medications such as carbamazepine, phenobarbital, or phenytoin and those taking certain over-the-counter supplements, such as St. John's Wort.[21] One double-blind, placebo-controlled trial compared an antidepressant plus modafinil 200 mg twice daily with a matching placebo in participants with TRD and reported a significant difference in the reduction of HAM-D scores as well as significantly more participants who achieved at least a 50% reduction in the HAM-D score. There were no statistically significant differences in safety outcomes between the 2 groups. The most common adverse effects were anxiety, decreased appetite, headache, nausea, and sweating.[20] A multicenter, randomized, double-blind, placebo-controlled study evaluated patients who were partial responders to an adequate course of an SSRI. Participants were randomized to receive either modafinil 200 mg/d or matching placebo while continuing their antidepressant. There was a statistically significant difference in Clinical Global Impression Scores in the modafinil group compared with the placebo group at the end of the study period. The authors also note that those in the modafinil group had a significantly greater reduction in Epworth Sleepiness Scales and higher remission rates (defined as HAM-D score $<$ 8). Regarding safety outcomes, nausea

and feeling jittery occurred significantly more frequently in the modafinil group; other adverse effects reported included headache, dizziness, and dry mouth. Six percent of the treatment group discontinued the study because of adverse effects.[22]

Additional Psychostimulant Considerations

Most of these agents are schedule II–controlled substances, except for modafinil, which is schedule IV, because of the Boxed Warning due to the potential for misuse. This means there needs to be additional considerations from providers before initiating therapy. In the United States, all states have their own prescription drug monitoring requirements, and providers should consider routinely checking to ensure they are aware of any other controlled substances their patients may be receiving. Urine drug screens may also be considered at initiation and/or throughout the course of therapy to assess adherence to treatment and the use of nonprescribed substances.

Caution may be warranted in those with anxiety disorders, significant cardiovascular concerns, or a family history of cardiac disease.[23] Cost is also an important consideration, as it will vary between the different preparations of the agents. All agents have generic availability, but not necessarily for each formulation. For those with generic availability, lisdexamfetamine is more costly compared with the other options. Given ongoing stimulant shortages, it is also helpful to be familiar with alternative options if a prescribed stimulant becomes unavailable.[24]

Case Continued

Because Mr. M declines another course of TMS, he is open to starting a psychostimulant for his TRD. He currently smokes cigarettes but denies all other substance use. He is agreeable to a urine drug screen, which results negative for all substances. A review of the state's Prescription Drug Monitoring Program does not reveal any other controlled substance prescriptions. An attempt was made to taper and discontinue bupropion before initiation of a psychostimulant, though this resulted in the patient reporting significantly worsening symptoms. He is agreeable to the discussion of tapering bupropion after symptoms have improved with a psychostimulant. All 3 of the other psychotropics were continued. Mr. M preferred once daily dosing of his medications.

Additionally, his provider wanted to minimize pharmacokinetic drug–drug interactions, resulting in methylphenidate being trialed. His starting dose was methylphenidate 10 mg by mouth once daily in the morning. Given that he is prescribed multiple serotonergic agents and medications that lower the seizure threshold, education was provided on signs and symptoms of serotonin syndrome and the risk of potential seizure. His symptoms were evaluated monthly, and his dose was titrated up to 20 mg by mouth once daily in the morning over several appointments. His PHQ-9 score 4 months later is 19 (moderately severe depression), and he has noticed a significant improvement in his fatigue. He is no longer reporting spending the entirety of his day in bed.

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