

## The role of methylphenidate in depression

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### Abstract

**Introduction:** Depression is a burdening disease state where up to 30% of individuals do not respond to first-line treatment. Adjunctive use of psychostimulants has been investigated for the treatment of depression in patient populations, including those with treatment-resistant depression or terminal illness. The purpose of this paper is to present a review of the literature on the efficacy of using methylphenidate to manage depression.

**Methods:** A search was conducted in PubMed, Ovid/MEDLINE, and PsychINFO using the following key words: *psychostimulants, stimulants, methylphenidate, alternative therapy, depression, and major depressive disorder*. All reports included were published before June 30, 2015.

**Results:** For this review 10 reports, including randomized controlled, case series, and retrospective chart review studies, were identified and assessed. Patient populations studied included patients with treatment-resistant depression, patients with terminal illness, geriatric patients, and patients with miscellaneous indications, such as history of stroke and human immunodeficiency virus (HIV), or acquired immune deficiency syndrome (AIDS). For treatment-resistant depression, treatment differences for fatigue and apathy in favor of methylphenidate were found, but no difference was found for response rates in depression. Additionally, in palliative care and hospice patients, methylphenidate was found to improve fatigue and depressive symptoms. Patients with other conditions (poststroke and HIV patients) achieved some relief of depressive symptoms.

**Conclusion:** The efficacy data for methylphenidate in depression are limited, with inconsistent results in specific patient populations that limit external validity. At this time, it should not be recommended as first-line treatment in depression. Future research should be developed focusing on long-term safety and efficacy in nonspecialized patient populations.

**Keywords:** methylphenidate, depression, psychostimulant, stimulant, alternative treatment

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### Introduction

Depression affects almost 1 in 10 adults living in the United States.<sup>1</sup> Up to 30% of individuals with depression may not respond to traditional antidepressant therapy; therefore, research into alternative treatments is impor-

tant.<sup>2</sup> Alternative or augmentation therapies have been studied to treat patients with refractory depression or patients who require response or remission quicker than that of currently available antidepressants.<sup>3</sup> One class of medications that has been studied as an alternative therapy but remains controversial for the treatment of depression is the psychostimulants, including methylphenidate.<sup>4</sup>

After amphetamine was developed in the 20th century, it and other similar agents were used in the treatment of narcolepsy, depression, and fatigue. Investigators have



studied the efficacy of using psychostimulant agents like dextroamphetamine, methamphetamine, modafinil, pemoline, and methylphenidate in depression<sup>5</sup> and found that the main advantages of these psychostimulants are rapid onset and reduction of fatigue.<sup>4-7</sup> Although the evidence for psychostimulants in depression is limited to small-scale studies (controlled and open-label) and case series, the notion of a fast-acting adjunct to antidepressants is compelling.

Of these psychostimulants, methylphenidate has been studied most widely in depression. Methylphenidate is currently approved by the US Food and Drug Administration for attention deficit hyperactivity disorder.<sup>8</sup> This agent increases the synaptic activity of dopamine and norepinephrine by blocking the reuptake of these monoamine transmitters and increasing release.<sup>7</sup> Methylphenidate has a quick onset, having a peak concentration at 60 to 90 minutes after administration. The psychostimulant has a half-life of approximately 3 hours and a duration of effect of 4 hours. In therapeutic doses, it blocks more than 50% of the dopamine transporters in the brain.<sup>9</sup>

The use of methylphenidate for depression has been studied in specific patient populations, including individuals with treatment-resistant depression (TRD) and those at risk of depression, such as patients with terminal illness and those receiving palliative care. Additional studies have been conducted in patients with cancer, geriatric patients, and miscellaneous patient populations, including those with a recent stroke, with human immunodeficiency virus (HIV), and with acquired immune deficiency syndrome (AIDS). By reviewing the literature on methylphenidate in depression, the goal is to determine what role this alternative option has in comparison among traditional pharmacologic agents and in which populations it may be most beneficial for treatment.

## Methods

Studies included for review were found using the search engines PubMed, PsychInfo, and Ovid/MEDLINE. The terms used in the search included *psychostimulants*, *stimulants*, *methylphenidate*, *alternative therapy*, *depression*, and *major depressive disorder*. The limits for the studies were human beings 18 years and older. All reports published after December 31, 2000, and before June 30, 2015, were assessed for inclusion in this review. Additionally, studies prior to December 21, 2000, were evaluated for inclusion if they contributed to the aim of this review in focusing on various patient populations. A Cochrane Review published in 2008 included studies prior to the inclusion criteria time period and found there were some positive data for use of psychostimulants in depression,

but that larger and more robust trials were needed before clinical significance could be concluded.<sup>5</sup> The studies included in this review assessed the effects of methylphenidate on depression or characteristics of depression as one of their primary objectives. No studies using animal models were included. After inclusion and exclusion criteria were applied, 1 case report and 9 studies were selected for review.

## Methylphenidate in TRD

The use of psychostimulants in TRD has shown some benefit in a case series including methylphenidate ( $n = 44$ ) and dexamphetamine ( $n = 6$ ).<sup>7</sup> Patients in the case series received a diagnosis of either unipolar depression or bipolar type I or II disorder and were experiencing a current episode of depression. The mean duration of treatment was 57 weeks, and 52% of patients were still on their psychostimulant at end point. Of those receiving psychostimulant treatments, 34% self-reported complete resolution or distinct improvement based on their impression of the effect, and 30% reported “some” level of improvement, whereas 36% reported no improvement or side effects. The mean dose of methylphenidate was 22 mg. Of the patients who had reported improvement, 36 of 50 received psychostimulant augmentation therapy to other antidepressants, such as selective serotonin reuptake inhibitors or tricyclic antidepressants, and 14 used the agents as monotherapy.<sup>7</sup>

In a controlled trial of 60 patients who had been on an antidepressant at a therapeutic dose for at least 6 weeks, patients were randomized 1:1 to receive either placebo or osmotic-release oral system methylphenidate starting at a dosage of 18 mg/d titrated up to a maximum dose of 54 mg/d for 4 weeks.<sup>10</sup> Depression was measured using the Hamilton Depression Rating Scale (HAM-D), the Beck Depression Rating Scale, and the Clinical Global Impression Improvement and Severity scores (CGI-I and CGI-S, respectively).<sup>10</sup> Although there were more responders (at least a 50% reduction in the HAM-D score) in the methylphenidate group (40%) compared with the placebo group (23.3%), this difference was not statistically significant. Similarly, there were no significant differences between the two groups on the CGI-I and CGI-S scores. This study may have been limited by its small sample size because it did not meet power according to the power analysis the researchers conducted. Additionally, the study duration was only 4 weeks, which may not have been enough time to see complete clinical benefit.<sup>10</sup>

Ravindran and colleagues<sup>11</sup> performed a randomized controlled trial to assess the effect of osmotic-release oral system methylphenidate as adjunctive therapy in patients who had failed 1 to 3 antidepressant trials.

Patients had to be on a therapeutic dose of an antidepressant—which included selective serotonin reuptake inhibitors, venlafaxine, or mirtazapine—for at least 4 weeks. Additionally, concomitant administration of tricyclic antidepressants, monoamine oxidase inhibitors, and antipsychotics, and initiation of new hypnotics, such as benzodiazepines, were allowed. Patients were initiated 1:1 on either methylphenidate 18 mg/d, titrated as tolerated, or placebo for 5 weeks. The results of the study demonstrated no significant difference in efficacy between the groups in decreasing depressive symptoms as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) scores. However, patients who received osmotic-release oral system methylphenidate showed a significant reduction in apathy compared with placebo based on the Apathy Evaluation Scale (AES) in the mixed-model analysis ( $P=.01$ ). Patients' fatigue symptoms also improved based on the Multi-dimensional Assessment of Fatigue (MAF) at all visits except for the end point in the osmotic-release oral system methylphenidate group ( $P < .05$ ,  $F=6.82$ ). Overall, the patients tolerated methylphenidate; specifically, there were no significant changes in heart rate or blood pressure reported for each group. Only 1 patient, in the methylphenidate group, experienced a serious adverse event of hospitalization due to bone fractures, which was considered unrelated to the study medication.<sup>11</sup>

At this time, there is no clear evidence that methylphenidate is an effective agent in TRD. Although some subjective benefit was seen in a case series, the 2 controlled studies did not show significant improvement in depressive symptoms as measured by various rating scales. Methylphenidate should not be recommended in TRD as first-line treatment, but it could be considered to help depression because of improvements in apathy and fatigue, as demonstrated in one controlled study.<sup>11</sup>

## Methylphenidate in Terminally Ill Patients

In patients with advanced disease who are receiving palliative care, about 15% have clinically significant depression. An additional 30% do not meet criteria for Major Depressive Disorder but have clinically significant depressive symptoms and may benefit from antidepressant therapy.<sup>12</sup> The goal in these patients is often to improve energy and to achieve response quickly, making methylphenidate an appealing option. In a randomized placebo-controlled study of 30 hospice and palliative care patients (inpatient and outpatient), the effect of methylphenidate on fatigue, anxiety, and depressive symptoms was analyzed.<sup>13</sup> The patients received either methylphenidate starting at 10 mg/d, titrated up to a maximum dose of 40 mg/d, or placebo. Although the primary objective of

this study was to assess the effect of methylphenidate on fatigue, the effect on depression was assessed as a secondary outcome.<sup>13</sup>

Treatment with methylphenidate was found to reduce fatigue by 50% or more from baseline based on the Piper Fatigue Scale (PFS) score, Visual Analogue Scale for Fatigue (VAS-F), and the Edmonton Symptom Assessment Scale (ESAS) fatigue score.<sup>13</sup> The improvement in fatigue based on the PFS score appeared to be dose dependent, with the positive effect initially identified at Day 3, when patients were taking 10 mg, and increasing up to Day 14, when the average dose was 20 mg. Patients treated with methylphenidate, including those with and without cancer, showed significant improvement from Days 0 to 14 on the depression rating scales. There was a 22% reduction in the Beck Depression Inventory-II (BDI-II) and a 33% reduction in the Center for Epidemiologic Studies Depression Scale (CES-D). Although there was a 35% reduction in ESAS depression score from baseline, the change was not as pronounced as the fatigue and anxiety score change. Because methylphenidate may have an effect on more than one condition in a terminally ill patient, from this article it cannot be concluded that methylphenidate solely works on depression.<sup>13</sup>

Guan and colleagues<sup>14</sup> completed a 28-day, randomized controlled study investigating the use of methylphenidate in patients with depression and any type of cancer who were receiving palliative care. Treatment arms consisted of fixed-dose mirtazapine 30 mg daily plus methylphenidate, initiated at 5 mg twice daily and increased to 10 mg twice daily at Day 3 at the discretion of the physician; or mirtazapine 30 mg daily plus placebo.<sup>14</sup> A total of 88 patients with cancer were enrolled in the study. The primary outcome of the effectiveness of treatment was measured using the MADRS and the CGI-S scales. The methylphenidate treatment arm had a reduction in the MADRS score starting at Day 3, and this effect was seen throughout the study, with the greatest decrease on Day 28, with the differences of the least square mean changes of MADRS at 6.28 at the completion of the study. Adverse effects, including psychosis, agitation, insomnia, tremor, and seizure, were more frequent in the participants receiving methylphenidate. Five patients stopped methylphenidate because of these symptoms, so this must be taken into consideration when assessing risks with treatment.<sup>14</sup> As seen from this study, methylphenidate is a potential agent for depression in patients with cancer.

## Miscellaneous Populations

Several small studies have focused on the response to treatment with methylphenidate in poststroke patients experiencing depression. In a retrospective chart review,

17 patients were analyzed who were receiving either methylphenidate or dextroamphetamine for poststroke depression occurring during a 5-year period,<sup>15</sup> and patients received a diagnosis of either major depression or adjustment disorder with depressed mood. The patients' responses to the psychostimulants were measured by the CGI scale. Dextroamphetamine was prescribed in 11 patients at a mean dose of 8.4 mg/d, and methylphenidate was prescribed to 6 patients with a mean dose of 9.2 mg/d. At least 82% of the patients showed some improvement in their mood, ranging from moderate improvement (improvement in several symptoms) to marked improvement (nearly complete resolution of all symptoms). Most patients started to improve within 1 to 2 days of treatment. Of those patients who met criteria for major depression, 50% demonstrated moderate or marked improvement. None of the patients experienced relapse, defined in this study as a return to baseline symptoms after a moderate or marked improvement in symptoms.<sup>15</sup> Adverse events resulted in discontinuation for 3 patients. Although the study reported no differences between the two treatment groups,<sup>15</sup> it should be noted that patients in the dextroamphetamine group were reported to have confusion, tachyarrhythmia, and nausea, whereas only one of the patients in the methylphenidate group experienced agitation. The study was limited by the nature of the design of a retrospective chart review, and the evaluator was not blinded to treatment.<sup>15</sup>

In a 3-week study of patients living in a community-based, poststroke rehabilitation unit, individuals received methylphenidate starting at 5 mg—increased by 5 mg every 3 days to the maximum dose of 30 mg twice daily during 3 weeks—plus physical therapy, or placebo plus physical therapy.<sup>16</sup> The medication was tapered off during the course of 5 days after the study period. Patients receiving methylphenidate had significant improvement compared with the placebo group in depression rating scales, including the HAM-D scale ( $P=.028$ ) and Zung Self-Rating Depression Scale (ZDS;  $P=.055$ ). There were no differences in the side effects of those in the treatment group versus the placebo arm, and no patients dropped out because of adverse events.<sup>16</sup>

In a small study conducted by Fernandez and colleagues,<sup>17</sup> 15 patients with HIV and depressive symptoms receiving either desipramine 25 mg or methylphenidate 5 mg were compared. Both medications had similar improvements in scores on depression-specific rating scales, including the HAM-D, Profile of Mood States (POMS), and Brief Symptom Inventory (BSI). Treatment-emergent side effects were more common with methylphenidate at treatment initiation and more common with desipramine as treatment progressed.<sup>17</sup> The results of this study showed methylphenidate had the same effect as an

antidepressant on depression rating scales, but the results were limited by a small sample size and the low dose of desipramine at 25 mg compared with the recommended maintenance doses of 100 to 200 mg.<sup>18</sup>

Elderly patients are another patient population where the use of methylphenidate in depression has been explored. In a 16-week randomized, double-blind, placebo-controlled trial, the effect of methylphenidate, citalopram, or a combination of the two medications on depression severity was compared in an outpatient geriatric population.<sup>19</sup> Those patients included were experiencing a current episode of unipolar major depressive disorder identified by a score of at least 16 on the 24-item HAM-D. Additionally, patients had a score of at least 26 on the Mini-Mental State Exam (MMSE). Patients could not have another psychiatric disorder or unstable acute illness and/or have taken any other psychotropic medication in the 2 weeks prior to trial initiation. For the first 4 weeks of the study patients were seen in person weekly. A total of 143 patients were randomized 1:1:1 to receive 20 mg of citalopram, 2.5 mg twice a day of methylphenidate, or a combination of the two medications initially. The methylphenidate dose could be titrated up to 40 mg during the first 4 weeks based on tolerability and response according to the CGI. If patients in the citalopram group showed minimal improvement—a CGI improvement score of 3 or more by week 4—the dose could be increased to 40 mg and even to 60 mg by weeks 7 and 8 if there was insufficient response. Baseline characteristics among the groups were similar, except that gender, baseline HAM-D score, and the Cumulative Illness Rating Scale-Geriatrics significantly differed, so these variables were controlled for in subsequent analyses.<sup>19</sup>

For the primary outcome, there was a significant difference among groups in the HAM-D score from baseline to study end ( $F=2.5$ ,  $P<.001$ ). The HAM-D score was significantly greater in the citalopram plus methylphenidate group as found in the post hoc analyses. As for the rate of change for the HAM-D score, the citalopram plus methylphenidate group experienced a significantly faster decrease in mean score from baseline to Week 4, as well as after Week 4, compared with the citalopram plus placebo group, but not compared with the methylphenidate plus placebo group. For the CGI scores, 84.4% of the citalopram plus methylphenidate group improved much or very much compared with the monotherapy groups of methylphenidate or citalopram at 39.4% and 56.7%, respectively. More patients in the combination treatment group remitted ( $n=29$ ) compared with the monotherapy groups (methylphenidate,  $n=14$  and citalopram,  $n=20$ ). The treatment groups did not differ in the rate of side effects, dropout rates, or dropout reasons.<sup>19</sup> This study showed positive effects of methyl-

phenidate in a broad population who may benefit the most when antidepressant treatment is augmented.

Lastly, in a 12-week open-label study, 25 patients with dementia of Alzheimer type were treated with the immediate-release methylphenidate formulation starting at 5 mg twice daily titrated to 10 mg twice daily.<sup>20</sup> Although the primary objective was to measure the effect of methylphenidate on apathy in these patients, investigators also assessed improvement on depression using the 15-item Geriatric Depression Scale (GDS). At the beginning of the study, 78% of the patients were reported as having comorbid depression. The results of the study indicated there was not only significant improvement in the AES, with a mean decrease of 20.26 points ( $P < .0001$ ), but also in the GDS and other measures, including Activities of Daily Living and CGI. Some of the patients experienced common side effects, such as loss of appetite, increase in blood pressure, and decrease in sleep, but none of the patients discontinued the study because of adverse events. Methylphenidate demonstrated a favorable effect in this sample of elderly patients, but it was limited by the open-label design and most patients being white males.<sup>20</sup>

## Discussion

Based on the currently available literature for methylphenidate in the treatment of depression, its role in treatment is limited to certain populations. The results of the studies are inconsistent in relation to the effect of methylphenidate on depressive symptoms, including response rates and remission. However, methylphenidate may still appear to be appealing as an alternative agent because of its theoretical quick onset of beneficial effects for depression. Patients should be monitored for the common side effects of methylphenidate, including nervousness, insomnia, and anorexia, which may be limited by adjustment of dose and timing (administer lower doses after morning and early afternoon meals). Dose-related systemic effects, such as an increase in heart rate and blood pressure, are rare but should be considered when patients have cardiac history.<sup>9</sup> Caution should be used with long-term treatment and for patients with a past history of drug abuse because methylphenidate can cause dependence and addiction.<sup>8</sup>

For patients with TRD, one study showed an increased number of responders with methylphenidate,<sup>10</sup> but for the most part there were no significant differences among the depression rating scales for patients receiving methylphenidate.<sup>6,10,11</sup> Significant outcomes occurred in other symptoms associated with depression. Specifically, a reduction in apathy and fatigue was seen in patients with TRD taking methylphenidate.<sup>11</sup> In this patient population,

methylphenidate showed the least amount of positive benefit; therefore, it should only be considered when other pharmacologic options have been exhausted. Additionally, it may only help in those patients demonstrating other symptoms associated with depression.

On the other hand, in two randomized controlled trials in patients with terminal illness, significant improvement was observed in both depression rating scales and fatigue symptom rating scales.<sup>13,14</sup> The studies included patients both with and without cancer. Moreover, there was an increased positive effect seen when higher doses of methylphenidate were used, specifically 20 mg.<sup>13</sup> Methylphenidate was used as monotherapy in one study and as adjunct therapy to an antidepressant in another, demonstrating that methylphenidate may be beneficial alone or as augmentation in this patient population.

Possible benefits in depression were additionally identified in other populations with specific medical conditions, including poststroke patients and HIV/AIDS patients. In both cases, there was improvement in various depression rating scales and no significant difference in adverse side effects or tolerability.<sup>16,17</sup> Furthermore, in a randomized controlled trial of geriatric patients receiving either monotherapy methylphenidate or a combination of methylphenidate plus citalopram, significant improvement in depression was identified.<sup>19</sup> The rate of the improvement was greatest in the combination arm.<sup>19</sup> Also, in a study in elderly patients with dementia of Alzheimer type, methylphenidate demonstrated positive effects on depression, apathy, and activities of daily living scales.<sup>20</sup> Similarly to those with terminally ill patients, these studies support the idea that methylphenidate plays a beneficial role as either augmentation therapy or monotherapy.

One strength of this review was that it encompassed trials of different patient populations that currently exist. Not only was the effect on depression assessed, but the findings of the effect on other associated symptoms as well as side effects were included. On the other hand, one of the limitations of the review was that the methods—including design of the trial, severity of the patients, and duration of the treatment—differed in each type of study, making it challenging to compare the trials side by side. Additionally, the limited number of trials completed in this area present difficulty in developing an overall conclusion. The small sample sizes in the studies on patients with HIV/AIDS and poststroke patients should also be considered when applying the results to practice.

Overall, evidence suggests methylphenidate should not be used as first-line therapy, but it could be considered as an alternative agent for depression depending on the specific patient characteristics and symptoms in individuals with

advanced age and illness. A patient's current medication regimen should be taken into account when making the decision to use methylphenidate. Future studies should be completed to further investigate and solidify the role of methylphenidate in depression in various patient populations.

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