Methylphenidate Use in the Elderly Population: What Do We Know Now?

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ABSTRACT: Stimulants have been used for centuries medicinally, recreationally, and to alleviate fatigue. Because of its favorable pharmacokinetics and low abuse potential, methylphenidate became a highly prescribed drug for the treatment of attention-deficit/hyperactivity disorder (ADHD) during the 1990s, and that clinical usage continues today. Although most methylphenidate prescriptions are written for children and adolescents, it is also used for the treatment of ADHD in adults. Despite the prevalent use of methylphenidate and its relatively low adverse-effect profile, its use in the older population has been slow to evolve, largely due to concerns about cardiovascular risk. This brief review presents an overview of methylphenidate use, its adverse-effect risk in older adults, and its potential usefulness for palliative care, poststroke recovery, cancer care, fall prevention, and ADHD treatment.

KEYWORDS: Methylphenidate, attention-deficit/hyperactivity disorder (ADHD), geriatrics, depression, poststroke recovery, palliative care

Despite the clinical utility, relatively mild adverse-effect profile, and strikingly wide use of methylphenidate in young patients, the range of possible uses for the medication in adult patients, particularly the elderly, remains underexplored.

Although methylphenidate has been written about and scrutinized since the 1950s, medical providers for the geriatric population have been slow to embrace its use given the medication's associated stigma, its classification as a US Drug Enforcement Agency schedule II controlled substance, and its potential adverse effects in frail elderly patients.[1-4]

We sought to understand the current use of this drug by reviewing a diverse body of literature and updating clinicians on the current knowledge about methylphenidate, its uses, and its safety.

HOW DOES METHYLPHENIDATE WORK?

Methylphenidate is a psychostimulant with a structure similar to that of amphetamine.[5] It differs from amphetamine in that it has a piperidine ring attached, which makes it lipid-soluble.[5]

Methylphenidate works by inhibiting the uptake of dopamine and norepinephrine, and to a lesser extent, serotonin. The D isomer of methylphenidate is the primary isomer that interferes with the uptake of these neurotransmitters. This inhibition of dopamine reuptake increases the level of dopamine in many areas of the brain, resulting in increased alertness.

In a study using positron emission tomography with methylphenidate labeled with carbon 11,[6] the authors hypothesized that the therapeutic effects of methylphenidate are due in part to its ability to enhance the magnitude of dopamine induced by stimuli that by themselves would generate weak responses. However, methylphenidate was found to enhance the salience of the stimuli presented, as well as the attention and interest on the part of the subjects.[6] The same research group[7] has also postulated that methylphenidate-induced increases in dopamine could improve attention and decrease distractibility and, because dopamine modulates motivation, the increases in dopamine would also result in increased cognitive performance by enhancing the salience of the task. This was observed in adults and children alike with attention-deficit/hyperactivity disorder (ADHD).

CLINICAL APPLICATIONS

Early studies of the clinical use of methylphenidate date back to the 1950s, were observational in nature, and focused on withdrawn and depressed older patients. One such study[1] involved 215 patients in a state-run facility who were older than 60 years and who had been treated with methylphenidate, the antipsychotic reserpine, or both. The patients' ages ranged from 60 to 84 years, and the length of time a given patient had been hospitalized varied from 1 year to 53 years. The outcome measures were crude: The authors wrote that improvement was evident by the "decrease in movement on the wards and the decrease in patients remaining in bed or lying on the floor."[1] As for adverse effects, neither advanced age nor the presence of cardiac disease were found to be a contraindication for pharmacotherapy, and the benefit was observed even in

patients who had been institutionalized for more than 40 years.[1]

In a smaller study of 20 "senile" patients who were treated either with methylphenidate, reserpine, or placebo, methylphenidate exerted a "beneficial" effect with respect to mental status in 11 of the patients.[2] Of note, the authors reported that 3 patients with Parkinson disease (PD) had a "marked improvement in their tremor" while on methylphenidate. This observation of a positive impact of methylphenidate on symptoms of PD is also evident in more recent studies (discussed below).

A 1975 study[8] with a double-blind, randomized design compared methylphenidate dosed at 10 mg twice daily with placebo in 44 institutionalized, chronically ill patients over 6 weeks. Outcome measures in this study were much more rigorous than in the studies carried out in the 1950s and included the use of a global rating form completed by a physician, a mental status checklist, a nurse's observation scale, and a physical examination with laboratory testing. Patients receiving methylphenidate improved to a significantly greater extent in all domains than those receiving placebo. Of note, no adverse effects were observed or reported in any patient in the active drug group. The author wrote in the discussion section of the study, "The clear-cut response came about in the absence of side effects."[8]

DEPRESSION

With respect to older, medically ill patients, Wallace and colleagues[9] studied 13 patients who either were inpatients in a 400-bed medical center or were homebound. The mean age was 72 years, both men and women participated, and all of the patients had a diagnosis of "major depression." Methylphenidate was titrated from 5 mg at 8 AM and noon to 10 mg within 2 days, and then placebo was administered for 4 days. A blinded investigator administered the Hamilton Depression Rating Scale and the Mini-Mental State Examination at baseline, on day 4, and on day 8. Despite the small number of patients, the benefit of methylphenidate over placebo was statistically and clinically significant. Of note, adverse effects were negligible, with no change in vital sign measurements. Only 1 patient complained of "nervousness" that resolved when the methylphenidate dose was reduced.[9]

The treatment of depression is important in older medically ill patients and terminally ill patients. In one article,[10] Block highlighted why psychostimulants deserve special consideration in the population of terminally ill patients. Methylphenidate and dextroamphetamine were highlighted in a table of antidepressants because of their quick onset of action, their tolerance among the elderly, and their value in enhancing opioid analgesia while countering opioid fatigue and serving as an appetite stimulant. Other published studies have focused on the value of psychostimulants in treating depression in older patients, particularly as an augmenting agent for other antidepressants—a role that the recent literature very much supports.[11-13]

POSTSTROKE RECOVERY

A number of studies published over the past 20 years have supported the use of methylphenidate in the setting of poststroke depression and recovery.

A study published by Grade and colleagues[14] showed methylphenidate to be both safe and effective in this setting, with improvements noted in mood, ability to conduct activities of daily living, and motor functioning in the 10 patients in the treatment group, with no increase in adverse effects.

Similarly, in a detailed study utilizing functional magnetic resonance imaging (fMRI),[15] 9 stroke outpatients who had received a diagnosis of major depression based on criteria set forth in the *Diagnostic and Statistical Manual of Mental Health*, 4th edition, underwent fMRI during 2 cognitive tasks. The main outcome measure was cognitive task-dependent brain activity. This was the first study to demonstrate the beneficial effects of methylphenidate on functional cognitive neural networks in patients with poststroke depression. While the pulse rate of patients in the methylphenidate group increased compared with the 9 age- and sex-matched healthy control subjects, there was no significant effect on blood pressure.[15]

MOTOR FUNCTION

Studies representing an additional application of methylphenidate focus on postural stability, walking, and PD. One randomized, controlled, double-blind study[16] examined the effects of a single dose of methylphenidate on gait and postural stability in 30 healthy adults with a mean age of 75 years in 4 different walking task conditions while performing concurrent cognitive tasks.[16] In that study, a single dose of methylphenidate improved gait function in older adults, especially in complex dual tasks that required higher executive control.

Similar findings have been reported with a single dose of methylphenidate in 21 patients with PD where gait speed, stride time variability, and measures of fall risk all significantly improved.[17] In a larger multicenter trial,[18] methylphenidate improved gait hypokinesia and freezing in 35 patients with advanced PD who were receiving subthalamic nucleus stimulation.

Thus for geriatric depression (both in medically ill and poststroke patients) and for older patients with PD and/or gait disorders, published data appear to support the use of methylphenidate for improving mobility.

PALLIATIVE CARE AND FATIGUE

While the disciplines of geriatrics and palliative care share many domains, a comprehensive review of methylphenidate in the sphere of palliative medicine is beyond the scope of this article. The reader is referred to 2 excellent reviews on the subject.[5,19] The review by Hardy[19] is exhaustive and provides the strongest review of methylphenidate and its safety

across its various uses in geriatric patients. Additionally, a robust literature exists on the use of methylphenidate in the treatment of cancer and cancer-related fatigue. The reviews support the use of methylphenidate in this role while pointing out particular aspects and limitations of the studies that leave room for improvement.[20-22]

The findings in the literature are favorable on the safety and effectiveness of methylphenidate use in patients with "advanced" cancer or who already are in hospice care. Researchers at the Harry R. Horvitz Center for Palliative Medicine at Cleveland Clinic Taussig Cancer Center collected data from 3 different studies that had enrolled patients with advanced cancer so as to assess the efficacy of methylphenidate in that setting and to elaborate on its safety and adverse- effect profile.[23] Fifty patients, with a median age of 69 years, completed 7 days of methylphenidate treatment. Nearly all of the patients (96%) showed diminished depression and/or fatigue. Agitation, dry mouth, and insomnia were the top 3 adverse effects in this cohort. Methylphenidate at dosages of 10 to 20 mg/d was well tolerated. The authors concluded that methylphenidate was safe to use in advanced cancer and can palliate multiple common symptoms.[23]

In addition, a double-blind, placebo-controlled trial enrolled 30 hospice patients who had significant fatigue scores.[24] Patients were assigned to receive either 5 mg of methylphenidate at 8 AM and 1 PM or placebo. The doses of methylphenidate were titrated every 3 days. Fatigue was assessed using the Piper Fatigue Scale and was validated by the Visual Analogue Scale to Evaluate Fatigue Severity and the Edmonton Symptom Assessment Scale (ESAS) fatigue score. Additionally, depressive symptoms were assessed using the Beck Depression Inventory-II, the Center for Epidemiologic Studies Depression Scale, and the ESAS depression score. All patients had hemoglobin concentrations greater than or equal to 11.0 g/dL. Fatigue was the most distressing symptom identified among patients in this group, with a median age of 75 years (range, 51-90 y). Outcomes were significantly improved for both depression and fatigue. No significant medication toxicities were observed, and the mean average effective dose of methylphenidate was 20 mg/d by day 14.[24]

SAFETY AND RISK ASSESSMENT

Risk and safety concerns are prominent when clinicians prescribe methylphenidate for elderly patients. In Hardy's review of 19 controlled trials of methylphenidate in medically ill older adults,[19] the evidence for tolerability was strong, although there were some studies with conflicting results about efficacy.

In 2007, the US Food and Drug Administration (FDA) required new warnings to be added to psychostimulant medication labeling regarding reports of serious cardiovascular events—including sudden death, stroke, and myocardial infarction—in those receiving psychostimulants for ADHD.[25]

Because all psychostimulants can increase heart rate and blood pressure, cardiovascular risk is often the adverse effect of most concern for clinicians treating older adults. A retrospective population-based cohort study[26] using electronic health care records from 4 study sites and analyzing 150,359 stimulant users aged 25 through 64 years who were matched to 2 controls, addressed that concern. Among those adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of cardiovascular events.[26] In another administrative database study that also employed matched controls, Schelleman and colleagues[27] found a 1.8-fold increase in the risk of sudden death or ventricular arrhythmia among 43,999 new users of methylphenidate, but it did not indicate a causal relationship because of a lack of dose-response relationship.

More data will be forthcoming from these large databases, including an FDA-supported review of more than 500,000 patients currently taking psychostimulant medications, the details of which were announced in 2007.[28] This likely will provide clinicians with more data that can be used to inform their decisions about the use of methylphenidate. In particular, it is likely that future studies will be stratified by age, given that less than 10% of the population studied by Schelleman et al[27] comprised people aged 65 years or older. Still, it would appear that at low doses (1.25-5 mg), methylphenidate can be used safely in medically ill, depressed patients, including those of very advanced age.[29]

ADHD AND AGE

The continuation of ADHD from childhood through middle age and beyond is well documented in an excellent and authoritative review by Volkow and Swanson.[30]

Wetzel and Burke[31] highlight the paucity of data to guide clinicians in assessing older patients with ADHD, stressing that the diagnosis of ADHD at any age is a clinical one based on patient interviews and corroborating data from sources who have known the patient over a lifetime. They allude to the challenges of making a firm diagnosis and warn against missing the diagnosis in older adults given the significant functional and psychosocial impairment associated with undiagnosed ADHD.[31] It has been described that as a patient ages, the diminishing symptoms of hyperactivity may be manifested as restlessness, whereas the persisting symptoms of inattention may be manifested as difficulties in carrying out tasks (eg, keeping appointments, meeting deadlines) and may affect important functions in various aspects of life.[30]

The burden of illness and its impact on quality of life was the focus of a study in 24 adults with an ADHD diagnosis who had a mean age of 66 years and a mean age at diagnosis of 57 years.[32] ADHD symptoms reported were inattention (71%), impulsivity (58%), and disorganization (54%). While the overall prevalence of these symptoms in older

adults in the United States is not known, the question of prevalence has been addressed by researchers in the Netherlands. A much larger study was conducted with the intent of estimating the prevalence of ADHD in a population aged 60 to 94 years.[33] In sum, the estimated prevalence in the Netherlands of syndromatic ADHD in older adults was 2.8% and for symptomatic ADHD the rate was 4.2%. Of note, younger elderly adults (aged 60-70 y) reported significantly more ADHD symptoms than did older elderly adults (aged 71-94 y). The authors concluded that ADHD does not fade or disappear in adulthood and needs further study.[33]

THE TAKE-HOME MESSAGE

So what do we know now about methylphenidate?

First, there is a body of literature to support the clinical efficacy of methylphenidate in many domains among individuals in their 70s and older, including ADHD, depression, and the prevention of falls.

Second, while we are cognizant of and ever vigilant about the medication list of our patients, the relative safety of methylphenidate, particularly at low doses, has been demonstrated in patients who even exceed 100 years of age.

Finally, it is clear from findings in the literature that when cancer-related fatigue, ADHD, or refractory depression are inadequately treated or untreated, the patient suffers. While we await the publication of larger, randomized, controlled trials, we feel confident that the literature overwhelmingly supports that methylphenidate has many applications in the clinical treatment of elderly patients, and that therapeutic nihilism regarding its use no longer can be supported. ■

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