

Psychostimulants for older adults

Certain agents may improve apathy, ADHD, depression, and other conditions

Psychostimulants are recognized for their role in managing attention-deficit/hyperactivity disorder (ADHD), but also have found a treatment niche in conditions such as apathy, fatigue, and depression.¹ Psychostimulants—methylphenidate, amphetamines, and their respective isomers—are known to promote wakefulness, increase energy, and help improve attention. Although these medications can provide much-needed relief to many older patients, clinicians need to be mindful of possible side effects and safety concerns when prescribing psychostimulants for geriatric patients.

Most psychostimulant research has evaluated children and younger adults; however, geriatric patients (age >65) deserve special consideration. Although these patients' changing physiology often presents treatment challenges and may predispose individuals to adverse events, emerging evidence suggests that psychostimulants are valuable in treating motivational and attentional symptoms that do not respond to other treatments. Older adults' diminished treatment response to antidepressants, fatigue, and comorbid medical illness make stimulants an attractive treatment option. However, there is a paucity of research addressing psychostimulant use in geriatric patients. Moreover, psychostimulants should be used in older patients only after carefully considering potential side effects and general medical safety.

This article will focus on clinical scenarios in late life—such as apathy, ADHD, and depression in medically ill patients—when treatment with psychostimulants may be useful. Psychostimulants are FDA-approved primarily for use in ADHD and other uses are considered off-label.

continued



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John D. Franzen, MD

Fourth-Year Psychiatry Resident
Department of Psychiatry
University of Nebraska Medical Center
Creighton University School
of Medicine
Omaha, NE

**Prasad R. Padala, MD,
MS, FACHE**

Associate Director for Clinical Programs
VISN 16/CAVHS Geriatric Research
Education and Clinical Center (GRECC)
Associate Professor of Psychiatry
University of Arkansas for Medical
Sciences
Little Rock, AR

Martin W. Wetzel, MD

Assistant Professor
Department of Psychiatry
University of Nebraska Medical Center
Omaha, NE

William J. Burke, MD

Anna O. Stake Professor of Psychiatry
Vice Chair of Research
Department of Psychiatry
University of Nebraska Medical Center
Omaha, NE



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Preliminary evidence indicates that psychostimulants may improve apathetic symptoms in patients with dementia



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Table

Using psychostimulants in older adults

Category	Comment(s)
Clinical utility	Apathy, ADHD, fatigue, depression in medically ill patients
Starting dosage	Methylphenidate: 10 mg/d (typical dose is 20 mg/d) Consider a 5 mg/d starting dosage for frail patients Give the second dose mid-afternoon to avoid insomnia Dextroamphetamine: 10 mg/d (typical dose is 20 mg/d) Consider a 5 mg/d starting dosage for frail patients Give the second dose mid-afternoon to avoid insomnia
Comorbid medical conditions that warrant concern	Cardiac or glaucoma history
Possible drug-drug interactions	MAOIs: Serotonin syndrome, hypertensive crisis TCAs: Increased antidepressant levels Warfarin: Increased warfarin levels
Safety monitoring	Heart rate, blood pressure, weight

ADHD: attention-deficit/hyperactivity disorder; MAOIs: monoamine oxidase inhibitors; TCAs: tricyclic antidepressants

We will highlight research in this population and use case vignettes as examples to present a sensible approach to treating geriatric patients with psychostimulants (*Table*).

Stimulants and apathy

Apathy is a loss of motivation, interest, or initiative that is not attributable to cognitive impairment, diminished consciousness, or emotional suffering.² Considered a distinct entity from depression, apathy is common late in life, particularly in persons with dementia of the Alzheimer's type (DAT); 70% to 90% of patients may experience apathy at some stage of dementia.³ Apathy is linked to impairment in activities of daily living and needing more assistance from caregivers, which increases caregiver burden. Treating apathetic symptoms may improve quality of life for the patient and caregivers. For a case study of an older patient with apathy treated with a psychostimulant, see *Box 1* (*page 26*).

Apathy has been treated successfully with a variety of stimulant medications. In an open-label study, patients with DAT who received methylphenidate, 10 to 20 mg/d, showed significant improvement in Apathy Evaluation Scale (AES) scores.⁴ Similarly, Herrmann et al⁵ also demonstrated improvements in AES scores in DAT patients taking methylphenidate, 20 mg/d, compared with placebo.

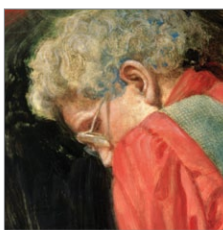
Although methylphenidate appears to have the strongest evidence for treating apathy, dextroamphetamine also has been shown to produce modest improvements in apathy scale measures.⁶ A double-blind, placebo-controlled crossover study showed that dextroamphetamine, 20 mg/d, significantly improved scores on neuropsychiatric inventory scales that were driven by apathy subscales.⁶ However, this trial was small (N = 8).

Preliminary evidence indicates that psychostimulants may improve apathetic symptoms in patients with dementia. In Mr. A's case (*Box 1, page 26*), he experienced apathy symptoms that affected his quality of life and that of those around him. He showed a clear lack of interest and motivation and indifference. This scenario is common among geriatric patients and may be misinterpreted as depression. Although the overlap may be considerable, screening for apathy may help determine a treatment course with psychostimulants instead of antidepressants, thus avoiding unnecessary medication trials.

Stimulants for ADHD

ADHD is a neurobehavioral disorder that is identified in approximately 8% of children and persists in 4% of adults.⁷ ADHD is characterized by impulsivity, motor restlessness, and inattention; the latter feature generally is

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The benefits of treating ADHD in older adults may outweigh the risks associated with psychostimulants

Box 1

Case 1: A dementia patient who loses interest in life

Mr. A, age 76, has dementia of the Alzheimer's type. His family brings him to a psychiatrist because Mr. A exhibits a generalized loss of interest. His history reveals a gradual onset of memory problems with steady decline. Current deficits include problems with forgetfulness, misplacing items, increasing difficulty with names, occasional repetitiveness, and mild word finding difficulty. His family complains that Mr. A does not take care of himself, sits all day long, is not interested in his favorite TV shows, is indifferent to his physical health, is not interested in catching up with friends, and has been doing very little from day to day. He does not seek food but cleans his plate when served. His family became concerned when Mr. A showed no excitement in going to his grandson's baseball game, which he had previously enjoyed. Mr. A denies

any concerns and scores a 3 out of 15 on the Geriatric Depression Scale. Mr. A's family rated him 4 on the same scale.

On the Apathy Evaluation Scale (AES), he scores 46 (moderate severity). We start methylphenidate, 5 mg administered in the morning and early evening (5 PM). Subsequent conversations 2 weeks later with Mr. A's family revealed Mr. A's interest levels have improved and reported no side effects. We increase methylphenidate to 10 mg twice a day. Mr. A has remarkably improved hygiene 1 month later and is more engaged in the interview. He scored a 32 (mild severity) on the AES and the family notes that he is interested in watching his grandson play baseball. During this treatment, we did not change Mr. A's other medications—donepezil, 10 mg/d, and bupropion, 150 mg/d.

more prominent with advancing age.⁸ If left untreated, ADHD has societal burdens, such as educational and occupational impairments.⁹ There is little data on ADHD in older adults and no placebo-controlled trials. For a case study of an older patient with ADHD treated with stimulants, see *Box 2*.¹⁰

Psychostimulants are considered the mainstay of ADHD treatment. First-line treatments include methylphenidate and amphetamines. A meta-analysis found a significant improvement in ADHD symptoms in adult patients taking psychostimulants compared with placebo, with no difference between immediate-release and long-acting formulations.¹¹ Although these findings were reported in younger adults, they may be relevant for older persons as well. Wetzel and Burke¹² described how ADHD presents in older adults and argued that the benefits of treating ADHD in this age group often outweigh the risks associated with psychostimulants, which can be diminished through careful screening.

Individuals who present with ADHD symptoms in late life often appear to be high functioning. Some may describe achieving academic and professional success, but may report chronic problems associated with inefficient learning and distraction compared with their peers because of untreated inattention symptoms. Faraone et al¹³ argue that

similar to other illnesses, ADHD is represented by a spectrum of disease, which may be diagnosed in late life or as subthreshold ADHD. Individuals who did not meet diagnostic criteria in childhood or were not evaluated or treated may experience unremitting symptoms that contribute to functional impairment, persistent discouragement, and distress. Frustrations with distractibility, disorganization, and incompleteness of tasks may have a psychological impact reflected by low self-esteem and irritability, and be a chronic source of occupational and relationship dysfunction. Diagnosing and treating ADHD in late life can improve longstanding functional impairments and overall quality of life.

Other uses

Depression. Although not a first-line treatment, psychostimulants have shown benefit for treating depressive disorders, particularly when patients require immediate improvement. These scenarios are common among medically ill patients, such as those with cancer, stroke, or human immunodeficiency virus (HIV), when it is urgent for patients to participate in their treatment plan. A double-blind, placebo-controlled, randomized study that looked at older depressed patients with medical comorbidities

Case 2: 'Forgetfulness' or undiagnosed ADHD?

Mr. J, age 66, is an attorney who presents for evaluation after he identified common features in friends who have attention-deficit/hyperactivity disorder (ADHD). In grade school, Mr. J's teachers told him that he employed very little effort and was not meeting his potential, although he performed exceptionally well. He reports similar experiences throughout his education and says he was careful to select classes that were interesting, but did not require demanding projects or burdensome homework. In law school, he felt academically challenged for the first time but realized he had limited study skills. Mr. J graduated in the top 26th percentile of his class using "an unbelievable amount of effort compared with other students."

Mr. J describes significant impairment in organizational skills and ability to keep track of time, procrastination, incompleteness of tasks, and substantial distractibility during conferences. He says he has difficulty reading briefs depending

on his emotional connection to the subject matter. Family history revealed that his mother likely had undiagnosed ADHD. He recently married and his wife encouraged him to seek treatment for "forgetfulness." Mr. J maintains a busy, successful law practice but has become increasingly frustrated by his inability to follow through on simple tasks that could help grow the practice and generate revenue.

Mr. J has an elevated score on the Adult ADHD Symptom Rating Scale.¹⁰ He is referred to his primary care physician to evaluate his general health before beginning medication. At follow-up, Mr. J was started on lisdexamfetamine, 20 mg/d, titrated to 40 mg/d. On subsequent visits he reports improved symptoms without side effects. His vital signs are normal and he reports feeling more productive in his work and achieving significant improvement in the day-to-day operations of his practice.

ties found that methylphenidate was well tolerated, worked quickly, and effectively treated depression.¹⁴ However, these results must be interpreted cautiously because the entire study was conducted in 8 days, which included a crossover design that administered methylphenidate 10 mg/d and 20 mg/d for 2 days each. A review of stimulant effectiveness in patients whose depression was associated with HIV, stroke, or cancer and in medically ill patients argued that although benefits have been reported, they must be interpreted tentatively because of a lack of randomized trials.¹⁵ However, limited evidence supports an effect of stimulants in treating fatigue, anorexia, pain, and sedation in these populations.¹⁵

Stimulants' immediate onset of action may be particularly useful in terminally ill patients who suffer from fatigue or depression. A double-blind, placebo-controlled, randomized study demonstrated that augmenting citalopram, 20 to 40 mg/d, with methylphenidate, mean dose 15 mg/d, for 3 weeks in older depressed patients significantly improved treatment response and accelerated time to remission compared with citalopram and placebo.¹⁶ However, a recent Cochrane review did not show clear efficacy for psychostimulants to treat depression.¹⁷

Fatigue. Along with depression, fatigue frequently is seen in older patients with medical illnesses. Mood disorders, medical comorbidities, and sleep disturbances are linked to fatigue. Underlying medical causes such as hypothyroidism, anemia, and electrolyte imbalances should be ruled out before starting a psychostimulant. A review by Minton et al¹⁸ that looked at cancer-related fatigue suggested that methylphenidate can be beneficial, although the evidence is mixed.

Interferon-alpha treatment for hepatitis C can cause depression and fatigue, and psychostimulants may help treat fatigue-related side effects.¹⁹ Fatigue may present as an isolated symptom in interferon-alpha treatment and psychostimulant use may prevent patients from taking an additional medication, therefore decreasing the risk of further side effects.

Fall risk. Some evidence supports using psychostimulants to lower the risk of falling and hypoactive delirium. A recent review by Elie et al²⁰ concluded that stimulants could improve cognitive function in end-of-life hypoactive delirium. Additionally, a randomized, placebo-controlled, double-blind study that evaluated fall risk concluded that methylphenidate, 20 mg/d, might improve some

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Stimulants' immediate onset of action may be particularly useful in terminally ill patients who suffer from fatigue or depression

Box 3

Psychostimulants: Prescribing limitations

As schedule II controlled substances, psychostimulants are subject to prescribing limitations. The current Drug Enforcement Administration (DEA) policy on schedule II controlled substances allows for the equivalent of a 90-day supply of medication to be written with multiple prescriptions. DEA requirements for multiple prescriptions include:

- Each prescription issued is for a legitimate medical purpose by an individual practitioner acting in the usual course of his/her professional practice

- The individual practitioner must provide written instructions on each prescription indicating the earliest date on which a pharmacy may fill each prescription

- The issuance of multiple prescriptions is permissible under applicable state laws

- The individual practitioner fully complies with all other applicable requirements under the Controlled Substances Act and implementing regulations, as well as any additional requirements under state law.²²

aspects of executive function and gait stability in older adults.²¹ The authors hypothesized that improved cognition associated with psychostimulant use may play a role in improving fall risk.

Safety concerns

Clinicians should be aware of safety considerations and possible side effects when prescribing psychostimulants. Psychostimulants are controlled substances and are subject to restrictions (Box 3).²² In 2007, the FDA issued warnings regarding an association between psychostimulant use and sudden death, myocardial infarction, and stroke in patients with preexisting cardiac abnormalities or heart problems.²³ Also, some evidence indicates that psychostimulants can increase heart rate and systolic blood pressure. These parameters should be monitored during treatment. Reducing or stopping psychostimulants generally reverses cardiovascular effects. Although the evidence to support these events appears sparse, perform a thorough history before beginning a stimulant and make appropriate referrals as indicated. In November 2011, the FDA reported that psychostimulant use in children and young adults is not associated with adverse cardiovascular events, including stroke, heart attack, and sudden cardiac death.²⁴

Less common side effects reported with psychostimulants include anxiety, insomnia, hallucinations, anorexia, delirium, palpitations, and headache. A meta-analysis of studies of adults with ADHD found that adverse events related to psychostimulants were

relatively rare; the most common side effects were diminished appetite and difficulty sleeping.²⁵ Sleep-related side effects can be avoided by dosing these medications earlier in the day, typically before 5 PM. Herrmann et al⁵ reported 2 cases of apparent delirium and 1 with irregular heartbeat in patients with DAT taking methylphenidate vs placebo. However, most patients in this study experienced mild or no adverse events.

Other safety concerns involve using methylphenidate in patients with glaucoma. In theory, stimulants could exacerbate an acute attack of glaucoma in patients with narrow-angle glaucoma. Patients at risk should be referred to an ophthalmologist for an assessment.

Review other medications the patient is taking and assess for possible drug-drug interactions. Combining monoamine oxidase inhibitors (MAOIs) and methylphenidate warrants caution because of the risk of serotonin syndrome and hypertensive crisis. However, there are case reports of successful MAOI/methylphenidate therapy.²⁶ Additionally, methylphenidate increases levels of warfarin and tricyclic antidepressants when taken with these agents.²⁷ Psychostimulants generally are well tolerated by most individuals and taking a careful history may help prevent adverse events.

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Psychostimulants can increase heart rate and systolic blood pressure; reducing or stopping these drugs generally reverses cardiovascular effects



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Sleep-related side effects can be avoided by dosing psychostimulants earlier in the day, typically before 5 PM

Related Resources

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Drug Brand Names

Bupropion • Wellbutrin, Zyban	Methamphetamine • Desoxyn
Citalopram • Celexa	Methylphenidate • Ritalin, Concerta
Dexmethylphenidate • Focalin	Mixed amphetamine salts
Dextroamphetamine	• Adderall
• Dexedrine	Warfarin • Coumadin
Donepezil • Aricept	
Lisdexamfetamine • Vyvanse	

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Bottom Line

Psychostimulants may benefit older adults with apathy, attention-deficit/hyperactivity disorder, fatigue, or depression. Initiate these medications cautiously and be aware geriatric patients may need a lower total dose than younger patients. Carefully evaluate risk/benefit profiles for older patients, paying particular attention to cardiovascular history.