New interest in stimulants

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The psychostimulants methylphenidate and dexamfetamine have been used safely in child psychiatry for attention deficit and hyperactivity disorder for more than two decades. Use of stimulants in elderly people probably predates that in children; however, interest was not sustained, and little progress has been made.

Mechanisms of action
Psychostimulants such as methylphenidate and dexamfetamine release dopamine from most brain regions including the prefrontal cortex, and inhibit reuptake of all biogenic amines. Methylphenidate increases the level of extracellular dopamine transporters. After oral administration and absorption in the gastrointestinal system, it crosses the blood-brain barrier readily, initiating its stimulant effect within 30–45 minutes.

Dexamfetamine, owing to its structural similarity to catecholamines and serotonin, can directly activate the receptors of these neurotransmitters. It also increases extracellular synaptic dopamine through selective binding of the dopamine transporter. The resultant effect is increased alertness, insomnia, euphoria, decreased appetite, and even psychosis in very high doses.

Modafinil is not regarded as a typical psychostimulant. Its dopamine-releasing action in the nucleus accumbens is weak, hence its low dependency potential. It inhibits noradrenergic reuptake, increases excitatory glutaminergic transmission, and has central alpha-1 adrenergic agonistic activity.

Possible uses of stimulants
According to the monoamine hypothesis of depression, this disorder results from decreased activity in the monoamine neurotransmitter system, especially norepinephrine and serotonin. By increasing the activity of these neurotransmitters in the brain, especially in the prefrontal cortex, methylphenidate could positively affect depressed elderly patients.

The efficacy of methylphenidate in withdrawn elderly patients was demonstrated in a randomised placebo-controlled trial,1 and in n=1 trials2 in depressed or apathetic geriatric patients aged 78–81 years. Three additional case studies of methylphenidate as an antidepressant in elderly patients showed no significant side-effects.3 Other older patients who might benefit from methylphenidate include those with terminal cancer and depression,4 and people with post-stroke depression.5 Treating bipolar depression is also difficult, and methylphenidate might have a role.6

Case reports have also been published of adjunctive treatment with methylphenidate in combination with venlafaxine7 and mianserin.8 Methylphenidate with citalopram9 showed positive results in open-label studies of ten elderly depressed patients aged 68–92 years. Another case study reported successful augmentation of fluoxetine with modafinil in a 78-year-old depressed patient with myocardial infarction after initially non-response to fluoxetine alone.10

Patients with dementia may also benefit from stimulant treatment. Negative symptoms of dementia in 27 elderly patients aged 62–92 years treated with methylphenidate showed some positive results.11 It was also useful for treating anorexia secondary to gradual onset of apathetic behaviour without appreciable side-effects in three patients with severe dementia who had been in long-term institutional care.12

One randomised double-blind, crossover trial showed methylphenidate to be better than placebo for treating apathy in patients with Alzheimer’s disease who were stabilised on cholinesterase inhibitors.13 Another randomised double-blind placebo-controlled single-dose crossover study was done in patients without dementia but reporting memory loss. In this study, methylphenidate seemed to improve some aspects of executive function, mobility, and stability of gait. The authors suggested that stimulants might have a role in reducing risk of falling in older adults.14

Stimulants have been used across adult age groups to treat depression, epilepsy, Parkinson’s disease, psychopathic states, attention deficit and hyperactivity disorder, and obesity.15 Such drugs may be of special benefit in terminally ill patients who, through alleviation of depressive symptoms, could live their last days with dignity.

A more recent review of 19 controlled trials reported possible efficacy of methylphenidate for depressive symptoms, fatigue, and...
apathy in medically ill older adults and terminally ill adults.\(^\text{16}\) Another review suggested some potential of stimulants in apathy and depression and apathy in older adults.\(^\text{17}\)

**Drawbacks and controversies**

Many of the reports of efficacy of psychostimulants in older patients cited here would not stand the rigorous scrutiny of today’s evidence-based medicine; however well-designed studies refuting these positive claims are lacking. Most of these studies are rather old, reflecting the lack of interest and activity in this area. Reawakening and sustaining interest in exploring the use of psychostimulants in elderly patients is warranted.

We recently treated a male patient aged 69 years with bilateral infarct of the basal ganglia initially presenting with depression. His depressive symptoms responded to antidepressants, but he still had disabling apathy that severely affected his quality of life and that of his spouse. He was unsuitable for electroconvulsive therapy because of a recent basal ganglia infarct seen on CT scanning. A visiting neuropsychiatrist suggested starting our patient on a small dose of stimulants, but we were reluctant to try this approach. Such patients make one wonder: what next? What do we do when nothing else works?

Although stimulants may have beneficial effects in older patients, one has to exercise caution. Stimulants have potentially serious side-effects including anorexia, insomnia, irritability, headache, stomach pain, mood swings, paranoia, tachycardia, high blood pressure, and even heart failure. Drug interactions are also important in this age group since many people are on multiple prescriptions.

The tendency to misuse stimulants, and the emergence of equally effective treatment options, with fewer side-effects have contributed to the decrease in prescriptions of stimulants over the years. However, drug misuse and dependence is very low in older people. A national epidemiological survey on alcohol and related conditions in the USA\(^\text{18}\) showed low levels of drug-use disorders (as categorised the *Diagnostic and stasticalmanualofmentaldisorders-IV*)\(^\text{19}\) in people older than 65 years compared with other age groups. In this study, the lifetime prevalence of drug dependence in the over 65s was 0.2%, compared with 1.9% in 45–64 year-olds, 3.5% in those aged 30–40 years, and 4.1% at 18–29 years.

We do not advocate the indiscriminate use of stimulants in older people, but to use these drugs carefully in a very select group of patients, after balancing the risks and benefits. However, interest in using stimulants in the elderly population appears almost non-existent in contemporary psychiatric practice. In our psychiatric training, stimulants were not mentioned, even as a theoretical treatment option for elderly people. New research of stimulants in all areas of potential use in the elderly population is needed.

**We have no conflict of interest.**

**References**

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