

2014

# Do Stimulant-Type Drugs Help Improve Cognitive Function and Apathy in Geriatric Patients?

Jacquelyn Menarde

*Philadelphia College of Osteopathic Medicine, jacquelynme@pcom.edu*

Follow this and additional works at: [http://digitalcommons.pcom.edu/pa\\_systematic\\_reviews](http://digitalcommons.pcom.edu/pa_systematic_reviews)



Part of the [Medicine and Health Sciences Commons](#)

---

## Recommended Citation

Menarde, Jacquelyn, "Do Stimulant-Type Drugs Help Improve Cognitive Function and Apathy in Geriatric Patients?" (2014). *PCOM Physician Assistant Studies Student Scholarship*. Paper 179.

This Selective Evidence-Based Medicine Review is brought to you for free and open access by the Student Dissertations, Theses and Papers at DigitalCommons@PCOM. It has been accepted for inclusion in PCOM Physician Assistant Studies Student Scholarship by an authorized administrator of DigitalCommons@PCOM. For more information, please contact [library@pcom.edu](mailto:library@pcom.edu).

**Do stimulant-type drugs help improve cognitive function and apathy in geriatric patients?**

Jacquelyn Menarde, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

December 20, 2013

## ABSTRACT

**OBJECTIVE:** The objective of this systematic review is to determine whether or not stimulant-type medications help to improve cognitive function and apathy in geriatric patients.

**STUDY DESIGN:** Systematic review of three English language primary studies published in 2001 and 2008.

**DATA SOURCES:** Two randomized control trials and one individual randomized control trial comparing methylphenidate administration to placebo for improvement in cognitive function and apathetic mood in elderly patients were obtained using PubMed.

**OUTCOMES MEASURED:** Clinical outcomes of apathy were measured according to the Apathy Evaluation Scale (AES), Neuropsychiatric Inventory (NPI), the Montgomery Asberg Depression Rating Scale (MADRS) and the Barthel Index both before and after the administration of methylphenidate or placebo. One study measured improvements in cognitive function after the administration of methylphenidate. Cognitive function was measured through a computerized neuropsychological test known as Go-NoGo.

**RESULTS:** In the study by Ben-Itzhak et al, cognitive function scores were significantly improved from baseline after the administration of methylphenidate ( $P = 0.03$ ), whereas there was no improvement from baseline after administration of a placebo ( $P = 0.96$ ). Herrmann and colleagues showed a statistically significant ( $P = 0.047$ ) improvement in AES scores (a decline in apathetic symptoms) after the administration of methylphenidate compared to the placebo. Unfortunately, multiple participants experienced adverse effects of the medication, which resolved upon discontinuation ( $NNH = 7$ ). In the study by Jansen et al, clinically significant treatment effect was shown in two depressed individuals with improvement in their MADRS score and one patient with improvement in their AES score. One patient could not complete the study.

**CONCLUSIONS:** Improvement in cognitive function and apathy were demonstrated by the administration of methylphenidate in all three studies. The results of the randomized control trial by Ben-Itzhak et al demonstrate overall improvement in executive function, specifically, higher cognitive processes, after the administration of methylphenidate. Herrmann and colleagues were able to prove that stimulants improve features of apathy, but adverse effects must be considered. Jansen et al concluded that single-patient trials are effective in determining the overall significance of methylphenidate use for apathy in depressed geriatric patients.

**KEY WORDS:** methylphenidate, apathy, elderly, cognitive function, aging.

## INTRODUCTION

Apathy, defined as a lack of motivation, is recognized as a psychiatric syndrome common among the elderly<sup>1</sup>. Apathetic states are associated with a decrease in executive function, specifically cognitive function and an overall decrease in daily function<sup>1</sup>. This paper evaluates two double blind, cross-over, randomized control trials (RCT) and one individual, cross-over RCT comparing the efficacy of methylphenidate as an oral medication for improving cognitive function and apathy in geriatric patients.

Apathy is frequently seen among geriatric patients solely as a psychiatric syndrome or it may be seen as a symptom in other diseases, specifically in dementia, Parkinson's disease or depression<sup>2</sup>. It is important to distinguish apathy from depression. Although each share common symptoms, those unique to apathetic patients include: blunted emotional response, indifference, low social engagement, diminished initiation and poor persistence<sup>1</sup>. Physiologically, it is known that apathy is a result of dysfunction in the frontal-subcortical circuits. This is significant in the scope of practice because the frontal-subcortical circuits aid in motivated behavior, the organization of information and the integration of limbic and emotional information<sup>3</sup>. Bonelli & Cummings described these circuits as effector mechanisms that allow a person to "act on their environment"<sup>3</sup>. There is a strong link between frontal-subcortical dysfunction and neurodegenerative disorders. In fact, apathy is present in seventy percent of patients diagnosed with Alzheimer's disease<sup>4</sup>.

Apathy can affect an individual's cognitive function. It is important to note the relationship between apathy and decreased cognitive functions in elderly patients because cognitive processes help regulate behavior and attention. As behavior and attention are altered, an individual will have a decrease in their overall executive function<sup>5</sup>. This decline in executive

function alters mobility and gait leaving elderly patients susceptible to falls and medical injuries<sup>5</sup>. In 2003, 1.8 million elderly patients were treated in the emergency room for fall injuries correlating with decreased executive and cognitive function<sup>5</sup>.

An exact number for the total healthcare cost for apathy and decreased cognitive function among elderly patients has not been identified. However, in 2003 the national health expenditure for mental health services was estimated to be over \$100 million<sup>6</sup>. There is not an exact estimate available for the number of healthcare visits each year associated with apathy. Yet, it is important to note the correlation between apathy and those with decreased cognitive function because a significant number of those patients are diagnosed with degenerative dementia with Alzheimer's being the most common type<sup>2</sup>.

Due to the strong correlation between neurodegenerative disorders, decreased cognitive function and apathy, the treatment options overlap. The pharmacological options are specifically formulated to treat the symptoms or progression of neurodegenerative disorders with improvement in apathy and cognitive function as an added bonus. Specifically, cholinesterase inhibitors (ChEi) showed improvement in apathy scores among patients diagnosed with dementia<sup>1</sup>. Dopaminergic agents showed improvement in apathy scores among those diagnosed with Parkinson's disease<sup>1</sup>. Non-pharmacological treatment alternatives for apathy include behavior, music and art therapy<sup>1</sup>.

The use of methylphenidate, a CNS stimulant medication, is being proposed for improving both apathy and cognitive function in geriatric patients. Currently, there is no definitive treatment for elderly patients suffering from apathy and diminished cognitive function. The pharmacological and nonpharmacological treatments listed above show slight improvement in only some patients. Therefore, it is important to further study methylphenidate as an oral

alternative to improve cognitive function and diminish apathy-like symptoms among the geriatric population.

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not stimulant-type medications help improve cognitive function and apathy in geriatric patients.

## **METHODS**

Specific criteria were set forth to ascertain proper selection of similar studies. The criteria used for the selection of the three studies included elderly patients with evidence of apathy, decreased cognitive function or both. Intervention included the administration of methylphenidate. The dosing and strength of medication varied among the three studies and included 5 mg, 10 mg or 20 mg tablets given orally once or twice per day. Each of the three studies compared the treatment group, receiving methylphenidate, to the experimental group, receiving a placebo. One double-blind, placebo controlled, cross-over RCT and one double-blind, individual, cross-over RCT measured the efficacy and tolerability of methylphenidate for the treatment of apathy in elderly patients. The other double-blind, placebo controlled, cross-over RCT measured the efficacy and tolerability of methylphenidate for the improvement of cognitive function in community-living elderly adults.

Data sources for the systematic review were selected from PubMed. Key words used to search for the articles included “methylphenidate”, “apathy”, “elderly”, “cognitive function” and “aging”. All articles were published in peer-reviewed journals and printed in English. All articles were selected based on their relevance to the clinical question and their inclusion of selected patient-oriented evidence that matters (POEMS). Inclusion criteria included subjects who were

older than 55 years of age; additional criteria were defined by specific studies (Table 1).

Exclusion criteria included certain medical conditions that would be negatively affected by the administration of a stimulant-type medication, most notably patients with heart disease (Table 1). Statistics reported and used to evaluate patient's outcomes included p-values, Z scores and numbers needed to harm (NNH). The demographics and characteristics of the studies are shown in Table 1.

**Table 1: Demographics and Characteristics of Included Studies**

Study	Type	# of pt's	Age (yr)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ben-tzhak <sup>5</sup> (2008)	Double-blind, placebo controlled, cross-over, RCT	26	65-90	Only subjects who complained about memory decline were included; Could ambulate independently; no use walking aid	Dementia, MMSE score <24, Clinically sig MSS, cardio, resp dz or vestibular d/o, Hx of sig. head trauma, PD or other neuro deg. d/o, MDD, Uncontrolled HTN, hf, arrhythmia or hx of epilepsy, Rx for MAOI's or TCA's	0	Administration of methylphenidate (20 mg) and placebo on resulting effects on pt's cognitive function
Jerrmann <sup>4</sup> (2008)	Double-blind, placebo controlled, cross-over, RCT	13	>55	Pt's were recruited from 3 different dementia clinics, age > 55, mild to moderate cognitive impairment based on MMSE (score > 10), presence of apathy based on the NPI (score >1), stabilized on a ChEI for at least 3 mo and no other psychotropic meds	Sig. medical or neuro conditions which diminish cognitive fx, A-fib, uncontrolled HTN, evidence of a seizure d/o, psychiatric dx, current use of any psychotropic medications other than a ChEI, psychotic sx or cardiac probs	2	The administration of methylphenidate for the treatment of apathy in elderly patients with Alzheimer's disease (5 mg PO BID. 3 days, then 10 mg PO BID x 11 days)
ansen <sup>2</sup> (2001)	Individual cross-over, double-blind, RCT	5	76-81	Geriatric, depression due to a general medical condition, resistance to antidepressant med & chronic apathy due to dementia	None b/c of the study design	1	methylphenidate for the treatment of depression or apathy in geriatric patients (5 mg BID and placebo)

## **OUTCOMES MEASURED**

All outcomes measured were POEMS related to improvement in apathy scores and cognitive function scores. Ben-Itzhak et al examined the effect of a single dose of methylphenidate on cognitive function. A computerized neuropsychological test, known as Go-NoGo, was used to measure cognitive function. Go-NoGo is a test of executive function that measures a participant's ability to illicit a response and continue with activity when faced with a competing stimuli. Outcomes were reported as p-values, where a p-value less than or equal to 0.05 deemed significant<sup>5</sup>.

Herrmann and colleagues designated the Apathy Evaluation Scale (AES) as the primary outcome variable. The AES score is reported between 0-72, where a higher score denotes worse apathy. They compared treatment AES score to the baseline AES score (treatment – baseline) and reported values as Wilcoxon Z signed-rank tests, an alternative to the simpler paired t-test<sup>4</sup>. Furthermore, this study also used the Neuropsychiatric Inventory (NPI) scale both as a baseline for the presence of apathy and again during the treatment and placebo phases. Negative change scores indicate improvement on the AES and NPI<sup>4</sup>.

In addition to measuring outcomes via AES, Jansen et al also measured depression using the Montgomery Asberg Depression Rating Scale (MADRS). Scores can range from 0-60, with higher scores representing worse depressive symptoms. Clinically significant outcomes were defined by statistically significant improvement of AES or MADRS scores that were analyzed with a one-sided paired t-test. The Barthel Index was used to report activities of daily living<sup>2</sup>.

## **RESULTS**

This systematic review examined three randomized control trials for the efficacy and tolerability of methylphenidate for the improvement of apathy and cognitive function in elderly



adults. All of the studies used a control group (placebo) and a treatment group (methylphenidate) with comparisons made to baseline assessments.

Ben-Itzhak and colleagues studied 26 elderly adults without a diagnosis of dementia, but with self-reported “memory problems”<sup>5</sup>. A randomized, double blind, crossover, placebo controlled trial was performed. Each participant underwent a 2-week study that began with an initial baseline assessment including a computerized cognitive test known as Go-NoGo. A single dose of methylphenidate 20 mg or a placebo were given to randomly chosen participants with measurements taken 2 hours post tablet administration. The time frame of 2 hours was carefully chosen as that is when the peak plasma concentration of methylphenidate occurs<sup>5</sup>. Statistical analysis revealed that methylphenidate significantly improved Go-NoGo accuracy when compared to the placebo ( $P = 0.03$ ) and when compared to baseline ( $P = 0.03$ ). There was no improvement in baseline compared to the placebo ( $P = 0.96$ ) further supporting the initial hypothesis (Table 2)<sup>5</sup>. No adverse events were reported in response to the administration of either methylphenidate or placebo. Blood pressure and heart rate were measured in half-hour intervals before and after the administration of medication to record possible cardiovascular effects due to the administration of a CNS stimulant<sup>5</sup>.

Herrmann and colleagues recruited 13 patients from 3 different community clinics. All of the participants had a previously established diagnosis of Alzheimer’s disease and showed evidence of apathy according to initial NPI apathy scores<sup>4</sup>. Herrmann et al performed a 5-week crossover study where participants received methylphenidate or a dose equivalent placebo for 2 weeks, followed by a placebo washout phase for 1 week and then a treatment phase for an additional 2 weeks. The medications started at 5 mg PO twice a day for 3 days and then increased to 10 mg PO twice a day for 11 days. The participants were assessed at the start of the

first treatment (week 0), the end of the first treatment (week 2), the start of the second treatment (week 3) and the end of the second treatment (week 5). Assessment consisted of total change scores from baseline to treatment in both the NPI apathy scale and AES scores. In general, the participants showed greater improvement in AES scores with methylphenidate when compared to a placebo ( $Z = -2.31$ ,  $P = 0.045$ ) (Table 3). There was also a difference in NPI apathy scale scores when looking at methylphenidate treatment versus the placebo, but the difference was not statistically significant ( $Z = -1.92$ ,  $P = 0.76$ ) (Table 3). Herrmann et al attribute this to the vast difference between the AES and NPI scale scores to the simple fact that the AES scale detects the presence of apathetic symptoms and the NPI scale determines the severity and frequency of apathetic symptoms<sup>4</sup>.

In a third study, Jansen et al recruited 5 geriatric patients to participate in an individual randomized control trial, also known as “N of 1” trials. All 5 of the participants were previously diagnosed with depression or apathy. The patients participated in a 5-week study where each week contained 2 double-blind drug periods (methylphenidate 5 mg twice a day or placebo) each lasting 2 days (Monday/Tuesday and Thursday/Friday)<sup>2</sup>. Assessments of MADRS and AES scores were done at the end of each period, which occurred on Tuesday and Friday afternoons. Statistically significant results were defined by improvement on the MADRS, AES or Barthel Index. The results demonstrated a significant improvement in the MADRS score of 2 participants ( $P = 0.089$ ,  $P = 0.001$ ) as well as significant improvement in the AES score of an apathetic patient ( $P = 0.077$ ) (Table 4). One participant showed no improvement in their depressive symptoms. None of the participants showed significant changes in functional performance as measured by the Barthel Index. One participant dropped out of the study after the first week due to the development of unrelated mutism<sup>2</sup>.

*SAFETY*

Unfortunately for Herrmann and colleagues, 3 of 13 participants experienced adverse effects when methylphenidate was administered. The adverse effects ranged from mild to severe, where dry mouth was classified as a mild event. The more severe events included, but are not limited to flushing of the face, anger, delirium, insomnia, nightmares, decreased appetite and physical aggression. The intensity of the adverse effects was severe enough to cause 2 of the 13 participants to drop out of the study. The third participant completed the study despite the mild effects of methylphenidate. The overall number needed to harm (NNH) was 7, which is large given the relatively small population size (Table 5). A NNH of 7 is significant because for every 7 individuals treated with methylphenidate, one of those will experience adverse effects that they would not have otherwise experienced without the drug.

**Table 2:** A comparison of the effects of methylphenidate and placebo on cognitive function<sup>5</sup>

Measurement of Cognitive Function	Baseline vs Placebo	Baseline vs Methylphenidate	Methylphenidate vs Placebo
Go-NoGo accuracy	.96	.03	.03

**Table 3:** Treatment change scores (end of treatment compared to baseline) comparing the effect of methylphenidate and placebo phases on apathy symptoms<sup>4</sup>

	Methylphenidate	Placebo	P (Wilcoxon Z)
<b>AES</b>	-2.31 (5.11)	0.50 (3.87)	0.045
<b>NPI</b>	-1.92 (7.56)	-2.08 (12.24)	0.76

**Table 4:** Individual changes in apathy or depression from baseline after the administration of methylphenidate<sup>2</sup>

Participant Number	Assessment Instrument	Mean Change (SD)	P-Value
1	MADRS	-1.6 (2.2)	0.089*
	Barthel	-0.2 (0.4)	0.187
2	MADRS	-4.0 (1.2)	0.001*
	Barthel	0.2 (0.4)	0.187
3	MADRS	3.4 (0.5)	0.089
	Barthel	-0.4 (7.9)	0.196
4	AES (clinician)	-2.8 (3.6)	0.077*
	AES (informant)	-6.2 (8.3)	0.086*
	Barthel	0.2 (0.8)	0.310

\*Clinically significant

**Table 5:** Analysis of adverse events from methylphenidate administration using dichotomous data<sup>4</sup>

CER	EER	RRI	ARI	NNH
0.077	0.23	1.98	.153	6.53 → 7

## DISCUSSION

This systematic review examined three RCTs for the efficacy and tolerability of methylphenidate for the improvement of apathy and cognitive function in elderly adults. Although proved to be an effective treatment by researchers, many practitioners may hesitate to initiate methylphenidate in geriatric patients due to its adverse reactions, most notably those that are psychiatric or cardiac related. Methylphenidate is a CNS stimulant FDA approved to control the symptoms of attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and narcolepsy, a sleeping disorder<sup>7</sup>. It works by increasing excitatory neurotransmitters in the brain, specifically dopamine and norepinephrine, precipitating addiction potential<sup>7</sup>. Common side effects of the medication include nervousness, weight loss, trouble sleeping, insomnia, nausea and headache. Methylphenidate should be used with caution in patients who have high blood pressure, glaucoma, heart problems and mental or mood conditions as the medication could exacerbate underlying disease<sup>7</sup>.

Methylphenidate is readily available in the United States. The drug comes in different variations including immediate release tablets and extended release capsules. The medication is routinely prescribed to children who are diagnosed with ADD or ADHD. In recent years, prescription insurance plans have declined to pay for CNS stimulant medications after the age of 30 and a complicated prior authorization process must be initiated before the patient can receive their medication. Therefore, methylphenidate use in elderly patients will come as a hassle to prescribers who need to fill out extra paperwork.

## **CONCLUSION**

Each of the three studies proved the administration of methylphenidate to be beneficial for geriatric patients suffering from apathy or decreased cognitive function. Although the three RCTs demonstrated improvement in apathy and cognitive function, the studies do not come without limitation. All 3 of the research teams recruited extremely small sample sizes. Research in this field needs to encompass larger population sizes due to the relatively high NNH compared to the small sample size, as demonstrated by Herrmann et al.

Future study to evaluate the effects of methylphenidate on elderly adults is warranted before consistent use is recommended. Fortunately, ongoing clinical trials and research studies are in motion. In fact, John Hopkins Bloomberg School of Public Health is doing just so. Hopkins clinical trial, The Apathy in Dementia Methylphenidate Trial (ADMET) is a placebo controlled, phase 2, clinical trial examining exactly what was enclosed in this systematic review: the efficacy and safety of methylphenidate for those already diagnosed with dementia<sup>8</sup>. It is important for researchers to examine the full extent of the benefits, safety and risks of medications that are being prescribed for off-label use.

## REFERENCES

1. Ishii S, Weintraub N, Mervis J. Apathy: a common psychiatric syndrome in the elderly. *J Am Med Dir Assoc*. 2009; 10: 381-393.
2. Jansen IH, Olde Rikkert MG, Hulsbos HA, Hoefnagels WH. Toward individualized evidence-based medicine: Five "N of 1" trials of methylphenidate in geriatric patients. *J Am Geriatr Soc*. 2001;49(4):474-476.
3. Bonelli, R, Cummings, J. Frontal-subcortical circuitry and behavior. *Dialogues in Clinical Neuroscience*. 2007; 9 (2): 141-151.
4. Herrmann N, Rothenburg L, Black S, Ryan M, Lanctot K, et al. Methylphenidate for the treatment of apathy in Alzheimer Disease. *Journal of Clinical Psychopharmacology (USA)*. 2008;28:296-301.
5. Ben-Itzhak R, Giladi N, Gruendlinger L, Hausdorff, J. Can methylphenidate reduce fall risk in community-living older adults? A double-blind, single-dose cross over study. *Journal of American Geriatrics Society*. 2008; 56: 695-700.
6. Depression. Centers for disease control and prevention website. <http://www.cdc.gov/workplacehealthpromotion/implementation/topics/depression.html>. Accessed September 22, 2013.
7. Drugs and Medication: Methylphenidate oral. WebMD website. <http://www.webmd.com/drugs/mono-94-METHYLPHENIDATE+-+ORAL.aspx?drugid=12114&drugname=methylphenidate+oral>. Accessed December 7, 2013.
8. Apathy in dementia methylphenidate trial (ADMET). Clinical trials.gov website. <http://clinicaltrials.gov/ct2/show/study/NCT01117181?term=NCT01117181&rank=1>. Accessed November 24, 2013.