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Is Methylphenidate Effective in Reducing Apathy among Alzheimer’s Disease Patients?

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Is methylphenidate effective in reducing apathy among Alzheimer’s disease patients?

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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

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ABSTRACT

OBJECTIVE

The objective of this selective EBM review is to determine whether or not “Is methylphenidate effective in reducing apathy among Alzheimer’s disease patients?”

STUDY DESIGN


DATA SOURCES

Two randomized controlled trials and one open label study were obtained using PubMed and Medline.

OUTCOMES MEASURED

The focus of this review is to determine the efficacy of methylphenidate in decreasing symptoms of apathy in Alzheimer’s disease patients. The efficacy of methylphenidate was assessed in all three studies by using the Apathy Evaluation Scale (AES). The significance of these outcomes was also determined by calculating the relative benefit increase, the absolute benefit increase and the numbers needed to treat.

RESULTS

All three studies demonstrated improvement of AES score when treated with methylphenidate. The study by Padala et al. demonstrated a 20.26-point improvement on the AES with methylphenidate treatment. The study by Herrmann et al. demonstrated a 2.31-point improvement on the AES in the experimental group and the study by Rosenberg et al. demonstrated a 1.9-point improvement on the AES in the experimental group.

CONCLUSIONS

The studies analyzed in this selective EBM review suggest that methylphenidate is effective at improving apathy in Alzheimer’s disease patients. The studies by Padala et al. and Herrmann et al. demonstrated statistically significant results of apathy improvement in Alzheimer’s patients with methylphenidate treatment. Further analysis is warranted to determine tolerability based on dosing.

KEY WORDS

Methylphenidate and Alzheimer’s disease
INTRODUCTION

Dementia is a degenerative and irreversible brain disease that affects aspects of brain function including but not limited to memory, language, motor function and problem solving. Alzheimer’s disease is the most common form of dementia. Alzheimer’s disease is typically an indolent condition in which cognitive function gradually deteriorates until a person needs support for basic activities of daily living. The disease is especially burdensome on those afflicted by it and their families. It is estimated that there are currently 5.7 million Americans among all age groups that have Alzheimer’s dementia.\(^1\) Alzheimer’s disease is so prevalent that it is ranked as the sixth leading cause of death in the United States and is believed to be the third leading cause of death among older age groups.\(^2\) The cost of Alzheimer’s and all other types of dementias in 2018 is estimated to be $277 billion.\(^1\) One report estimated that in 2017 the comprehensive lifetime cost of care for someone with dementia was $341,840.\(^1\) The same report shows that people with some type of dementia have more hospital and nursing home stays than people who do not have dementia.\(^1\) It is difficult to approximate how many healthcare visits there are each year as a result of dementia but one report found that there are 538 hospital stays per 1,000 Medicare beneficiaries with some type of dementia compared to only 266 hospital stays per 1,000 Medicare beneficiaries without dementia.\(^1\)

There are still a surprising number of things that are not well understood about Alzheimer’s disease such as the etiology, speed of progression, prevention, management and treatment of the disease. Some of the anatomical changes in the brain seen in Alzheimer’s disease include the development and buildup of extracellular beta-amyloid plaques and intracellular neurofibrillary tangles. These changes ultimately lead to inflammation and atrophy of the brain. Some research suggests that the anatomical changes seen in Alzheimer’s disease
may take place up to twenty years before symptoms are manifested. The greatest risk factors for developing Alzheimer’s disease include old age, family history and certain forms of the APOE gene.

Alzheimer’s disease most likely develops due to changes that occur in the brain over time from a combination of genetic, environmental and lifestyle factors. Early symptoms of Alzheimer’s disease can include memory difficulties, apathy and depression. Later in the course of Alzheimer’s disease, symptoms can include problems with communication, confusion, disorientation, poor judgement and behavioral changes. Treatment options for Alzheimer’s disease are limited to medications that may help with relief of symptoms due to the disease. There are no treatment options that can reverse or cure Alzheimer’s disease. FDA approved medications to treat Alzheimer’s disease include cholinesterase inhibitors such as donepezil, rivastigmine, galantamine, and N-methyl D-aspartate (NMDA) antagonists such as memantine. After careful analysis of risks vs. benefits, other treatments can include antidepressants for depression, sleep aids for insomnia or other sleeping disturbances, anxiolytics for agitation and antipsychotics for agitation and aggression.

One study investigating the prevalence of neuropsychiatric symptoms in Alzheimer’s disease found that the symptoms with the highest prevalence included depression and apathy. Apathy in Alzheimer’s disease is defined as a decrease in enthusiasm and motivation and as well as a loss of interest in things that one previously found intriguing. Alzheimer’s disease patients experiencing apathy often have impaired activities of daily living which can lead to an increased dependence on caretakers, a higher risk of long-term care and increased health care costs. Thus, improving symptoms of apathy in Alzheimer’s disease could help improve quality of life. The same study revealed that activity in the dopaminergic mesolimbic brain reward system is
significantly associated with motivation and using a dopamine uptake inhibitor like methylphenidate may help to reduce symptoms of apathy.\textsuperscript{6}

**OBJECTIVE**

The objective of this selective EBM review is to determine whether or not “Is methylphenidate effective in reducing apathy among Alzheimer’s disease patients?”

**METHODS**

The three studies selected for this review were found in the PubMed and Medline databases. Key words used while searching for relevant studies included “methylphenidate” and “Alzheimer”. Inclusion criteria for study selection consisted of studies that assessed apathy with the Apathy Evaluation Scale (AES), studies that were written in English during 2008 or later, studies that involved primary research and studies that were published in a peer reviewed journal. Exclusion criteria for study selection consisted of studies that used medications other than methylphenidate and studies that investigated treatment for symptoms other than apathy among Alzheimer patients. The articles selected for this review were chosen based on relevance to the clinical question and having patient-oriented outcomes (POEMs). The statistics reported in these studies include: Z scores, p-values and mean change from baseline. Similar statistics were used in all studies with p values determined to be significant if values were $\leq 0.05$.

Two randomized controlled trials from 2008 and 2013 and one open label study from 2010 were selected for this systematic review. The target population used to aid in selection of studies included male and female patients diagnosed with Alzheimer’s disease who were experiencing symptoms of apathy. Methylphenidate, the intervention being evaluated for this review, was used in all three studies selected. All three studies selected initiated patients on a
10mg daily dose of methylphenidate and then increased the dose to 20mg daily. Table 1 shows the characteristics and demographics of the selected studies for this review.

**Table 1: Demographics & characteristics of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Mean age (SD)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrmann, et al.⁶</td>
<td>Double Blind RCT</td>
<td>13</td>
<td>78 (8)</td>
<td>Dx of possible or probable AD, ≥ 55y/o, MMSE ≥ 10, presence of apathy on Neuropsychiatric Inventory (NPI), stable on ChEI for three months</td>
<td>Current use of any psychotropic medication other than a ChEI, A-fib, uncontrolled HTN, seizure disorder</td>
<td>2</td>
<td>Methylphenidate (5mg BID for 3 days, then 10mg BID for the remaining 11 days)</td>
</tr>
<tr>
<td>Padala, et al.⁷</td>
<td>Open label study</td>
<td>23</td>
<td>70 (10)</td>
<td>Diagnosis of DAT (Dementia of the Alzheimer’s type), AES &gt;40, MMSE &gt;18, stable dose of ChEI for 2 months,</td>
<td>History of hypersensitivity to methylphenidate, uncontrolled HTN, MI in the last 6 months, use of MAOI’s, use of other stimulant or Clonidine, Tourette syndrome, Closed angle glaucoma</td>
<td>0</td>
<td>Methylphenidate (5mg BID for the first two weeks, then 10mg BID for the remaining 10 weeks)</td>
</tr>
<tr>
<td>Rosenberg, et al.⁵</td>
<td>Double Blind RCT, cross-over trial</td>
<td>60</td>
<td>76 (8)</td>
<td>Dx of possible or probable AD, MMSE ≥10, clinically significant apathy for at least four weeks determined by NPI, Stable dose if on SSRI</td>
<td>Dx of major depressive Episode, agitation, aggression, delusions, hallucinations, psychotropic medication use except Trazadone or SSRI</td>
<td>6</td>
<td>Methylphenidate (10mg QD for 3 days, then increased to 20mg QD for the remainder of the study)</td>
</tr>
</tbody>
</table>
OUTCOMES MEASURED

Apathy among participants was measured in all three studies using the Apathy Evaluation Scale (AES), the most reliable scale to measure apathy in Alzheimer’s disease.\(^5\) The AES is an 18-item scale that can be scored from one to four for each item. The AES evaluates apathy in behavioral, cognitive and emotional domains. Scores on the AES can range from 18 to 72, with lower scores indicating that the patient is experiencing less apathy. All three studies chosen for this review measured the mean change in apathy based on the AES before and after treatment with methylphenidate.

In the study by Herrmann et al., AES scores were assessed at weeks zero, two, three and five.\(^6\) In Padala et al.’s open label study, AES was measured at weeks zero, four, eight and twelve.\(^7\) Adverse effects were documented at each visit and physicians were allowed to lower the dose if needed due to adverse effects.\(^7\) The primary outcome measured in the study by Rosenberg et al.\(^5\) was the change in apathy based on the AES from baseline to the end of the study. The length of the study by Rosenberg et al. was six weeks. The researchers in the study by Rosenberg et al. documented adverse effects using a symptom checklist for expected side effects of methylphenidate and also asked open ended questions for unanticipated side effects.\(^5\) The focus of this EBM review will be to analyze the change in AES score from baseline to the end of treatment in order to determine the efficacy of methylphenidate in reducing apathetic symptoms.

RESULTS

In Herrmann et al.’s crossover study, the primary outcome measured was the change in AES from baseline to the end of treatment (EOT).\(^6\) In this study, subjects were randomly assigned to the experimental or comparison group. Participants were started on 5mg of methylphenidate twice a day for three days which was then increased to 10mg twice a day for the
remaining eleven days. All subjects participated for two weeks in the experimental phase and two weeks in the control phase with a one-week washout period on placebo between each phase. The participants were given methylphenidate as treatment during the experimental phase and were given a visually matched placebo during the control phase. The mean age of participants was 78 years with a standard deviation of eight years. Inclusion/exclusion criteria for this study can be found in Table 1. Two withdrawals occurred during the experimental phase of this study due to adverse effects. The data from one of the withdrawals was not included in the control group analysis because the participant never started the control phase. The other withdrawal had already completed the control phase and the data from that participant was still utilized for data analysis. Documented adverse effects that resulted in withdrawal included delusions, physical aggression, insomnia and hallucinations. Other documented adverse effects that did not result in withdrawal included irregular heartbeat, nausea and dry mouth.

In the study by Herrmann et al., the mean change in AES score (EOT – Baseline) among the experimental group was a decrease of 2.31 points with a standard deviation of 5.11. In comparison, there was an increase of 0.50 points with a standard deviation of 3.87 among the control group. A decrease of 2.31 points is a relatively small decrease on the AES however, this small magnitude of change still represents an improvement of apathetic symptoms. The efficacy of the intervention was assessed using the Wilcoxon Z test which calculated a Z score of -2.0 with a p-value of 0.045. With statistical significance defined as a p-value < .05, these results were statistically significant. These statistics are summarized in Table 2.
Table 2: Mean change in AES scores from end of treatment to baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean change in AES, methylphenidate group</th>
<th>Mean change in AES, placebo group</th>
<th>P-value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrmann et al.</td>
<td>-2.31 ± 5.11</td>
<td>0.50 ± 3.87</td>
<td>0.045</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Padala et al.</td>
<td>-20.26</td>
<td>Not calculated</td>
<td>&lt; 0.0001</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Rosenberg et al.</td>
<td>-1.9</td>
<td>0.6</td>
<td>0.23</td>
<td>-6.5 to 1.6</td>
</tr>
</tbody>
</table>

Herrmann et al. also reported that 54% of participants showed a decline in AES score with methylphenidate treatment, while only 8% showed a decline in AES score when given placebo. From this data, the relative benefit increase (RBI) was calculated to be 5.75, the absolute benefit increase (ABI) was calculated to be 0.46 and the numbers needed to treat (NNT) was calculated to be 3. This means that for every 3 patients treated with methylphenidate one more patient will have a decrease in AES score than if treated with placebo. A decrease on the AES corresponds with a reduction in the severity or frequency of apathetic symptoms. The summary for these statistics can be found in Table 3.

Table 3: Efficacy and statistical significance of methylphenidate in the treatment of apathy in Alzheimer’s disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Control Event Rate</th>
<th>Experimental Event Rate</th>
<th>Relative Benefit Increase</th>
<th>Absolute Benefit Increase</th>
<th>Numbers Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrmann, et al.</td>
<td>0.08</td>
<td>0.54</td>
<td>5.75</td>
<td>0.46</td>
<td>3</td>
</tr>
<tr>
<td>Rosenberg, et al.</td>
<td>0.10</td>
<td>0.18</td>
<td>0.8</td>
<td>0.08</td>
<td>13</td>
</tr>
</tbody>
</table>

In the open label study by Padala et al., all participants were initiated on methylphenidate 5mg twice daily for two weeks which was then increased to 10mg twice daily for the remaining ten weeks. The mean age of participants was 70 years with a standard deviation of 10 years. Mean AES scores decreased throughout this study with methylphenidate treatment. The mean
decrease in AES score from baseline to the end of the study was 20.26 with a p-value of < 0.0001. This result demonstrates a statistically significant decrease in apathy after treatment with methylphenidate. A reduction of 20.26 on the AES is a substantial decrease and corresponds with significant improvement of apathetic symptoms. The summary for these results can be found in Table 2. None of the participants withdrew from this study due to adverse effects. Documented adverse effects that occurred during this study included decreased appetite, increased blood pressure, cough, dizziness, decreased sleep, irritability, restless legs, mouth sores and increased arthritic knuckle pain.

The primary assessment in the study by Rosenberg et al. was comparing AES scores from the end of treatment to baseline. Of the sixty subjects selected for this study, twenty-nine were randomly assigned to the experimental group and thirty-one were randomly assigned to the control group. Participants in the experimental group were started on 10mg of methylphenidate daily for three days which was then increased to 20mg daily for the remainder of the study. The mean change in AES score from the end of treatment to baseline among the experimental group was a decrease of 1.9 points and an increase of 0.6 points in the control group. The estimated treatment effect (methylphenidate – placebo) was calculated to be -2.5 with a p-value of 0.23 and a 95% confidence interval of (-6.5 to 1.6). These results indicate that the AES score change from end of treatment to baseline are not statistically significant. The decrease in AES score with methylphenidate treatment indicates improvement of apathy, but a decrease of 1.9 points on this 72-point scale is a relatively small decrease. Rosenberg et al. also documented that 18% of participants in the experimental group had a greater than eight-point improvement on AES score after treatment compared to only 10% in the control group. From this data, a NNT value of 13 was calculated. This means that for every thirteen Alzheimer’s disease patients experiencing
apathy treated with methylphenidate one more patient will have a greater than eight-point improvement on AES score than if treated with placebo. These results can be found in Table 3.

In the study by Rosenberg et al., compliance to taking the medication or placebo was calculated by checking the remaining number of pills per bottle at the end of the study. There was a calculated 88.3% compliance in the experimental group and 86.8% compliance in the control group. The studies by Herrmann et al. and Padala et al. did not include information about compliance. Rosenberg et al. defined serious adverse effects as adverse effects that led to hospitalization or emergency room visits. There were two incidents of serious adverse effects which included a drop in hemoglobin in one participant from the control group and abdominal pain in one participant from the experimental group. Adverse effects including hypertension, nervousness, nausea and anxiety led to four withdrawals in the experimental group. Adverse effects including insomnia and a drop in hemoglobin led to two withdrawals in the control group.

DISCUSSION

The purpose of this review is to investigate the efficacy of methylphenidate in reducing symptoms of apathy in patients with Alzheimer’s disease. All three studies analyzed in this review demonstrated improvement of apathy on the AES in Alzheimer’s disease patients when treated with methylphenidate, but only Padala et al. and Herrmann et al. had statistically significant results. The study by Herrmann et al. was limited by having a particularly small sample size and a short treatment duration. Herrmann et al. also stated that the small sample size and study length may have impeded the ability to detect a more prominent response to methylphenidate. Herrmann et al. suggested that conditions such as ADHD and age-related declines in dopamine function may also be reasons for minimal responses to dopaminergic agents. The dose of methylphenidate chosen for this study was determined to be appropriate
based on other studies that investigated the use of methylphenidate in elderly Alzheimer’s disease patients experiencing apathy. Further investigation should be done to compare the tolerability and efficacy of different dosing formulations of methylphenidate.

Padala et al. pointed out that there were several limitations in the study they conducted. One major limitation is due to the nature of this study. Padala et al. performed an open label study, meaning that the participants and the physicians were both cognizant of the treatment being administered. Some of the other limitations in this study are that there was no blinding for participants or providers and that there was no control group for comparison. Another shortcoming for this study is that the participants recruited were mostly males and only veterans, which limits the generalizability of the results.

Rosenburg et al. identifies the following as some of the limitations of their study: recruiting a small sample size, having a limited set of measured outcomes, performing the study over a short duration and assessing only one dose of methylphenidate.

Methylphenidate is a stimulant medication that blocks the reuptake of noradrenaline and dopamine and is currently indicated for the treatment of ADHD and narcolepsy. Methylphenidate is a controlled substance but is still used commonly when indicated. Some of the most common adverse drug reactions from methylphenidate include decreased appetite, motor tics, sleep disturbances, changes in mood and increases in blood pressure and heart rate. Some research suggests that methylphenidate may improve depression secondary to surgery or medical illness and in select groups such as stroke patients, cancer patients and HIV infected patients. Insurance coverage and access to the medication were not issues in the studies chosen for this review.
CONCLUSIONS

The results from the studies selected for this review demonstrate that methylphenidate may be an effective treatment option for apathy in Alzheimer’s disease. Statistically significant reductions in apathy on the AES were observed in two of the studies reviewed. Improvement in apathy may lead to less dependence on caregivers and improved quality of life. In addition to having longer trial durations and more participants, future research should be done to compare different dosage formulations of methylphenidate in order to determine an optimal therapeutic dose in terms of tolerability and efficacy. While methylphenidate cannot reverse or cure Alzheimer’s disease, many trials are currently being done to discover new interventions that may be curative.
REFERENCES


