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Effect of methylphenidate on attention in apathetic AD patients in a randomized, placebo controlled trial

Krista L. Lanctôt¹, Sarah A. Chau¹, Nathan Herrmann¹, Lea T. Drye², Paul B. Rosenberg³, Roberta W. Scherer², Sandra E. Black¹, Vijay Vaidya², David L. Bachman, MD^{4,5}, and Jacobo E. Mintzer^{4,5} for the ADMET investigators

¹Departments of Psychiatry and Medicine (Neurology), and Brain Sciences Research Program, Sunnybrook Research Institute, Departments of Psychiatry, Pharmacology/Toxicology and Medicine (Neurology), University of Toronto

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

³Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine

⁴Department of Neurosciences, Alzheimer's Research and Clinical Programs, Medical University of South Carolina

⁵Ralph H. Johnson VA Medical Center

Abstract

Background—Little is known about the effect of methylphenidate (MPH) on attention in Alzheimer's disease (AD). MPH has shown to improve apathy in AD, and both apathy and attention have been related to dopaminergic function. The goal was to investigate MPH effects on attention in AD and assess the relationship between attention and apathy responses.

Methods—MPH (10mg PO twice daily) or placebo was administered for 6 weeks in a randomized, double-blind trial in mild-to-moderate AD outpatients with apathy (Neuropsychiatric Inventory [NPI] Apathy 4). Attention was measured with the Wechsler Adult Intelligence Scale - Digit Span (DS) subtest (DS forward, selective attention) and apathy with the Apathy Evaluation Scale (AES). A mixed effects linear regression estimated the difference in change from baseline between treatment groups, defined as δ {[MPH (DS week 6–DS baseline)] - [placebo (DS week 6–DS baseline)]}.

Results—In 60 patients (37 females, age=76±8, Mini-Mental State Exam [MMSE]=20±5, NPI Apathy=7±2), the change in DS forward (δ =0.87 (95% CI: 0.06–1.68), p =0.03) and DS total (δ =1.01 (95% CI: 0.09–1.93), p =0.03) favoured MPH over placebo. Of 57 completers, 17 patients had improved apathy (3.3 points on the AES from baseline to end point) and 40 did not. There

Corresponding Author: Krista L. Lanctôt, 2075 Bayview Avenue Room FG-08, Toronto, Ontario Canada M4N 3M5, Krista.lanctot@sunnybrook.ca, 416-480-6100 ext. 2241, 416-480-6022 (fax).

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were no significant associations between AES and NPI Apathy with DS change scores in the MPH, placebo, AES responder or non-responder groups. DS scores did not predict apathy response to MPH treatment.

Conclusion—These results suggest MPH can improve attention and apathy in AD; however, the effects appear independent in this population.

ClinicalTrials.gov Identifier—NCT01117181

Keywords

Alzheimer's disease; apathy; neuropharmacology; psychopharmacology; behavioral and psychological symptoms of dementia (BPSD)

Background

Alzheimer's disease (AD) is characterized by cognitive impairment including deficits in measures of attention (McGuinness *et al.*, 2010). Attention deficits emerge during the early stages of dementia (Perry *et al.*, 2000) and may predict increased deterioration and progression to AD in mild cognitively impaired elderly (Rapp and Reischies, 2005). Attention has recently become of interest as a cognitive domain as it has been shown to be specifically associated with executive dysfunction (Perry and Hodges, 1999) and decline in activities of daily living (Bronnick *et al.*, 2006) in AD patients.

Psychostimulants, which work by increasing central dopamine (DA) and norepinephrine levels, are known to enhance alertness, reward salience and motivation (Koob, 1996) and are the standard treatment for attention-deficit hyperactive disorder. The psychostimulant methylphenidate (MPH) has also been shown to significantly improve attention deficits in other DAergic disorders such as Parkinson's disease (Auriel *et al.*, 2006). Herrmann *et al* (2008) found that increased inattention following a single dose of dextro-amphetamine predicted greater improvements in apathy ($p = -0.69$, $p = 0.02$) in AD patients being treated with methylphenidate. The authors proposed that lack of attention may be a predictor of treatment response to MPH, which is consistent with literature in normal controls suggesting that the effects of MPH vary depending on baseline dopamine levels (Cools *et al.*, 2009). However, the study by Herrmann *et al* (2008) did not assess attention as an outcome.

While attention is a distinct cognitive domain, it may also be associated with apathy. Links between apathy and attention are rational considering that DAergic neurons make projections to attention networks in the brain and attention-associated areas show reduced activity in apathetic patients (Lancôt *et al.*, 2007). Motivation, identified as one of the key deficits in apathy, is thought to be closely associated with attentional components in reward processing (Ivanov *et al.*, 2012; Nieoullon and Coquerel, 2003). Despite a theoretical common neurobiology, little is known about the relationship between apathy and attention in AD.

A recent randomized placebo-controlled trial (ADMET) suggested that MPH was well tolerated and had positive effects on apathy, with a trend for increases in global cognition (Rosenberg *et al.*, 2013). In this secondary analysis, we investigated the effect of MPH on attention in patients with apathy, as well as the relationship between attention and apathy changes following MPH treatment.

Methods

Study Sample

Patients enrolled in ADMET (Rosenberg *et al.*) at Sunnybrook Health Sciences Centre, Johns Hopkins University and the Medical University of South Carolina were used in this pre-planned secondary analysis. All study sites received approval from their individual research ethics board. ADMET was a phase II, randomized, double-blind, placebo-controlled study investigating the safety and efficacy of MPH (10mg PO twice daily) versus placebo for 6 weeks for the treatment of apathy in AD patients. Patients were recruited from outpatient clinics, assisted living facilities affiliated with the clinics, referrals from local physicians and advertisements in local media.

Procedures

The study methods have been described elsewhere (Drye *et al.*, 2013). Informed consent was provided by study participants or a legally authorized representative before the start of the trial. Eligible patients with mild-to-moderate AD (Mini-Mental Status Examination, MMSE 10–26 inclusive) and clinically significant apathy (Neuropsychiatric Inventory, NPI Apathy 4) were randomized, with a 1:1 assignment ratio, to either MPH or placebo for 6 weeks. ADMET allowed use of stable doses of cognitive enhancers, selective-serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors as well as trazodone for sleep, but not treatment with other psychotropic medications. Study drugs (either MPH or placebo) were initiated at 5 mg PO twice daily, for 3 days. This was increased to the target dose of 10 mg PO twice daily (total of 20 mg per day) for the remainder of the trial.

Assessments were performed every 2 weeks (baseline, week 2, week 4 and week 6). Patients completed the Wechsler Adult Intelligence Scale Revised - Digit Span (DS) (Wheeler, 1981), MMSE (Folstein *et al.*, 1975) and modified AD Cooperative Study-Global Clinical Impression of Change (ADCS-CGIC) (Schneider *et al.*, 1997). Caregivers provided information for the patient regarding the eligibility criteria, medical history, NPI (Cummings *et al.*, 1994), Apathy Evaluation Scale (AES) (Marin *et al.*, 1991) and CGIC (Schneider *et al.*, 1997). Vital signs, electrolyte panels and ECG tests were also obtained from patients and adverse events solicited at each study visit to monitor safety throughout the trial. Procedures for test administration were standardized across all study sites.

For this pre-planned secondary analysis of the ADMET study, the DS (Wheeler, 1981) was used to assess auditory attention and working memory. Digit sequences of progressively increasing length were read by the examiner and patients were instructed to repeat them in the same order for the forward condition. In the backward condition, patients were required to repeat the digits in the reverse order. One point was given for each correct sequence and the test was terminated when patients were unsuccessful on two trials of the same sequence length. Performance was summarized by DS forward (selective attention), DS backward (working memory) and DS total scores. Additionally, a scaled score based on standardized age norms was converted from the raw total score.

Statistical Analysis

Baseline clinical and demographic characteristics were compared between response groups using Kruskal-Wallis test for continuous variables and chi-square or Fisher's exact test for categorical variables. All analyses of treatment effects were conducted according to the intention to treat principle. The treatment effect of MPH [8] on attention measures compared the difference in change in DS measures from baseline to week 6 between MPH and placebo. This was assessed using linear mixed effects models with random intercept for each participant and adjusting for stratification by clinic. Specifically, differences between MPH

compared with PLB for changes from baseline were examined. Cohen's *d* (the difference between two means divided by the pooled standard deviation) was calculated for the crude difference in digit span forward change scores.

Apathy responders were those patients who had an improvement of at least 3.3 points on the AES from baseline to end point based on the difference observed in the published pilot study (Herrmann *et al.*, 2008) and power calculations for ADMET (Drye *et al.*, 2013). The relationship between baseline attention measures and treatment response was assessed by: i) linear regression models of the change in AES score from baseline to week 6; ii) logistic regression models of apathy response. We also considered models of the association between attention and apathy response that controlled for education and explored response defined as a decrease in NPI apathy score by 1 point or more at week 6 and response defined as any improvement at CGIC scale from baseline (minimal, moderate, and marked improvement). Pearson correlation and 95% confidence intervals were calculated for change in attention measures (DS total, forward and backward) from baseline to week 6 versus change in apathy measures (AES) from baseline to week 6 for study completers.

Two sided *p*-value at 5% significance level were used to assess statistical significance. Results were not adjusted for multiple comparisons. Statistical analyses were used using SAS version 9.3 Copyright (c) 2002–2010 by SAS Institute Inc., Cary, NC, USA.

Results

Sixty AD patients (37 women), with a mean $\pm$ SD age of 76 ± 8 , MMSE scores of 20 ± 5 , NPI total scores of 16 ± 8 , NPI apathy scores of 7 ± 2 and AES scores of 51 ± 12 were randomized. The patients in each treatment arm (29 in the MPH group and 31 in the placebo group) were comparable on baseline characteristics (Rosenberg *et al.*, 2013). While the number of participants taking ChEIs or SSRIs at baseline (Table 1) was balanced by treatment group, memantine use was slightly imbalanced (MPH 21/29, placebo 16/31) (Rosenberg *et al.*, 2013).

Estimated difference in change in attention for the 60 patients from baseline to week 6 showed larger improvements (positive δ favors MPH) in DS forward score ($\delta = 0.87$ (95% CIs: 0.06–1.68), $p=0.03$, Cohen's *d* = 0.62) (Figure 1) and DS total score ($\delta = 1.01$ (95% CIs: 0.09–1.93), $p=0.03$) in those on MPH. The difference in improvement was not statistically significant for DS backward ($\delta = 0.17$ (95% CIs: –0.66, 1.02), $p=0.68$) though it showed a numerically greater improvement in the MPH group. Controlling for use of memantine did not change treatment effects on DS forward scores ($\delta = 0.87$ (95% CIs: 0.06–1.68), $p=0.03$).

Of the 60 randomized, 57 participants completed the study with 17 patients showing improved apathy and 40 who did not improve (Table 1). Responders and non-responders were comparable on baseline measurements of attention except that responders had a trend towards higher baseline AES scores ($p = 0.06$). There were no significant correlations between change in AES and change in any of the attention measures for the 57 completers, the MPH group or the PLB group (data not shown). Baseline attention scores did not predict apathy outcome as measured by linear regression model (group differences in change scores) or logistic regression (log odds of improvement in MPH and placebo group by baseline score) (Tables 2 and 3). Controlling for education did not substantially change the size of the association between response and baseline attention. Sensitivity analysis with response using NPI apathy and CGIC apathy also showed no relationship (data not shown).

Conclusion

The results of this study suggest that MPH improves selective attention in an elderly dementia population with apathy. While sustained attention or vigilance refers to the ability to maintain focus over long periods of time and divided attention is required to process multiple stimuli simultaneously, selective attention is defined as focus and concentration on a target stimulus while filtering out distractions (Perry and Hodges, 1999). Previous randomized placebo controlled trials with galantamine, a cholinesterase inhibitor that modulates nicotinic receptors, showed positive effects on different measures of attention, including both vigilance and selective attention (Galvin *et al.*, 2008; Gorus *et al.*, 2007; Vellas *et al.*, 2005). While there is evidence for the use of psychostimulants such as MPH for the treatment of apathy in AD (Herrmann *et al.*, 2008; Rosenberg *et al.*, 2013) data on their effects on attention in this population are limited. In children and young adults with ADHD, psychostimulants have been shown to improve performance on tasks of divided, sustained, focused and selective attention (Tucha *et al.*, 2006). Our findings indicate that improvements on selective attention did favour MPH in apathetic dementia patients following 6 weeks of treatment. Further, the estimated change in DS forward found in this study ($\delta = 0.87$) is greater than the difference found between those with mild versus moderate cognitive impairment in the ADNI study (0.7) (Park *et al.*, 2012), and demonstrates a moderate to high effect size (0.62), suggesting that MPH may have clinically significant effects on attention.

The correlation and response prediction analyses also suggest that attention and apathy may respond independently to MPH in this cohort of patients. There are several possible reasons for this. The neural substrates for apathy, thought to be the anterior cingulate and orbitofrontal cortex (Lanctôt *et al.*, 2007), are likely not directly involved in all types of attention processing. It may be that the selective attention test used in this study measured a component of attention that is not closely associated with anterior cingulate or orbitofrontal mediated motivation. Second, differing sensitivity to MPH may account for these differences. Low and therapeutically relevant doses of psychostimulants are cognitively enhancing via preferential stimulation of the prefrontal cortex (Berridge and Devilbiss, 2011). In contrast, higher doses, by amplifying catecholaminergic tone more globally throughout the brain, are behaviourally activating (Kuczenski *et al.*, 1995). In the dementia population, the presence of irritability, agitation and psychosis reported in trials of patients treated with MPH (Galynker *et al.*, 1997; Herrmann *et al.*, 2008; Padala *et al.*, 2010) could signify behavioural effects in a subset of patients even at low doses. This is also consistent with the previous suggestion that the effects of dopaminergic agents depends on baseline dopaminergic activity (Cools and D'Esposito, 2011).

The differing responses may also indicate regional variability in dopaminergic disruption associated with AD. Post-mortem brains of AD patients show lower levels of dopamine (Storga *et al.*, 1996) and D₂ receptor expression (Cross *et al.*, 1984) compared with age-matched controls, but the extent of this disruption varies substantially. Consistent with this variability, the DAergic mesocorticolimbic reward pathway is thought to be compromised in AD patients to a greater degree in those with apathy compared to those without (Mitchell *et al.*, 2010). In a SPECT study of non-depressed AD patients, those with apathy had a distinct pattern of differences in areas associated with the DAergic mesocorticolimbic reward pathway (Lanctôt *et al.*, 2007). Reduced striatal DA transporter uptake has also been correlated with greater apathy in dementia patients (David *et al.*, 2008). A probe of the DA reward system demonstrated that compared with controls, apathetic AD patients given d-amphetamine scored lower on tests of subjective positive effects (Lanctôt *et al.*, 2008), possibly representing either loss or decreased sensitivity of post-synaptic DAergic receptors. As such, DAergic dysfunction is likely to be present and variable in an AD population with

apathy and may be a factor in driving MPH to have independent effects on apathy and attention.

These results contrast with findings of a drug challenge study (Herrmann *et al.*, 2008), where inattention with d-amphetamine was predictive of a positive response to MPH for apathy. Conceptual differences, including the use of a different psychostimulant, may account for the contradictory findings. The purpose of the drug challenge was to probe the functional integrity of the DA reward system using a single dose of d-amphetamine rather than testing whether MPH-naïve attention abilities could predict response. In fact, the authors suggested that the behaviourally activating mechanisms which caused distractibility and subsequently inattention, might also be involved in ameliorating apathetic symptoms. This is consistent with the interpretation of the results discussed above.

There are some limitations to consider when interpreting the results of this study. The sample size was based on power calculations performed to evaluate efficacy of MPH (Drye *et al.*, 2013) with apathy and not attention as the primary outcome. While this study had sufficient power to detect changes in attention, the sample size may not have been adequate to detect significant associations between our two outcome measures. The definition of a responder was based on a previous pilot study and thus far has not been validated. Nevertheless, results from ADMET indicated that clinicians' impression of change in apathy, measured by the CGIC, favoured MPH, suggesting that a 3.3 point change on the AES was large enough to be clinically relevant. Another limitation is the use of a single measure of selective attention. The Digit Span test, a measure of selective attention (DS forward) and working memory (DS backward), may not be tapping into the attention domains which might be more relevant to the motivation factor characteristic of apathy. While its short length and ease of administration is a benefit in studies with cognitively impaired patients, it would be interesting to explore more comprehensive assessments which target other types of attention. Similarly, activities of daily living, which have been linked with both attention and apathy (Bronnick *et al.*, 2006; McPherson *et al.*, 2002), were not measured in the present study. Finally, given the exploratory nature of this secondary analysis, adjustment was not made for multiple comparisons.

In addition to positive benefits for apathy, as demonstrated by NPI apathy score and modified ADCS-CGIC, as well as a trend for global cognition, as measured by the MMSE recently reported for MPH (Rosenberg *et al.*, 2013), this analysis provides an initial signal supporting benefits on attention, suggesting multiple avenues for future research. For example, since these patient all exhibited apathy, methylphenidate could be studied in non-apathetic patients, specifically as a cognitive enhancer. Also, in this study MPH was given as an adjunctive therapy, thus its use as a monotherapy could be explored. Similarly, MPH was administered for 6 weeks and therefore the effects of long-term use are an important focus for future research, particularly in light of the fact that AD is neurodegenerative and evidence of tolerance in other populations (Swanson *et al.*, 1999). Given that an impact on activities of daily living is important in establishing clinical relevance, future studies should evaluate whether MPH administration improves function. Finally, these results apply only to those patients with mild-to-moderate AD and it would be interesting to investigate patients with more severe AD and non-AD dementias, where the link between DA and attention have yet to be clarified. These data will be particularly important to better define the therapeutic role of MPH in clinical practice.

In summary, the benefit for selective attention found in this study, in addition to previously noted benefits for apathy, adds to the limited knowledge of MPH effects on AD patients and provides further support for its use in this population. Heterogeneity in response to treatment has prompted recent recognition of the importance of evaluating specific cognitive domains

(Hendrix and Welsh-Bohmer, 2013). Attention is needed for working and episodic memory, and may also have positive effects on functional abilities (Baddeley *et al.*, 1986; Perry and Hodges, 1999). This study provides some insight into the different effects MPH can produce in a heterogeneous disease such as AD.

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Figure 1.

Estimated change score ($\pm$ SE) for Digit Span forward over time. Improvement (positive change scores) over 6 weeks in the MPH (methylphenidate) group ($n=29$) was significantly greater than that found in the PLB (placebo) group ($n=31$).

Table 1

Baseline characteristics by responders in the AES

Baseline Characteristics	Total (n=57)	Responders (n=17)	Non-responders (n=40)	P-value
Age	77±8	76±10	77±7	0.79
Gender	60% female	53% female	63% female	0.50
Concomitant Medication				
SSRIs	32%	29%	33%	0.81
ChEIs	72%	71%	72%	0.88
Memantine	61%	65%	60%	0.77
MMSE	20±5	20±5	20±5	0.79
AES	51±12	55±11	49±12	0.06
NPI Total	16±8	18±9	15±7	0.38
Apathy subscore	7±2	8±2	7±2	0.73
Depression subscore	1±2	2±3	1±2	0.14
Digit Span				
Forward score	8±2	8±3	8±2	0.55
Backward score	4±2	4±2	4±2	0.90
Total raw score	12±4	12±4	12±4	0.90
Total scaled score	8±3	8±3	8±3	0.75

AES=Apathy Evaluation Scale, SSRIs=serotonin reuptake inhibitor, ChEI=cholinesterase inhibitor, MMSE=Mini-Mental Status Exam, NPI=Neuropsychiatric Inventory. Values indicate mean ± SD. Adjusted for unequal variances as needed.

Table 2

Linear slope of AES change scores by baseline attention scores and treatment group. Negative difference in slopes (MPH-PLB) favours MPH.

Predictors	MPH slope		PLB slope		MPH - PLB	
	B (95% CI)	P-value	B (95% CI)	P-value	B (95% CI)	P-value
DS forward	0.9 (-0.4, 2.1)	0.16	-0.3 (-1.8, 1.2)	0.69	1.2 (-0.8, 3.1)	0.23
DS backward	0.1 (-1.1, 1.4)	0.82	0 (-1.3, 1.4)	0.95	0.1 (-1.7, 2.0)	0.91
DS scaled total	0.3 (-0.6, 1.3)	0.47	-0.2 (-1.3, 0.9)	0.72	0.5 (-0.9, 2.0)	0.46

Abbreviations: MPH=methylphenidate, PLB=placebo, DS=digit span

* p<0.05 significance

Table 3

Odds ratios for baseline attention as predictors of AES response based on logistic regression.

Predictors	MPH		PLB	
	OR (95% CI)	P-value	OR (95% CI)	P-value
DS forward	0.8 (0.5–1.1)	0.18	1.5 (0.9–2.5)	0.11
DS backward	0.8 (0.6–1.2)	0.38	1.2 (0.8–1.9)	0.30
DS total scaled	0.8 (0.6–1.1)	0.23	1.3 (0.9–1.9)	0.12

Abbreviations: MPH=methylphenidate, DS=digit span, PLB=placebo

*
p<0.05 significance