Effect of Methylphenidate on Attention in Apathetic Alzheimer’s Disease Patients and Association with Apathy Changes in a Randomized, Placebo-Controlled Trial

By: Sarah Chau

A thesis submitted in conformity with the requirements for
the degree of Master of Science (MSc.)

Department of Pharmacology and Toxicology
University of Toronto

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Department of Pharmacology and Toxicology, University of Toronto

Abstract

Emerging evidence supports the use of methylphenidate (MPH) for the treatment of apathy in Alzheimer’s disease (AD). This study aimed to investigate the additional effects of MPH on attention in an AD sample and the relationship between apathy and attention. AD patients enrolled in a randomized, double-blind placebo-controlled study to examine the safety and efficacy of MPH (10mg PO twice daily) for the treatment of apathetic symptoms were tested on attention and apathy every 2 weeks for 6 weeks. A mixed effects linear regression revealed attention change scores (endpoint - baseline) over time favouring MPH (δ=1.01, p=0.03), though there were no significant associations between apathy and attention change scores (r=-0.08, p=0.54). These results suggest that while MPH can improve both apathy and attention, the effects appear independent in this patient population. This study provides insight into the different effects MPH can produce in a heterogeneous disease such as AD.
Acknowledgements

First and foremost, I would like to extend my deepest gratitude to my supervisor, Dr. Krista Lanctôt and my advisor, Dr. Nathan Herrmann. Without their mentorship, this thesis would not be possible. They have challenged me every step of the way, pushing me to think more critically and to explore every question from many different angles. They have also encouraged independence and provided me with opportunities to transform ideas into possibilities. I look forward with enthusiasm to continuing to learn and grow as a scientist under their exceptional guidance.

This thesis would also not be possible without our ADMET colleagues, whom have provided us with constant support throughout the project. Vijay Vaidya and Dr. Lea Drye, deserve a special mention - their expertise in statistical analyses has been a tremendous help to me.

The excellent teamwork within the Neuropsychopharmacology group has made this the best environment for me to achieve my project goals. I would like to thank Abby Li, Jaclyn Cappell and Julia Hussman for helping to ensure ADMET ran smoothly and the other members of my lab for their support during the writing of this thesis. The energy and camaraderie within my team has helped maintain the sanity during times of high pressure.

Finally, I would like to thank my family for their endless support and especially my first teachers, my parents, whom have inspired in me a thirst for knowledge and taught me the work ethic necessary to realize my goals.
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<tbody>
<tr>
<td>5-HT</td>
<td>serotonin</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>ADCS</td>
<td>Alzheimer’s Disease Cooperative Study</td>
</tr>
<tr>
<td>ADHD</td>
<td>attention deficit/hyperactive disorder</td>
</tr>
<tr>
<td>ADMET</td>
<td>Attention in Alzheimer’s Disease Methylphenidate Trial</td>
</tr>
<tr>
<td>AES</td>
<td>apathy evaluation scale</td>
</tr>
<tr>
<td>AI</td>
<td>apathy inventory</td>
</tr>
<tr>
<td>AS</td>
<td>apathy scale</td>
</tr>
<tr>
<td>BPSD</td>
<td>behavioural and psychiatric symptoms of dementia</td>
</tr>
<tr>
<td>CANTAB</td>
<td>Cambridge neuropsychological test automated battery</td>
</tr>
<tr>
<td>CGIC</td>
<td>clinical global impression of change</td>
</tr>
<tr>
<td>ChEi</td>
<td>cholinesterase inhibitor</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CPT</td>
<td>continuous performance test</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>d-AMPH</td>
<td>dextroamphetamine</td>
</tr>
<tr>
<td>DAT</td>
<td>dopamine transporter</td>
</tr>
<tr>
<td>DS</td>
<td>digit span</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>FTD</td>
<td>frontotemporal dementia</td>
</tr>
<tr>
<td>GABA</td>
<td>γ-aminobutyric acid</td>
</tr>
<tr>
<td>MAO</td>
<td>monoamine oxidase</td>
</tr>
<tr>
<td>MCI</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>MMSE</td>
<td>mini-mental status examination</td>
</tr>
<tr>
<td>MPH</td>
<td>methylphenidate</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
</tr>
<tr>
<td>NET</td>
<td>norepinephrine transporter</td>
</tr>
<tr>
<td>NINCDS-ADRDA</td>
<td>National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer’s Disease and Related Disorders Association</td>
</tr>
<tr>
<td>NPI</td>
<td>neuropsychiatric inventory</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PLB</td>
<td>placebo</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SANS</td>
<td>scale for the assessment of negative symptoms</td>
</tr>
<tr>
<td>SERT</td>
<td>serotonin transporter</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
</tr>
<tr>
<td>TBI</td>
<td>traumatic brain injury</td>
</tr>
<tr>
<td>UPDRS</td>
<td>unified Parkinson’s disease rating scale</td>
</tr>
<tr>
<td>VaD</td>
<td>vascular dementia</td>
</tr>
<tr>
<td>WAIS</td>
<td>Wechsler adult intelligence scale</td>
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1 INTRODUCTION

1.1 Statement of Problem

Apathy is one of the most prevalent behavioural and psychological symptoms of dementia (BPSD) in Alzheimer’s disease (AD). Studies have demonstrated that apathy is associated with diminished global functioning and ability to carry out instrumental and basic activities of daily living, independent of cognitive deficits and depression (Boyle et al., 2003; Senanarong et al., 2012; Wadsworth et al., 2012). Additionally, apathetic symptoms can contribute to faster progression of cognitive and functional decline in AD (Lechowski et al., 2009; Starkstein et al., 2006). Studies have also indicated that the presence of apathy in elderly with mild cognitive impairment (MCI) is associated with higher risk of conversion to AD (Palmer et al., 2010; Richard et al., 2012; Rosenberg et al., 2012; Vicini Chilovi et al., 2009). Given these factors, BPSD in AD can lead to increased rates of institutionalization (Banerjee et al., 2003) and consequently, higher costs of health care for dementia patients (Herrmann et al., 2006).

Though there have been some debate in the past about its relationship with depression, apathy is now considered a separate syndrome or set of frequently co-occurring symptoms (Ishii et al., 2009; Marin, 1991; Starkstein et al., 2005; Tagariello et al., 2009). However, current treatment for apathy is hampered due to its overlap in symptoms with depression. Although management of apathy in dementia is not an official indication for psychostimulants, there is some evidence supporting the use of this class of drugs (Galynker et al., 1997; Herrmann et al., 2008; Padala et al., 2007a; Padala et al., 2007b; Padala et al., 2010). However, the mechanisms underlying the apathy-mitigating effects of psychostimulants are not well understood. Given that many psychostimulants, such as methylphenidate (MPH), act on dopamine (DA) and norepinephrine (NE), neurotransmitters involved in the regulation of attention (Nieoullon and
Coquerel, 2003; Robbins, 1984) and thus are the first line of treatment for attention-deficit hyperactive disorder (ADHD), the modulation of attention may play an important role in managing apathetic symptoms. A closer examination of the processes associated with apathy in AD and the involvement of attention will lead to better understanding of this syndrome and its treatment.

1.2 Purpose of Study and Objective

Despite underlying links with the dopaminergic system, little is known of the connection between apathy and attention in AD. The overall objective of this study was to explore the associations between attention and apathy in a sample of apathetic AD patients and the function of DA in this relationship. Specifically, the primary objective was to determine the effects of dopaminergic modulation on attention in this dementia population diagnosed with apathy. As DA is known to regulate attention (Nieoullon and Coquerel, 2003; Robbins, 1984), the secondary objective of this study was to determine the relationship between apathy and attention in these patients as well as exploring attention as predictors of apathy outcomes.

1.3 Statement of Research Hypotheses and Rationale for Hypotheses

1.3.1 Primary Hypothesis

| Compared to placebo, patients on methylphenidate will show greater improvement in attention over the 6-week study period, as measured by Digit Span forward. |

Rationale: This was the first study to investigate the effects of MPH on attention in this patient population, which may be important in informing treatment decisions. While the effects of MPH on attention in younger populations have been established (Lopez et al, 2004; Tucha et
al, 2006a; Tucha et al, 2006b), the data on elderly populations are limited. One study on healthy elderly participants found no effect of a single dose of MPH on working memory, spatial memory span, digit span and sustained attention (Turner et al, 2003). However, evidence of MPH treatment in elderly patients with Parkinson’s disease (PD) suggests some positive effects on attention (Auriel et al, 2006; Yogev et al, 2005). Thus, in patients with a neurodegenerative disorder such as AD, MPH use over the course of 6 weeks is likely to improve overall attention abilities. The Digit Span (DS) forward component, in particular, was identified to significantly improve as it more specifically measures attention, compared with the backward component, which requires added executive functions and working memory capacities (Colom et al, 2005; Gathercole et al, 2004; Groeger et al, 1999; St Clair-Thompson, 2010).

1.3.2 Secondary Hypothesis

| Change in attention from baseline to week 6, measured by Digit Span forward, will be associated with change in apathy scores from baseline to week 6, measured by the Apathy Evaluation Scale, for all participants. |

**Rationale:** MPH has known effects on both attention and apathy, though the relationship between these processes has yet to be clarified. The DA and NE systems have connections throughout the prefrontal and limbic areas and they are important in modulating attention, arousal and emotion (Harley, 1987; Nieoullon and Coquerel, 2003; Robbins, 1984), components which may be disordered and subsequently lead to apathy. Neuroimaging evidence indicates decreased activity in reward and attention-associated brain regions, including the orbitofrontal cortex and anterior cingulate gyrus in apathetic compared with non-apathetic AD patients (Benoit et al, 2004; Benoit et al, 2002; Craig et al, 1996; Lanctôt et al,
Thus, increasing neurotransmission of DA and NE in these brain regions through MPH may mitigate apathy in AD patients by modulating their attention.

### 1.3.3 *Exploratory Hypotheses*

1. **Compared to placebo, patients on methylphenidate will show greater improvement in attention over the 6-week study period, as measured by Digit Span backward, scaled total and Mini-Mental Status Examination attention.**

2. **Change in attention from baseline to week 6, measured by Digit Span backward, scaled total and Mini-Mental Status Examination attention, will be associated with change in apathy scores from baseline to week 6, measured by the Apathy Evaluation Scale and Neuropsychiatric Inventory apathy.**

3. **Higher baseline attention scores, measured by Digit Span forward, backward, scaled total and Mini-Mental Status Examination attention tests, will predict better response to treatment, as indicated by improved scores on Apathy Evaluation Scale, Neuropsychiatric Inventory apathy and Clinical Global Impression of Change apathy.**

**Rationale:**

1. **As per the primary hypothesis, MPH is proposed to have positive effects on attention.**

   Although the Digit Span backward is more associated with working memory (Colom *et al.*, 2005; Gathercole *et al.*, 2004; Groeger *et al.*, 1999; St Clair-Thompson, 2010), attention may still be important in supporting working memory and more complex executive functions. Thus, performance is hypothesized to improve on this measure as well as the other attention measures.
2) Similar to the secondary hypothesis, correlations of changes on other apathy and attention tests were explored. The apathy assessments (Apathy Evaluation Scale, AES and Neuropsychiatric Inventory, NPI) used in this study may have subtle differences and thus could be associated with different components of attention, as measured by the DS subscores and Mini-Mental Status Examination (MMSE) attention.

3) Identifying reliable predictors of treatment outcomes is particularly important in avoiding polypharmacy and adverse side-effects in vulnerable populations where co-occurring medical conditions are common. In a study utilizing a drug challenge to probe the function of the DA system in apathetic AD patients, it was found that greater inattention levels induced by dextroamphetamine (d-AMPH) was predictive of better response to subsequent MPH treatment (Herrmann et al, 2008). The observed inattention or increase in susceptibility to distracters may signify activation of the DA system in response to d-AMPH, suggesting that these patients have a more intact neurotransmitter system. Though the drug challenge may or may not reflect outcomes with multiple doses of a psychostimulant, we hypothesized that better initial attention abilities could be indicative of a more functional DA system, and thus might predict better ability to respond to MPH treatment for apathy.

The primary results of this study will enhance knowledge of the effects of MPH on attention in the AD population, providing more information for physicians to make better treatment decisions. Secondary analyses will also help clarify the relationship between apathy and attention and whether they might be mechanistically related. This can further understanding of underlying factors involved in the expression of apathy in AD, which may
potentially aid in the identification of biomarkers for diagnosis and treatment response prediction.

1.4 Review of the Literature

1.4.1 AD

Alzheimer’s disease, characterized by disorientation and severe impairments in memory, reasoning and communication, is the most common form of dementia, accounting for approximately 50-75% of cases (World Health Organization, 2012). Alzheimer’s Disease International and the World Health Organization estimated that in 2010, 35.6 million people worldwide were living with dementia, with 7.7 million new cases emerging each year and numbers projected to double every 20 years (Alzheimer's Disease International, 2009; World Health Organization, 2012). In Canada, the prevalence rate of dementia, counting people of all ages, was 1.5% in 2008 and is expected to increase to 2.8% in 2038 (Alzheimer Society, 2010). Additionally, the total economic burden in 2008 was $CAD15 billion and is projected to reach $CAD97 billion by 2038 (Alzheimer Society, 2010). Finally, the risk of mortality in people with dementia is more than doubled compared with age-matched non-demented elderly (Alzheimer's Disease International, 2009), further underscoring the global impact of this disease.

The cause of AD is currently not known, though most experts agree that it is the result of several different aberrant changes in the brain. The amyloid hypothesis has been the most studied pathway associated with AD. Under normal circumstances, the transmembrane protein APP is cleaved by α-secretase to generate a soluble protein (sAPPα) (Selkoe, 1996). Under disease conditions, the cleavage of APP by β-secretase and γ-secretase produces two major species of hydrophobic Aβ fragments (Glenner and Wong, 1984a, b). Compared with the
species containing 40 amino acids (Aβ40), the fragments containing 42 amino acids (Aβ42) are more susceptible to aggregation and formation of toxic extracellular amyloid plaques (Cappai and Barnham, 2008; Hardy and Higgins, 1992; Selkoe, 1991). Other proposed mechanisms of the amyloidogenic pathway point to an increase in Aβ42/Aβ40 ratio and elevation of soluble Aβ oligomers, rather than polymeric plaques as the cause of disease pathology (Kumar-Singh et al, 2006; Pimplikar, 2009; Suzuki et al, 1994; Younkin, 1995). Evidence also suggests that within the neuron, axonal microtubule instability may also contribute to AD pathology. Hyperphosphorylation of tau, a protein involved in stabilizing microtubules during polymerization, and subsequent aggregation causes the formation of cytotoxic neurofibrillary tangles and loss of cytoskeletal structural integrity (Goedert et al, 2006; Lee and Trojanowski, 2006; Schneider and Mandelkow, 2008; Thal et al, 2000). Amyloid and tau pathology have been observed with presence of inflammatory cytokines, cyclo-oxygenase and activated microglia, suggesting a role of neuro-inflammatory pathways in the expression of AD (Cagnin et al, 2001; Floyd, 1999; Swardfager et al, 2010). Furthermore, toxic amyloid species can interfere with mitochondrial functioning by activating reactive oxygen species, leading to further neuronal damage (Hansson Petersen et al, 2008; Reddy and Beal, 2008). Taken together, these aberrant changes in normal neuron synaptic functioning can result in the marked neurodegeneration observed in AD.

### 1.4.2 AD and BPSD

Given the changes in the brain discussed above, cognitive deficits characteristic of Alzheimer’s disease (AD) commonly occur in conjunction with neuropsychiatric symptoms. Within the dementia population, prevalence rates of BPSD are estimated to be between 60% and 90% (Lyketsos et al, 2002; Mack et al, 1999; McKeith and Cummings, 2005). BPSD have been associated with decreased quality of life for patients and are a good predictor of increase
caregiver burden (Banerjee et al, 2006; Coen et al, 1997). BPSD, including apathy, agitation, delusions, hallucinations, depression, euphoria, aberrant motor behaviour, irritability, disinhibition, anxiety, sleeping behaviours, and eating disorders, are a prime example of the heterogeneous nature of AD. Of these neuropsychiatric disturbances, apathy appears to be the most frequently reported, warranting further investigation of the causes and treatments of this syndrome.

1.4.3 Apathy in AD

1.4.3.1 Diagnosis

Marin (1990) described apathy as a syndrome characterized by lack of motivation that is not due to reduced consciousness, cognitive deficits or emotional distress. The proposed clinical expression was structured around decreased goal-directed overt behaviour (including lack of effort, initiative, perseverance and productivity), decreased goal-directed cognition (including reduced interests, lack of planning and concern about one’s health and function), and decreased emotional concomitants of goal-directed behavior (including flat affect and lack of emotional responsivity to positive or negative events) (Marin, 1991). As there may be difficulties in establishing a clear definition for the concept of motivation, which is a psychological explanation for a behavioural observation, others have proposed a definition of apathy with more focus on the voluntary behaviour domain rather than the cognitive or emotional domains (Levy and Czernecki, 2006; van Reekum et al, 2005).

<table>
<thead>
<tr>
<th>Domain A</th>
<th>Loss of or diminished motivation in comparison to previous level of functioning and not consistent with age or culture. These changes may be reported by the patient or by the observations of others.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain B</td>
<td>Presence of at least 1 symptom in at least 2 of the following domains for a period of at least 4 weeks and present most of the time.</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td><strong>Goal-directed Behaviour:</strong></td>
</tr>
<tr>
<td></td>
<td>Initiation: loss of self-initiated behaviour (eg: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)</td>
</tr>
<tr>
<td></td>
<td>Responsiveness: loss of environment-stimulated behaviour (eg: responding to conversation, participating in social activities)</td>
</tr>
<tr>
<td></td>
<td><strong>Goal-directed Cognition:</strong></td>
</tr>
<tr>
<td></td>
<td>Initiation: loss of spontaneous ideas and curiosity for routine and new events (ie, challenging tasks, recent news, social opportunities, personal/family and social affairs).</td>
</tr>
<tr>
<td></td>
<td>Responsiveness: loss of environment-stimulated ideas and curiosity for routine and new events (ie, in the person’s residence, neighbourhood or community).</td>
</tr>
<tr>
<td></td>
<td><strong>Goal-directed Emotion:</strong></td>
</tr>
<tr>
<td></td>
<td>Initiation: loss of spontaneous emotion, observed or self-reported (eg: subjective feeling of weak or absent emotions, or observation by others of a blunted affect).</td>
</tr>
<tr>
<td></td>
<td>Responsiveness: loss of emotional responsiveness to positive or negative stimuli or events (eg: observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news).</td>
</tr>
<tr>
<td>Domain C</td>
<td>Symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.</td>
</tr>
<tr>
<td>Domain D</td>
<td>Symptoms (A - B) not exclusively explained or due to physical disabilities (eg: blindness and loss of hearing), motor disabilities, diminished level of consciousness or physiological effects of a substance.</td>
</tr>
</tbody>
</table>

From these definitions, diagnostic criteria for apathy (Robert *et al*, 2009), specific to AD have been proposed (Table 1). Diagnosis requires the presence of diminished motivation, initiation and environmental responsiveness - all of which are rooted in the domains of behaviour, cognition and emotion. Additionally, symptoms must significantly affect daily functioning and not be attributable to disabilities or the effect of a substance. To date, two studies have tested these criteria, reporting good internal consistency, inter-rater reliability and
concurrent validity with the NPI (Mulin et al., 2011; Zhao et al., 2012). As can be seen, these research diagnostic criteria are still in the process of being adopted. Research to date has generally relied upon the NPI and AES to screen and assess apathy.

1.4.3.2 Prevalence and Impact

Apathy is the most frequently reported syndrome with several studies indicating a point prevalence in the range of 32% and 93% in outpatients using the NPI as a measure (Holthoff et al., 2005; Landes et al., 2005; Levy et al., 1998; Mega et al., 1996; Mirakhur et al., 2004; Srikanth et al., 2005; Tatsch et al., 2006; Thomas et al., 2001). Studies using more specific measures of apathy, such as the AES, Apathy Scale (AS) and Apathy Inventory (AI) report prevalence rates of 24% to 86% in community dwelling AD patients (Lyketsos et al., 2000; Robert et al., 2006; Starkstein et al., 2006; Starkstein et al., 2001; Tatsch et al., 2006; Thomas et al., 2001). Rates for dementia patients in nursing homes and long-term care facilities were similar (Margallo-Lana et al., 2001; Pitkala et al., 2004; Zuidema et al., 2007).

There is evidence that apathy, independent of depression, is associated with deficits in global functioning, cognition, instrumental and basic activities of daily living and overall executive functioning (Benoit et al., 2008; Boyle et al., 2003; McPherson et al., 2002; Senanarong et al., 2012; Wadsworth et al., 2012). Apathy has also been associated with increase caregiver burden (Benoit et al., 2008; Kaufer et al., 1998; Pang et al., 2002), poorer insight into personal difficulties (Derouesne et al., 1999; Robert et al., 2002; Starkstein et al., 1996) and increased mortality rate in a cohort of nursing home patients (van Dijk et al., 1994). Longitudinal studies indicate that apathetic symptoms can contribute to more rapid progression of cognitive and functional decline in AD (Lechowski et al., 2009; Starkstein et al., 2006; Wadsworth et al., 2012). Furthermore, MCI patients diagnosed with apathy had a higher risk of developing AD later on (Palmer et al., 2010; Richard et al., 2012; Vicini Chilovi et al., 2009). In
these studies, diagnosis of depression or a combination of depression and apathy, in contrast, was not associated with increased risk of conversion to dementia. Other studies (Gao et al., 2012; Green et al., 2003) have found an association between lifetime major depression and higher risk of developing dementia, though these studies have not separated apathetic symptoms from depression.

1.4.4 Pathways in BPSD

Factors that are considered key to AD pathogenesis, including amyloid plaque formation (Blessed et al., 1968; Cohen et al., 1988; Hardy and Higgins, 1992; Terry et al., 1964), hyperphosphorylated tau aggregation (Goedert et al., 2006; Hanger et al., 1998; Luterman et al., 2000; Vincent and Davies, 1992), neuro-inflammation (Hauss-Wegrzyniak et al., 1998; Luterman et al., 2000; Swardfager et al., 2010) and mitochondria dysfunction (Hansson Petersen et al., 2008; Harris et al., 1995; Mecocci et al., 1994; Saraiva et al., 1985), may contribute to neuronal damage and neurotransmitter system dysfunction, giving rise to cognitive deterioration as well as a wide range of neuropsychiatric disturbances. Aberrant neurotransmission systems such as dopamine (Tanaka et al., 2003), norepinephrine (Lanctôt et al., 2001), serotonin (5-HT) (Lanctôt et al., 2001), γ-aminobutyric acid (GABA) (Lanctôt et al., 2004) and acetylcholine (ACh) (Pinto et al., 2011) have all been implicated in the manifestation of BPSD including depression, agitation, psychosis, apathy and others.

Central DAergic projections begin in the ventral tegmental area and substantia nigra of the midbrain and ascend to limbic and cortical areas through the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular pathways (Albanese et al., 1986; Ikemoto, 2007). The mesolimbic pathway, beginning in the ventral tegmental area and projecting to the nucleus accumbens, amygdala, hippocampus and prefrontal cortex, is thought to mediate incentive salience (Alcaro et al., 2007; Berridge and Robinson, 1998). The mesocortical pathway, also
beginning in the ventral tegmental area, primarily innervates the frontal lobes and interacts closely with the mesolimbic circuit. Together, the mesocorticolimbic dopamine system is believed to be a key mediator of reward-motivated behaviours (Koob, 1996; Nieoullon and Coquerel, 2003; Wise, 2004). This system may be compromised in apathetic AD patients (Mitchell et al, 2010). Post-mortem brains of AD patients show lower levels of dopamine (Arai et al, 1984; Reinikainen et al, 1988; Storga et al, 1996) and reduced D2-like receptor expression (Cross et al, 1984b; Kumar and Patel, 2007; Murray et al, 1995; Sweet et al, 2001) but not D1-like receptors (Cross et al, 1984b; De Keyser et al, 1990; Seeman et al, 1987) compared with age-matched controls. In vivo neuroimaging studies examining DA receptor and uptake activity largely agree with the in vitro post-mortem data (Allard et al, 1990; Itoh et al, 1994; Pizzolato et al, 1996; Tanaka et al, 2003). While evidence indicates that DA dysfunction exists in AD, it remains unclear whether these changes are associated with manifestation of BPSD. However, a single-photon emission computed tomography (SPECT) study found reduced striatal DA transporter uptake was correlated with greater apathy in dementia patients (David et al, 2008). Furthermore, a probe of the DA reward system demonstrated that compared with controls, apathetic AD patients given a single dose of d-AMPH scored lower on tests of subjective positive effects (Lanctôt et al, 2008). These findings suggest that dysfunction in the mesocorticolimbic system may be associated with expression of apathy.

Though DA appears to be the neurotransmitter most prominently involved in apathy, dysfunction in other neurotransmission systems, particularly those that interact with DA may also play a role. Abnormalities in the function of NE, a direct analog of DA via the enzymatic activity of DA β-hydroxylase (Bain and Fielden, 1957) (Figure I), has also been proposed to affect BPSD in dementia (Herrmann et al, 2004). NE neurotransmission, originating from the
locus coeruleus and lateral tegmental area (Moore and Bloom, 1979), is believed to play a role regulating vigilance, attention and memory (Arnsten et al, 1996; Aston-Jones et al, 1991). Dysfunction in NE activity is observed in AD (Bierer et al, 1995; Bondareff et al, 1982; Mann et al, 1982; Mann et al, 1984; Nyberg et al, 1985) and has been linked with BPSD (Forstl et al, 1992; Perry et al, 1981; Russo-Neustadt and Cotman, 1997; Zubenko and Moossy, 1988).

![Catecholamine biosynthesis pathway](image)

**Figure I: Catecholamine biosynthesis pathway.** DA is synthesized through decarboxylation of DOPA. DA β-hydroxylase containing vesicles of NE neurons convert DA to its analog, NE.

Deficits in the 5-HT system are also observed in the AD brain (Arai et al, 1984; Blin et al, 1993; Cross et al, 1984a; Francis et al, 1985; Jansen et al, 1990; Mann and Yates, 1983; Yamamoto and Hirano, 1985) and as well as BPSD (Hoogendijk et al, 1999; Zweig et al, 1988). Interestingly, clinicians have noted the development of apathy associated with the use of a selective-serotonin reuptake inhibitor (SSRI) in cases of non-AD psychiatric patients.
and geriatric patients (Padala et al., 2012). It was also noted that these symptoms were improved or resolved upon discontinuation or reduction of SSRI medication (Barnhart et al., 2004; George and Trimble, 1992; Hoehn-Saric et al., 1991; Hoehn-Saric et al., 1990; Padala et al., 2012). Though the mechanism of action is unclear, it has been suggested that SSRIs indirectly modulate DA neurotransmission via its effect on the frontal cortex (Hoehn-Saric et al., 1990). Evidence indicates that serotonergic neurotransmission can inhibit (Kapur and Remington, 1996) and excite (Benloucif et al., 1993) endogenous DA release in both the forebrain and midbrain. Alternatively, the underlying presence of apathy may be unmasked following successful treatment of the depressed symptoms. However, SSRIs were not used specifically to target depression in some of the cases reported.

There also exist evidence of a link between GABA neurotransmission and BPSD in AD (Lanctôt et al., 2004). GABA, the major inhibitory neurotransmitter in the central nervous system (CNS), opposes the excitatory action of glutamate, as well as interacting with other neurotransmitter systems including dopamine (Dewey et al., 1992; Scheel-Kruger, 1986; Trevitt et al., 2002). In regards to apathy, members of our lab previously showed that plasma GABA levels positively correlated with apathy and depression in a sample of AD patients (Lanctôt et al., 2004).

The link between cholinergic disturbances and AD is well established (Bartus, 2000; Bowen et al., 1976; Davies and Maloney, 1976), considering that cholinesterase inhibitors (ChEIs) are used to manage cognitive and functional deterioration in AD. The cholinergic neurons originate primarily in the basal forebrain and project to all cortical and limbic areas (Bigl et al., 1982). It has been suggested that disruptions along the cholinergic pathways associated with the limbic structures might explain the emotional blunting present in apathy
A new theory has emerged, proposing that attention deficits, as a result of aberrations in the cholinergic system, underlies both cognitive and neuropsychiatric symptoms in AD (Lemstra et al., 2003). In line with this hypothesis, galantamine, a ChEI that additionally stimulates the nicotinic receptors, had positive effects on attention in randomized controlled trials (RCTs) of AD patients (Galvin et al., 2008; Gorus et al., 2007; Vellas et al., 2005). As nicotinic ACh receptor activity has been shown to regulate DA release (Johnson et al., 2000; Marshall et al., 1997; Zhou et al., 2001), it was further proposed that galantamine’s additional association with the DA system may contribute to its benefit for non-cognitive symptoms (Blesa, 2000; Erkinjuntti, 2002; Zhang et al., 2004). In summary, other neurotransmitters are disrupted in AD and multiple neurotransmitters likely play a role in BPSD.

### Pharmacological Treatments for Apathy

#### Cholinesterase Inhibitors

ChEIs, including donepezil, rivastigmine, galantamine and tacrine (not approved in Canada), are generally prescribed for the symptomatic treatment of the progressive cognitive deterioration observed in AD. However, evidence suggests that this class of drugs may also have some benefit for BPSDs such as apathy (Kaufer, 1998; Mega et al., 1999; Rodda et al., 2009). ChEIs primarily block the hydrolyzing activity of the enzyme acetylcholinesterase to increase central ACh neurotransmission, which is thought to be dysfunctional in AD brains (Bartus, 2000; Bowen et al., 1976; Davies and Maloney, 1976). Restoring cholinergic activity via ChEIs has produced modest improvements in memory and overall function in AD patients (Birks, 2006; Hansen et al., 2007; Lanctôt et al., 2003). Thus, RCTs have focused on global cognition and function as primary outcomes while assessing behaviour changes as secondary outcomes. Donepezil, the most commonly prescribed ChEI, shows modest benefits in some
trials (Feldman et al, 2001; Gauthier et al, 2002; Holmes et al, 2004; Mega et al, 1996; Rockwood et al, 2007; Tanaka et al, 2004) and no significant effect on apathy in others (Seltzer et al, 2004; Tariot et al, 2001). Conflicting evidence also exists across studies of rivastigmine (Cummings et al, 2005; Dartigues et al, 2002; Gauthier et al, 2007), tacrine (Kaufer, 1998; Kaufer et al, 1996) and galantamine (Brodaty et al, 2006; Herrmann et al, 2005). Herrmann and colleagues (2005) pooled data from 3 RCTs (2 of which have been published) evaluating the efficacy of galantamine for AD treatment (Rockwood et al, 2001; Tariot et al, 2000). The results showed no difference in NPI apathy outcome between treatment and placebo groups. A meta-analysis of 2 studies (Morris et al, 1998; Raskind et al, 1999) revealed that metrifonate, a ChEI not currently recommended for AD, significantly reduced apathy in treated patients (Cummings et al, 2001). Taken together, these studies (summarized in Table 2) highlight the inconsistent data supporting the effectiveness of ChEIs for the treatment of apathetic symptoms in AD.

Table 2: Studies assessing ChEIs for the treatment of apathy in AD. All studies analyzed apathy as secondary outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrmann et al (2005)</td>
<td>n=2033 mild to moderate AD</td>
<td>Galantamine (16-24 mg/day) or placebo</td>
<td>13, 22, 26 weeks</td>
<td>NPI apathy ↔</td>
</tr>
<tr>
<td>Cummings et al (2001)</td>
<td>n=672 mild to moderate AD</td>
<td>Metrifonate (30-60 mg/day) or placebo</td>
<td>26 weeks</td>
<td>NPI apathy ↓</td>
</tr>
<tr>
<td>Feldman et al (2001)</td>
<td>n=290 moderate to severe AD</td>
<td>Donepezil (5-10 mg/day) or placebo</td>
<td>24 weeks</td>
<td>NPI apathy ↓</td>
</tr>
<tr>
<td>Study</td>
<td>n=</td>
<td>Condition</td>
<td>Treatment</td>
<td>Duration</td>
</tr>
<tr>
<td>------------------------</td>
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<td>----------------------------------</td>
<td>------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Tariot et al (2001)</td>
<td>208</td>
<td>AD in nursing home</td>
<td>Donepezil (5-10 mg/day) or placebo</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Gauthier et al (2002)</td>
<td>290</td>
<td>moderate to severe AD</td>
<td>Donepezil (5-10 mg/day) or placebo</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Holmes et al (2004)</td>
<td>134</td>
<td>mild to moderate AD</td>
<td>Donepezil (10 mg/day) or placebo</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Seltzer et al (2004)</td>
<td>153</td>
<td>early stage AD</td>
<td>Donepezil (10 mg/day) or placebo</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

**Open-label studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>n=</th>
<th>Condition</th>
<th>Treatment</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mega et al (1996)</td>
<td>86</td>
<td>AD</td>
<td>Donepezil (10 mg/day)</td>
<td>8 weeks</td>
<td>NPI apathy ↓ (in 41% of patients)</td>
</tr>
<tr>
<td>Tanaka et al (2004)</td>
<td>70</td>
<td>mild to moderate AD</td>
<td>Donepezil (5 mg/day)</td>
<td>12 weeks</td>
<td>NPI apathy ↓ (30% of patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NPI apathy ↑ (10% of patients)</td>
</tr>
<tr>
<td>Rockwood et al (2007)</td>
<td>101</td>
<td>AD</td>
<td>Donepezil (5 mg or 10 mg)</td>
<td>24 weeks</td>
<td>NPI apathy ↓</td>
</tr>
<tr>
<td>Brodaty et al (2006)</td>
<td>345</td>
<td>mild to moderate AD</td>
<td>Galantamine (mean of 15.2±2.7 mg/day)</td>
<td>26 weeks</td>
<td>behaviour assessment scale apathy ↓ (in 87% of patients)</td>
</tr>
<tr>
<td>Dartigues et al (2002)</td>
<td>696</td>
<td>mild to moderate AD</td>
<td>Rivastigmine (6-12 mg/day)</td>
<td>26 weeks</td>
<td>NPI apathy ↔</td>
</tr>
<tr>
<td>Cummings et al (2005)</td>
<td>173</td>
<td>moderate to severe AD in nursing home</td>
<td>Rivastigmine (3-12 mg/day)</td>
<td>26 weeks</td>
<td>NPI-NH apathy ↓ (by 60%)</td>
</tr>
<tr>
<td>Gauthier et al (2007)</td>
<td>2119</td>
<td>mild to moderate AD</td>
<td>Rivastigmine (6-12 mg/day)</td>
<td>26 weeks</td>
<td>CGIC apathy ↓ (in 63% of patients)</td>
</tr>
<tr>
<td>Kaufer et al (1996)</td>
<td>28</td>
<td>AD</td>
<td>Tacrine (40-160 mg/day)</td>
<td>24 weeks</td>
<td>NPI apathy ↔</td>
</tr>
<tr>
<td>Kaufer et al (1998)</td>
<td>40</td>
<td>AD</td>
<td>Tacrine (40-160 mg/day)</td>
<td>24 weeks</td>
<td>NPI apathy ↓</td>
</tr>
</tbody>
</table>
1.4.5.2 Psychostimulants

Given the role of dopamine in mediating motivation (Koob, 1996; Wise, 2004), identified as one of the key deficits in apathy, psychostimulants have been proposed as treatment for apathy. Psychostimulants, the preferred drug for the treatment of ADHD, can improve attention in younger populations (Lopez et al., 2004; Tucha et al., 2006a; Tucha et al., 2006b). Table 3 provides a summary of studies assessing efficacy of the psychostimulants, including methylphenidate, dextroamphetamine and modafinil, for the treatment of apathy in patients with dementia.

Methylphenidate has thus far, been the most studied psychostimulant in regards to apathy treatment. Its mode of action include inhibition of DA and NE reuptake in the synapse through interaction with the dopamine transporter (DAT) and norepinephrine transporter (NET) on the presynaptic membrane (Andersen, 1987; Ferris et al., 1972; Wall et al., 1995) (Figure II). In vitro studies indicate that MPH possesses affinity for DAT and NET (Easton et al., 2007; Ferris et al., 1972) while having no effect on 5-HT reuptake (Andersen, 1989; Richelson and Pfenning, 1984). Additionally, MPH does not appear to mediate monoamine release, particularly at low therapeutic doses (Easton et al., 2007; Heal et al., 2009; Kuczenski and Segal, 1997; Patrick et al., 1987). The use of MPH to manage symptoms of apathy in dementia has shown promise in case reports (Padala et al., 2007a; Padala et al., 2007b) and open label trials (Galynerker et al., 1997; Padala et al., 2010). The first randomized placebo-controlled crossover trial of MPH in 13 apathetic AD patients found modest but significant improvements
in the active treatment group following 5 weeks (2 weeks in each treatment arm with a 1-week wash-out period) (Herrmann et al, 2008). However, a significantly greater number of drop-outs were observed in the treatment group compared with placebo, suggesting that tolerability of MPH may be of concern in this patient population. The results of this study encouraged researchers to initiate the Apathy in Dementia Methylphenidate Trial (ADMET), a larger multi-centre study. Further evidence for the use of psychostimulants in the AD population was established in ADMET. In this phase 2 double-blind, randomized placebo-controlled study to evaluate the efficacy and safety of MPH for the treatment of apathy in 60 AD patients, significant improvements were observed in the active drug group compared with placebo (Rosenberg et al, under review).

Figure II: Methylphenidate mechanism of action. MPH binds DAT and NET to block reuptake of DA and NE into the presynaptic terminal, resulting in increase concentrations of these neurotransmitters in the synapse.
Dextroamphetamine, alternatively, has generally not been well studied in dementia patients to treat apathy. d-AMPH binds DAT and NET to inhibit reuptake of DA and NE more potently than MPH and can also block, albeit weakly, the reuptake of 5-HT (Heal et al, 1998b; Richelson and Pfenning, 1984; Rothman et al, 2001). In addition to interactions with reuptake transporters, d-AMPH also exerts action within the neuron by facilitating the release of monoamines into the synapse by the process of retro-transport (Heal et al, 1998a; Holmes and Rutledge, 1976; Rothman et al, 2001). d-AMPH enters the intracellular space via NET, DAT (and the serotonin transporter, SERT, to a lesser extent), where it displaces catecholamines in storage vesicles, causing efflux from the presynaptic transporters (Floor and Meng, 1996a, b; Sulzer and Rayport, 1990). Finally, d-AMPH can also act as weak monoamine oxidase (MAO) inhibitors (Miller et al, 1980; Robinson, 1985). Given its wider range of action in the brain, there may be higher risk for adverse effects compared with MPH, particularly in vulnerable elderly populations. In a study of frontotemporal dementia (FTD) patients, d-AMPH demonstrated positive effects on apathy with good tolerability observed in all participants (Huey et al, 2008).

Modafinil, prescribed for the treatment of narcolepsy due to its positive effects on vigilance (Billiard et al, 1994; Broughton et al, 1997; Moldofsky et al, 2000), has shown moderate benefits for apathy in one case report of a patient with dementia and depression (Padala et al, 2007a). However no significant improvements with modafinil were found in a recent RCT of mild to moderate AD (Frakey et al, 2012). The pharmacology of this psychostimulant is currently poorly understood (Minzenberg and Carter, 2008), though some evidence suggests that it may demonstrate effects on DA and NE neurotransmission (Ferraro et al, 1997; Madras et al, 2006; Mignot et al, 1994). In summary, while there is encouraging
evidence for the use of psychostimulants, particularly MPH, for the treatment of apathy in dementia patients, larger clinical trials to investigate efficacy and safety are required.

Table 3: Studies assessing psychostimulants for the treatment of apathy in patients with dementia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind randomized controlled trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Rosenburg et al (under review)</td>
<td>n=60 mild to moderate AD</td>
<td>Methylphenidate (20 mg/day) or placebo</td>
<td>6 weeks</td>
<td>NPI apathy ↓ (in MPH compared with placebo)</td>
</tr>
<tr>
<td>Frakey et al (2012)</td>
<td>n=23 mild to moderate AD</td>
<td>Modafinil (200 mg/day) or placebo</td>
<td>8 weeks</td>
<td>Family observations of apathy ↔</td>
</tr>
<tr>
<td>*Herrmann et al (2008)</td>
<td>n=13 AD</td>
<td>Methylphenidate (20 mg/day) or placebo</td>
<td>2 weeks</td>
<td>AES ↓ (in MPH compared with placebo)</td>
</tr>
<tr>
<td>Huey et al (2008)</td>
<td>n=8 FTD</td>
<td>Dextroamphetamine (20 mg/day) or Quentiapine (150 mg/day)</td>
<td>3 weeks</td>
<td>NPI apathy ↓ (in d-AMPH group)</td>
</tr>
<tr>
<td>Open-label studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Padala et al (2010)</td>
<td>n=23 AD</td>
<td>Methylphenidate (20 mg/day)</td>
<td>12 weeks</td>
<td>AES ↓</td>
</tr>
<tr>
<td>Galyanker et al (1997)</td>
<td>n=27 AD &amp; VaD</td>
<td>Methylphenidate (10-20 mg/day)</td>
<td>3-14 days</td>
<td>SANS ↓</td>
</tr>
<tr>
<td>Case reports</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Padala et al (2007b)</td>
<td>n=1 VaD</td>
<td>Methylphenidate (20 mg/day)</td>
<td>4 weeks</td>
<td>AES ↓</td>
</tr>
<tr>
<td>Padala et al (2007a)</td>
<td>n=1 dementia &amp; depression</td>
<td>Modafinil (200mg/day)</td>
<td>24 weeks</td>
<td>AES ↓</td>
</tr>
<tr>
<td>Chatterjee et al (2002)</td>
<td>n=1 PD</td>
<td>Methylphenidate (10 mg/day)</td>
<td></td>
<td>UPDRS apathy ↓</td>
</tr>
</tbody>
</table>
Maletta et al (1993)  
n=3  
AD with anorexia secondary to apathy  
Methylphenidate (10-20 mg/day)  
-  
clinical observation of apathy ↓

Abbreviations: AD=Alzheimer`s disease, FTD=frontotemporal dementia, VaD=vascular dementia, PD=Parkinson’s disease, MPH=methylphenidate, d-AMPH=dextroamphetamine, NPI=neuropsychiatric inventory, AES=apathy evaluation scale, SANS=scale for the assessment of negative symptoms, UPDRS=unified Parkinson’s disease rating scale  
↓ indicates decrease in apathy scores, ↔ indicates no change in apathy scores, ↑ indicates increase in apathy scores, * indicates studies using apathy as the primary outcome

1.4.5.3 Other Drugs

As most psychostimulants are thought to interact with both DA and NE neurotransmission, it may be practical to investigate the effects of compounds which act more exclusively with one system. Table 4 summarizes the mechanisms of NE- and DA-ergic drugs which may be relevant to apathy.

Amantadine, an anti-parkinsonian drug which has been shown to stimulate DA receptors and facilitate DA release (Bailey and Stone, 1975; Farnebo et al, 1971), has been studied in apathetic patients with a variety of conditions including traumatic brain injury (TBI), meningitis, multiple sclerosis and dementia. Overall improvements were reported based on clinical observations (Cohen and Fisher, 1989; Drayton et al, 2004; Erkulwater and Pillai, 1989; Kraus and Maki, 1997; Van Reekum et al, 1995).

Bromocriptine, another anti-parkinsonian drug which acts as a DA agonist (Boyd, 1995; Johnson et al, 1976), has been studied in post-stroke and neurological patients. Participants reportedly demonstrated improvements in motivation and apathy (Catsman-Berrevoets and von Harskamp, 1988; Crismon et al, 1988; Marin et al, 1995; Powell et al, 1996).
The selective NE reuptake inhibitor prescribed for ADHD, atomoxetine, has been studied in one RCT of depression in PD (Weintraub et al, 2010). Apathy, assessed as a secondary outcome, did not improve in the active treatment group compared with placebo.

Results from these small case studies were based on clinical observations and not systematic assessments of apathy. Thus, it is difficult draw definitive conclusions on whether the DA or NE system is more relevant to apathy. However, the positive data from studies of psychostimulants suggest that both DA and NE neurotransmission plays a necessary role in ameliorating symptoms.

Table 4: Mechanisms of action for drugs in apathy treatment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>DA, NE</td>
<td>neuronal reuptake inhibitor</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>DA, NE, 5-HT</td>
<td>neuronal reuptake inhibitor, releasing agent, vesicular reuptake inhibitor, MAO inhibitor</td>
</tr>
<tr>
<td>Modafinil</td>
<td>DA? NE?</td>
<td>-</td>
</tr>
<tr>
<td>Amantadine</td>
<td>DA</td>
<td>indirect releasing agent, receptor agonist</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>DA</td>
<td>receptor agonist</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>NE</td>
<td>neuronal reuptake inhibitor</td>
</tr>
</tbody>
</table>

Abbreviations: DA=dopamine, NE=norepinephrine, 5-HT=serotonin, MAO=monoamine oxidase

1.4.6 Attention in AD

As mentioned above, the cognitive deterioration characteristic of AD is accompanied by difficulties in attention, which has been hypothesized to be the underlying basis of many deficits in cognition and function. The subsystems of attention, though interrelated, can be anatomically and functionally separable and consequently may have unique susceptibilities to
the effects of AD pathology (Perry and Hodges, 1999). Perry and Hodges structured attention into 3 categories: selective, sustained and divided to study these processes in AD. Selective attention is related to focus and concentration on a target stimulus, while filtering out distractions. Sustained attention refers to ability to maintain focus on a stimulus over a period of time. Finally, Perry and Hodges defined divided attention as the capacity to distribute cognitive resources in order to simultaneously maintain focus on several stimuli. Evidence indicates that deficits in selective and divided attention are associated with the early stages of AD while sustained attention remains relatively intact until the later stages (Belleville et al., 2007; Johannsen et al., 1999; Levinoff et al., 2004; McGuinness et al., 2010; Perry and Hodges, 1999; Perry et al., 2000; Pignatti et al., 2005). Neuroimaging studies have shown hypoperfusion of temporal and parietal areas associated with these attentional deficits but no change in frontal regions linked with higher attention and executive functions until the later stages of AD (Brown et al., 1996; Jagust et al., 1997; Rapoport, 1991). These studies, however, did not consider the interaction of BPSDs such as apathy and depression, which have been linked with abnormalities in frontal lobe activity (Kataoka et al., 2010; Levy-Cooperman et al., 2008; Marshall et al., 2007; Mayberg, 1994). The specific loss of motivation and goal-directed cognition and behaviour, symptoms observed in apathy, may be mediated by frontal lobe dysfunction (Niedermeyer, 1998).

1.4.7 Apathy, Attention and Dopamine

Apathy may reflect deficits in higher attention networks that interact closely with frontal lobe-mediated executive control. Following this line of thinking, one study found that apathetic AD patients had reduced attention towards novel stimuli (Daffner et al., 1999). As well, studies have reported correlations between executive dysfunction and apathy in AD patients (Drijgers et al., 2011; McPherson et al., 2002; Senanarong et al., 2005). The link between apathy and
attention is also apparent considering that DAergic neurons make projections to attention networks in the brain, including apathy associated regions in the frontal lobe (Albanese et al., 1986; Ikemoto, 2007; Watanabe et al., 1997). Thus, apathy and attention may be operating under similar or related mechanisms.

Neuroimaging studies (summarized in Table 5) provide further evidence for this premise. Functional neuroimaging studies using SPECT consistently show hypoperfusion in the orbitofrontal cortex and anterior cingulate gyrus of apathetic AD patients (Benoit et al., 1999; Benoit et al., 2002; Craig et al., 1996; Lopez et al., 2001; Migneco et al., 2001; Ott et al., 1996; Robert et al., 2006), with some studies controlling for the confounding effects of depression (Benoit et al., 2004; Kang et al., 2012; Lanctôt et al., 2007). A positron emission tomography (PET) study found similar results using a negative symptoms scale (Marshall et al., 2007). In addition, structural magnetic resonance imaging (MRI) studies found that decreased white matter (axonal) integrity and reduced gray matter volume was correlated with increased apathy severity in the anterior cingulate and frontal areas (Apostolova et al., 2007; Kim et al., 2011; Ota et al., 2012; Starkstein et al., 2009). This suggests that the neuronal tracts (possibly the mesocorticolimbic DAergic pathway) within these regions may be compromised. A SPECT study using a DAT radioligand to measure DA reuptake provides clearer evidence for the role of DA in apathy (David et al., 2008). Decreased DAT availability in the striatum, particularly the putamen and caudate of the basal ganglia, was associated with lack of initiative and interest on a measure of apathy, suggesting loss of DAergic neurons and involvement of subcortical systems in the expression of apathy. Specifically, the interaction between midbrain DAergic limbic pathways and the motor striatum, occurring indirectly through several circuits, work to link motivation with motor outcomes (Haber et al., 2000).
Table 5: Neuroimaging correlates of apathy in AD patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Apathy Measure</th>
<th>Areas correlated with presence of apathy or apathy severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benoit et al (1999)</td>
<td>20 AD</td>
<td>NPI apathy</td>
<td>hypoperfusion in right cingulate</td>
</tr>
<tr>
<td>Benoit et al (2002)</td>
<td>30 AD (15 apathetic)</td>
<td>NPI apathy</td>
<td>hypoperfusion in left anterior cingulate, right inferior frontal gyrus, left orbitofrontal gyrus, right gyrus lingualis</td>
</tr>
<tr>
<td>Benoit et al (2004)</td>
<td>30 AD (14 apathetic)</td>
<td>AI (lack of initiative &amp; interest score)</td>
<td>hypoperfusion in bilateral superior orbitofrontal, right anterior cingulate</td>
</tr>
<tr>
<td>Craig et al (1996)</td>
<td>31 AD (21 apathetic)</td>
<td>NPI apathy</td>
<td>hypoperfusion in anterior cingulate, orbitofrontal, dorsolateral, anterior temporal areas</td>
</tr>
<tr>
<td>Lanctôt et al (2007)</td>
<td>51 AD (23 apathetic)</td>
<td>NPI apathy</td>
<td>hypoperfusion in right orbitofrontal cortex, left anterior cingulate</td>
</tr>
<tr>
<td>Robert et al (2006)</td>
<td>31 AD (19 apathetic)</td>
<td>AI (lack of initiative &amp; interest score)</td>
<td>hypoperfusion in right frontal lobe, right anterior cingulate, right inferior temporal lobe</td>
</tr>
<tr>
<td>Robert et al (2006)</td>
<td>31 AD (19 apathetic)</td>
<td>AI (lack of initiative &amp; interest score)</td>
<td>hypoperfusion in right frontal lobe, right anterior cingulate, right inferior temporal lobe</td>
</tr>
<tr>
<td>David et al (2008)</td>
<td>14 AD + 8 DLB</td>
<td>AI (lack of initiative &amp; interest score)</td>
<td>decreased DAT uptake in bilateral putamen</td>
</tr>
<tr>
<td>Kang et al (2012)</td>
<td>81 AD (9 apathetic)</td>
<td>NPI apathy</td>
<td>hypoperfusion in right amygdala, temporal, posterior cingulate, right superior frontal, postcentral &amp; left superior temporal gyrus</td>
</tr>
</tbody>
</table>
The relationship between attention and DA is demonstrated by the treatment of ADHD. Studies suggest that in children with ADHD, treatment with psychostimulants can improve selective, sustained and divided attention (Lopez et al, 2004; Tucha et al, 2006a; Tucha et al, 2006b). The regulation of both motivation and attention through the actions of dopamine may signify that attention and apathy is operating under the same mechanism. Lanctôt et al (2008) used a dextroamphetamine drug challenge to probe the function of the DA system in apathetic AD patients (Lanctôt et al, 2008). Compared with non-apathetic patients, AD patients with apathy had reduced feelings of positive effects after a single dose of drug, suggesting response to DAergic agents is blunted in apathy. Interestingly, the patients who demonstrated inattention

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>Ota et al (2012)</td>
<td>21 AD</td>
<td>AS</td>
<td>decreased white matter integrity in right anterior cingulate, right thalamus, bilateral parietal regions</td>
</tr>
<tr>
<td></td>
<td>Starkstein et al (2009)</td>
<td>79 AD (14 apathetic + 10 depressed and apathetic)</td>
<td>AES</td>
<td>increased volume of white matter hyperintensities in the frontal lobe</td>
</tr>
<tr>
<td></td>
<td>Kim et al (2011)</td>
<td>51 AD</td>
<td>NPI apathy</td>
<td>decrease white matter integrity in left anterior cingulate</td>
</tr>
<tr>
<td></td>
<td>Apostolova et al (2007)</td>
<td>35 AD (17 apathetic)</td>
<td>NPI apathy</td>
<td>increased gray matter atrophy in bilateral anterior cingulate, left medial frontal cortex</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease, NPI=neuropsychiatric inventory, AI=apathy inventory, AES=apathy evaluation scale, SANS=scale for the assessment of negative symptoms, AS=apathy scale, SPECT=single-photon emission computerized tomography, PET=positron emission tomography, MRI=magnetic resonance imaging
in response to d-AMPH showed improvements in apathy in a trial of MPH to treat their apathy symptoms (Herrmann et al, 2008). This suggests that attention may be a predictor of apathy treatment response. In other words, attention, as an indicator of intrinsic DA functioning, might be telling of a patient’s ability to respond to treatment outcomes. Although apathy and attention (McGuinness et al, 2010; Perry and Hodges, 1999) are both disordered in AD, share common pathways and can be modulated by DAergic drugs, no studies have aimed to explore their relationship. Better insight into the neurological processes associated with apathy in AD will help identify targets within the disease pathways for pharmacological treatment, in order to more effectively manage this syndrome.
2 MATERIALS AND METHODS

2.1 Study Design

This is a planned secondary analysis of a multi-centre, randomized, double-blind, placebo-controlled trial examining the association between attention and apathy in clinically apathetic AD patients who were receiving either MPH or placebo. Caregivers were also participants in the study as many of the neuropsychological tests relied on information provided by the primary caregiver about the patient. Eligible participants were tested at baseline and every 2 weeks for 6 weeks (Refer to Table 6 for assessment schedule).

Table 6: Study Assessment Schedule

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Baseline</th>
<th></th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screening</td>
<td>After Randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/Interim History</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>NPI</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>AES</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CGIC</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DS</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Electrolyte Panels</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ECG</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: NPI=neuropsychiatric inventory, MMSE=mini-mental status examination, AES=apathy evaluation scale, CGIC=clinician’s global impression of change, DS=digit span, ECG=electrocardiogram
2.2 Participant Selection

Patients enrolled in the Apathy in Dementia Methylphenidate Trial at Sunnybrook Health Sciences Centre, Johns Hopkins University and the Medical University of South Carolina were used in this study. ADMET is a phase 2, randomized, double-blind placebo-controlled study to investigate the safety and efficacy of MPH (10mg PO twice daily) versus placebo (PLB) for 6 weeks for the treatment of apathy in AD patients. At each site, patients were recruited from outpatient clinics, assisted living facilities affiliated with the clinics, referrals from local physicians and advertisements in local media. Before randomization, patients were screened according to the eligibility criteria and written consent was obtained from both patients and their accompanying caregivers. Eligible patients were randomized, with a 1:1 assignment ratio, to either methylphenidate or placebo for 6 weeks.

2.3 Eligibility Criteria

2.3.1 Inclusion

- Diagnosis of possible or probable AD based on National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria AND MMSE score of 10-26 inclusive
- Clinically significant apathy for at least 4 weeks: Apathy on the NPI was “very frequent” or “frequent/often” AND severity was “moderate” or “marked” (NPI apathy ≥ 4)
- Medication for apathy was appropriate, in the opinion of the study physician
- Availability of primary caregiver who spent greater than 10 hours/week with the patient and could attend study visits and participate in the study
- Sufficient fluency, of both the patient and caregiver, in written and spoken English to participate in study assessments
- No change to AD medications for at least 1 month prior to randomization, including starting, stopping, or dosage modifications

2.3.2 Exclusion

- Met criteria for Major Depressive Episode, by Diagnostic Statistical Manual of Mental Disorder - IV (TR) criteria
- Clinically significant agitation/aggression, hallucinations and delusions (NPI score ≥ 4 on each item)
- Treatment with psychotropic medications in the 2 weeks prior to randomization with the exception of:
  - approved treatments for dementia (ChEIs and memantine),
  - SSRIs/SNRIs, if stable for 3 months prior to randomization
  - trazodone, if used as an aid to facilitate sleep and not as an antidepressant
  - other psychotropics, if stable for 3 months, may be allowed only with approval from the ADMET Steering Committee on a case by case basis (antipsychotics are prohibited)
- Treatment with MPH was contraindicated in the opinion of the study physician
- Failure of treatment with MPH for apathy in the past
- Treatment with a medication that would prohibit the safe concurrent use of MPH such as MAO inhibitors and tricyclic antidepressants
- Need for acute psychiatric hospitalization or is suicidal
- Uncontrolled hypertension (e.g. medication non-compliance)
Symptomatic coronary artery disease deemed to be significant by study physician at the time of screening

Lack of appetite that resulted in significant unintentional weight loss as determined by the study physician in the last three months

Significant communicative impairments

Current participation in a clinical trial or in any study that may add significant burden or affect study outcomes

Hyperthyroidism, advanced arteriosclerosis, symptomatic cardiovascular disease, serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or a family history of sudden death or death related to heart problems

Glaucoma, pheochromocytoma, or known or suspected hypersensitivity to methylphenidate or its excipients

CNS abnormalities (e.g., cerebral aneurysm) and/or other vascular abnormalities such as vasculitis or pre-existing stroke, motor tics or a family history or diagnosis of Tourette’s syndrome, seizures (convulsions, epilepsy), or abnormal electrocardiogram (ECG)

Any condition that, in the opinion of the study physician, made it medically inappropriate or risky for the patient to enroll in the trial

2.4 Study Drug

This study used Ritalin® (methylphenidate hydrochloride), the immediate release formulation of racemic dL-threo-MPH, as the active treatment. MPH is observed to reach peak plasma concentrations after 2 hours and has a pharmacokinetic half-life of 2-3 hours (Kimko et al., 1999). In the present study, drugs (either MPH or placebo) were initiated at 5 mg PO twice
daily with meals, once at in the morning and once in the afternoon, 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. This dose schedule was determined based on the previous trial conducted by our group (Herrmann et al, 2008). The placebo capsule consisted of a 1:1 mixture of microcrystalline cellulose and lactose. Both the active and inert compounds were identical in appearance. After randomization, study drugs were issued to caregivers with usage instructions. At each subsequent visit, compliance was determined through pill counting and interview with caregivers.

2.5 Demographics

Caregivers provided information for the patient regarding age, ethnicity, level of education, duration of dementia, current medications, medical and psychiatric history. Physiological measures such as blood pressure and ECG were also taken during the 4 study visits.

2.6 Procedures

At each visit, the study physician completed a physical assessment to ensure that patients were able to safely continue in the clinical trial. The NPI, AES and Alzheimer’s Disease Cooperative Study - Global Clinical Impression of Change (ADCS-CGIC) were administered using information provided by caregivers. Patients completed the Wechsler Adult Intelligence Scale – Digit Span (WAIS-DS) subtest and MMSE and also provided information for the CGIC. In order to monitor safety throughout the trial, vital signs, adverse events reports, electrolyte panels and ECG tests were also obtained from patients. The ADMET study also consisted of a psychosocial intervention for primary caregivers to provide emotional support,
education and counseling regarding caregiver skills. Sessions were delivered by a certified clinician during each study visit. The safety measures and psychosocial interventions were not specifically examined in this study. In the weeks between every study visit, patients received a telephone follow-up in order to monitor progress and record adverse events.

2.7 Neuropsychological Assessments

2.7.1 WAIS-DS

The Digit Span subtest (Wheeler, 1981) was used as a valid tool for the assessment of auditory attention and working memory. Digit sequences of progressively increasing length were read by the examiner (following a rhythm of 1 digit per second) and patients were instructed to repeat them in 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. The forward task consisted of 8 items, 2 trials of the same digit length for each item, with a maximum score of 16. The backward task consisted of 7 items, giving a possible maximum score of 14. Performance was summarized by a forward, backward and total score. Additionally, a scaled score, based on standardized age norms, could be converted from the raw total score. Training for administration of the Digit Span was provided by the Lanctôt lab during an Investigator’s meeting under the guidance of a registered practising psychologist.

2.7.2 AES

The AES, considered the most widely used and psychometrically robust evaluation of apathy (Clarke et al, 2011), was developed and validated by Marin et al (1991) to provide a measure of apathy in the context of goal-related overt behaviour, cognition and emotional
responsivity. The 3 available versions - clinician-rated (AES-C), informant-rated (AES-I) and self-rated (AES-S) - were reported to have good inter-rater and test-retest reliability (Marin et al, 1991). One study found that the AES-I had greater sensitivity and stronger positive and negative predictive values for apathy compared with the other versions (Clarke et al, 2007a). In the present study, the AES-I was administered to caregivers to assess the presence of patients’ symptoms in the past 2 weeks. Severity on each of the 18 items was characterized with a 4-point Likert scale using the following descriptions: “Not at All”, “Slightly”, “Somewhat” and “Very Much”. Scores ranged from 18 to 72. Higher values were allocated to stronger presence of specific symptoms and thus, a higher total score indicated greater apathy. Marin et al (1991) recommended a cut-off score of 37.5 for clinically significant apathy. However, Clarke et al (2011) proposed cut-off scores of 40.5, 41.5, and 36.5 for the AES-C, AES-I and AES-S, respectively.

2.7.3 ADCS-CGIC

The ADCS-CGIC (Schneider et al, 1997) was used as a method of determining clinically significant change in a patient’s overall apathy level in the clinical trial. A trained clinician assessed the status of each patient’s apathy at baseline. In order to maintain the blind and independence of this rating scale, clinicians were blinded to treatment allocation as well as all clinical information after randomization. Subsequent follow-up assessments were completed through patient and caregiver interviews and information was compared with baseline notes. The clinician’s overall impression of change in apathy was rated using categorical values with the following designations: “Marked Worsening” (7), “Moderate Worsening” (6), “Minimal Worsening” (5), “No Change” (4), “Minimal Improvement” (3), “Moderate Improvement” (2) and “Marked Improvement” (1).
2.7.4 NPI

The NPI (Cummings et al, 1994) is a widely used screen of behaviour disturbances in dementia, including: apathy, agitation, delusions, hallucinations, depression, euphoria, aberrant motor behaviour, irritability, disinhibition, anxiety, sleeping, and eating. Caregivers were asked to judge the frequency and severity of all existing symptoms in the past 4 weeks and in relation to the patient’s behaviour before development of dementia. The frequency score is judged on a 4-point scale from “Occasionally” (1) to “Often” (2) to “Frequently” (3) to “Very Frequently” (4). The severity score is judged on a 3-point scale from “Mild” (1) to “Moderate” (2) to “Marked” (3). The frequency and severity scores are multiplied to generate a score, range from 0 to 12, for each domain. A 5-point scale is additionally used to evaluate caregiver distress. Domain scores were added to determine a total, with higher values indicating greater disturbance.

2.7.5 MMSE

The MMSE (Folstein et al, 1975) was used as an instrument of detecting dementia and describing severity of cognitive impairment. This 10-item scale, administered directly to AD patients, measured domains such as orientation, memory, attention and language abilities. For the attention task, patients were instructed to verbally spell “WORLD” backwards and given a score, out of a possible 5, for each correctly placed letter. Total scores may range from 0-30, with higher values indicating better cognitive function.

2.8 Statistical Analysis

Statistical analyses were performed using SAS version 9.3 Copyright © 2002-2010 by SAS Institute Inc., Cary, NC, USA. Baseline clinical and demographic characteristics were compared between these response groups using Kruskal-Wallis test for continuous variables.
and chi-square of Fisher’s exact test for categorical variables. Two sided p-value at 5% significance level were used to assess statistical significance. Results were not adjusted for multiple comparisons.

2.8.1 Primary Hypothesis

Compared to placebo, patients on methylphenidate will show greater improvement in attention over the 6-week study period, as measured by Digit Span forward.

All analyses of treatment effects were conducted according to the intention to treat principle. For the primary hypothesis, the treatment effect of MPH on DS forward was assessed by longitudinal analysis of DS forward scores using linear mixed effects models with random intercept for each participant. Models were created to compare the difference in change in attention score from baseline to week 6 between MPH and placebo.

2.8.2 Secondary Hypotheses

Change in attention from baseline to week 6, measured by Digit Span forward, will be associated with change in apathy scores from baseline to week 6, measured by the Apathy Evaluation Scale, for all participants.

For this hypothesis, Pearson coefficient correlations and 95% confidence intervals were calculated for change in DS forward from baseline to week 6 versus change in AES from baseline to week 6 to determine associations.
2.8.3 Exploratory Hypotheses

4) Compared to placebo, patients on methylphenidate will show greater improvement in attention over the 6-week study period, as measured by Digit Span backward, scaled total and Mini-Mental Status Examination attention.

5) Change in attention from baseline to week 6, measured by Digit Span backward, scaled total and Mini-Mental Status Examination attention, will be associated with change in apathy scores from baseline to week 6, measured by the Apathy Evaluation Scale and Neuropsychiatric Inventory apathy.

6) Higher baseline attention scores, measured by Digit Span forward, backward, scaled total and Mini-Mental Status Examination attention tests, will predict better response to treatment, as indicated by improved scores on Apathy Evaluation Scale, Neuropsychiatric Inventory apathy and Clinical Global Impression of Change apathy.

1) The analysis for the primary hypothesis was repeated for DS backward, scaled total and MMSE attention as treatment outcomes.

2) The Pearson coefficient correlations were performed for the other attention (DS scaled total, DS backward, MMSE attention subscale) and apathy measures (NPI apathy).

3) Patients were divided into responders and non-responders based on improvements on the AES, NPI apathy and CGIC apathy. Presently, there is no validated definition of clinically significant treatment response on the AES. However, response to treatment as an improvement of at least 3.3 points on the AES from baseline to week 6, based on results from the trial conducted by Herrmann et al. (2008) and power calculations for the ADMET trial design (Drye et al, 2012). The effect of baseline attention measure on treatment response was measured by: i) linear regression models of the change in AES score from baseline to week 6 with baseline attention scores, treatment and their
interaction as predictors; ii) logistic regression models of apathy response with baseline attention scores, treatment group and their interaction as predictors. For sensitivity analyses, different definitions of responders were explored using the NPI and CGIC to examine whether results were affected. Responders were defined as patients who showed decrease in NPI apathy score by 1 or more points at week 6 and improvement at CGIC scale from baseline (minimal, moderate, and marked improvement). The models described above were repeated using these definitions of response.

2.9 Sample Size Considerations

A sample size calculation was performed for the primary hypothesis. For a multivariate linear regression with 3 covariates (age, education and MMSE scores), 61 total patients are required to detect a large effect size (f=0.35) with an alpha of 0.05 and power of 0.80. In our previous study (Lanctôt et al., 2008) of a smaller sample size (23 apathetic AD patients), a single dose of d-AMPH was sufficient to improve an attention subscore of the Conners’ Continuous Performance Test (CPT) following 60 minutes (unpublished data). The included covariates were based on findings suggesting interaction with attention and Digit Span test. Firstly, the WAIS-DS standardized total scores correct for age (Wheeler, 1981), indicating age-related decline in performance on this test (Hester et al., 2004; Sun et al., 2005). As scaled scores are not available for the DS forward, age was added as a covariate for this analysis. Education level is also known to influence neuropsychological assessments such as the DS (Hester et al., 2004; Muangpaisan et al., 2010). Finally, patients with cognitive deficits have decreased performance ability on the DS (Araujo et al., 2011; Huntley et al., 2011; Muangpaisan et al., 2010), justifying the inclusion of the MMSE as a covariate. Thus, a sample size of 60 should be adequate to test our hypothesis and adjust for likely important covariates.
3 RESULTS

3.1 Patient Recruitment

For the ADMET study, 80 patients with possible or probable AD were screened for inclusion and 60 patients (19 at Sunnybrook Health Sciences Centre, 23 at the Medical University of South Carolina, 18 at Johns Hopkins University) were randomized between June 2010 and October 2011. The 20 ineligible patients were excluded for one or more of the following reasons: MMSE not 10-26 inclusive, non-significant apathy, no available caregiver, unstable AD treatment, treatment with MPH was contraindicated, no informed consent or other. The number of patients randomly assigned to receive MPH and PLB were 29 and 31, respectively. In the MPH group, 6 discontinued treatment before study end point due to medication conflict (n = 2) and adverse events or side effects (n=4). In the PLB group, 4 were taken off placebo before 6 weeks due to refusal to continue (n = 2) and adverse events or side effects (n = 2). In accordance with an intention to treat analysis, data for participants who did not adhere to treatment were included in the final analyses. Three patients did not complete a week 6 visit - 1 from the MPH group did not return for a follow-up visit and 2 patients from the PLB group refused to continue in the study - but were included in the final analysis. A flow chart of patient recruitment and inclusion is illustrated in Figure III.
Figure III: CONSORT diagram of participant flow.
3.2 Demographics and Clinical Characteristics

The baseline demographic and clinical characteristics of all 60 patients included in ADMET are indicated in Table 7. At baseline, participants had NPI apathy scores of 7 ± 2 and AES scores of 51 ± 12, which indicated significant apathy. The patients in each treatment arm (29 in the MPH group and 31 in the placebo group) were not significantly different in any baseline parameter.

Table 7: Baseline characteristics of all patients assigned to each treatment group. Values are mean ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=60)</th>
<th>MPH (n=29)</th>
<th>PLB (n=31)</th>
<th>K or χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>76±8</td>
<td>78±8</td>
<td>75±9</td>
<td>0.72</td>
<td>0.39</td>
</tr>
<tr>
<td>Women, (%)</td>
<td>62</td>
<td>59</td>
<td>65</td>
<td>0.22</td>
<td>0.64</td>
</tr>
<tr>
<td>Racial / ethnic group, (%)</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>0.19†</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>95</td>
<td>97</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American, non-Hispanic</td>
<td>8</td>
<td>3</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic / Latino</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, non-Hispanic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education, (%)</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>0.33†</td>
</tr>
<tr>
<td>No High school diploma</td>
<td>12</td>
<td>11</td>
<td>13</td>
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<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>29</td>
<td>18</td>
<td>39</td>
<td></td>
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</tr>
<tr>
<td>Some college / associates degree</td>
<td>22</td>
<td>21</td>
<td>23</td>
<td></td>
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</tr>
<tr>
<td>Bachelor's degree</td>
<td>22</td>
<td>29</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional / graduate degree</td>
<td>15</td>
<td>21</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure in mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133±16</td>
<td>135±14</td>
<td>130±18</td>
<td>1.89</td>
<td>0.16</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75±11</td>
<td>75±10</td>
<td>75±12</td>
<td>0.03</td>
<td>0.85</td>
</tr>
<tr>
<td>Abnormal ECG results, (%)</td>
<td>60</td>
<td>62</td>
<td>58</td>
<td>0.10</td>
<td>0.75</td>
</tr>
<tr>
<td>Duration of dementia in years</td>
<td>3±3</td>
<td>3±3</td>
<td>3±3</td>
<td>0.17</td>
<td>0.68</td>
</tr>
<tr>
<td>Concomitant medications, (%)</td>
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<tr>
<td>SSRIs</td>
<td>37</td>
<td>38</td>
<td>35</td>
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<td>0.32</td>
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<td>ChEIs</td>
<td>72</td>
<td>72</td>
<td>71</td>
<td>0.02</td>
<td>0.90</td>
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<tr>
<td>Memantine</td>
<td>62</td>
<td>72</td>
<td>52</td>
<td>2.74</td>
<td>0.10</td>
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<tr>
<td>History of mood disorder before AD, (%)</td>
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<td>7</td>
<td>19</td>
<td>-</td>
<td>0.26†</td>
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<tr>
<td>AES</td>
<td>51±12</td>
<td>50±13</td>
<td>51±11</td>
<td>0.00</td>
<td>0.95</td>
</tr>
<tr>
<td>NPI</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>
### Apathy subscore

<table>
<thead>
<tr>
<th>Subscore</th>
<th>MPH</th>
<th>Placebo</th>
<th>Significant Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>7±2</td>
<td>7±2</td>
<td>0.65</td>
<td>0.42</td>
</tr>
<tr>
<td>Depression subscore</td>
<td>2±2</td>
<td>1±2</td>
<td>0.69</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### MMSE

<table>
<thead>
<tr>
<th>Subscore</th>
<th>MPH</th>
<th>Placebo</th>
<th>Significant Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>20±5</td>
<td>19±5</td>
<td>1.03</td>
<td>0.31</td>
</tr>
<tr>
<td>Attention subscore</td>
<td>3±2</td>
<td>3±2</td>
<td>0.28</td>
<td>0.59</td>
</tr>
</tbody>
</table>

### DS

<table>
<thead>
<tr>
<th>Subscore</th>
<th>MPH</th>
<th>Placebo</th>
<th>Significant Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward score</td>
<td>8±2</td>
<td>8±3</td>
<td>1.01</td>
<td>0.31</td>
</tr>
<tr>
<td>Backward score</td>
<td>4±2</td>
<td>4±2</td>
<td>0.28</td>
<td>0.59</td>
</tr>
<tr>
<td>Raw total score</td>
<td>12±4</td>
<td>11±5</td>
<td>0.70</td>
<td>0.40</td>
</tr>
<tr>
<td>Scaled total score</td>
<td>8±3</td>
<td>8±3</td>
<td>0.74</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Abbreviations: MPH=methylphenidate, PLB=placebo, SSRI=selective serotonin reuptake inhibitor, ChEI=cholinesterase inhibitor, AES=apathy evaluation scale, NPI=neuropsychiatric inventory, MMSE=mini-mental status examination, DS=digit span, ECG=electrocardiogram

* p<0.05 significance † P-value for Fisher’s exact test

### 3.3 Planned Analyses

#### 3.3.1 Effect of MPH on Attention

**Primary Hypothesis:** Compared to placebo, patients on methylphenidate will show greater improvement in attention over the 6-week study period, as measured by Digit Span forward.

At the week 6 visit, DS forward scores showed greater improvement in MPH group compared to placebo (Table 8). A linear regression model with mixed effects was used to calculate estimate scores and standard error of estimates for each attention subtest in order to determine the effect of MPH on DS forward, taking into consideration the proximity of the sample mean relative to the population mean. This model assumed random intercept for each participant and controlled for the stratification variable (by clinic). For baseline, the difference between the estimates for MPH and PLB is calculated with standard error. For follow-up visits, the estimated difference in the change from baseline (δ) for treatment groups is calculated with 95% confidence intervals (CI). Table 8 summarizes the difference in estimated changes scores.
(week 6 - baseline) between treatment groups for DS forward. Although baseline attention scores were higher in the placebo group, estimated difference in change in attention from the baseline to week 6 showed larger improvements favouring MPH (positive δ) (δ = 0.87, 95% CIs: 0.06 to 1.08, p = 0.03). Figure IV shows estimated change scores (and standard error) in DS forward at each time point, with higher attention scores indicating better function. Scores in the MPH group were lower than placebo at baseline but increased in the subsequent time points, while placebo attention scores remained stable.

**Table 8: DS forward scores over time.** The estimated score is given with standard error (SE) and the estimated difference in the change from baseline (δ) for MPH (n=29) and PLB (n=31) is calculated with 95% confidence intervals (CI). Positive values favour MPH.

<table>
<thead>
<tr>
<th></th>
<th>Estimated Score (±SE)</th>
<th>Estimated Change Score (±SE)</th>
<th>δ (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPH</td>
<td>PLB</td>
<td>MPH</td>
<td>PLB</td>
</tr>
<tr>
<td>Baseline</td>
<td>7.71±0.44</td>
<td>8.58±0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>7.65±0.44</td>
<td>8.34±0.43</td>
<td>-0.06±0.28</td>
<td>-0.23±0.28</td>
</tr>
<tr>
<td>Week 4</td>
<td>7.98±0.44</td>
<td>8.79±0.44</td>
<td>0.26±0.28</td>
<td>-0.20±0.28</td>
</tr>
<tr>
<td>Week 6</td>
<td>8.54±0.45</td>
<td>8.54±0.44</td>
<td>0.83±0.29</td>
<td>-0.04±0.28</td>
</tr>
</tbody>
</table>

Abbreviations: MPH=methylphenidate, PLB=placebo, DS=digit span, MMSE=mini-mental status examination
*p<0.05 significance
Improvement (positive change scores) over 6 weeks in the MPH group (n=29) was significantly greater than in the PLB group (n=31).

3.4.2 Association between Attention and Apathy

Secondary Hypothesis: Change in attention from baseline to week 6, measured by Digit Span forward, will be associated with change in apathy scores from baseline to week 6, measured by the Apathy Evaluation Scale, for all participants.

Correlation analyses were conducted to determine whether changes in apathy and attention scores are associated. Pearson correlation coefficients were not significantly different from zero for AES versus the DS forward overall (n = 60) and by treatment group (MPH and PLB), as illustrated by Table 9. This suggests that changes in attention and apathy were not associated, regardless of treatment assignment.
Table 9: Pearson correlation coefficients of AES and DS forward change scores for all participants, MPH group and PLB group.

<table>
<thead>
<tr>
<th></th>
<th>ALL (n = 60)</th>
<th>MPH (n = 29)</th>
<th>PLB (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>-0.08</td>
<td>0.07</td>
<td>-0.19</td>
</tr>
<tr>
<td>P-value</td>
<td>0.54</td>
<td>0.72</td>
<td>0.33</td>
</tr>
</tbody>
</table>

3.4 Exploratory Analyses

3.4.1 Effects of MPH on Attention

1) Compared to placebo, patients on methylphenidate will show greater improvement in attention over the 6-week study period, as measured by Digit Span backward, scaled total and Mini-Mental Status Examination attention.

Table 10 illustrates the difference in estimated changes scores (week 6 - baseline) between treatment groups for the attention scores under consideration.

Estimated difference in change in attention from the baseline to week 6 showed larger improvements in the MPH group on DS scaled total scores ($\delta = 1.01$, 95% CIs: 0.09 to 1.93, $p = 0.03$). Similar to the trend observed in DS forward, DS scaled total was lower than placebo at baseline but increased across time while attention scores in the placebo group remained stable. For the other attention measures, MMSE ($\delta = 0.45$, 95% CIs: -0.29 to 1.21) and DS backward ($\delta = 0.17$, 95% CIs: -0.66 to 1.02) differences in improvement were not statistically significant. Figure V demonstrates that compared with PLB, DS scaled total in the MPH group had lower
initial scores but improved over time. Conversely, DS forward and MMSE attention scores did not improve in the MPH condition compared with placebo.

Table 10: Attention measures over time. The estimated score is given with standard error (SE) and the estimated difference in the change from baseline (δ) for MPH (n=29) and PLB (n=31) is calculated with 95% confidence intervals (CI). Positive values favour MPH.

<table>
<thead>
<tr>
<th></th>
<th>Estimated Score (±SE)</th>
<th>Estimated Change Score (±SE)</th>
<th>δ (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPH</td>
<td>PLB</td>
<td>MPH</td>
<td>PLB</td>
</tr>
<tr>
<td><strong>DS backward</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.78±0.42</td>
<td>4.10±0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>4.17±0.42</td>
<td>4.02±0.41</td>
<td>0.39±0.30</td>
<td>-0.08±0.29</td>
</tr>
<tr>
<td>Week 4</td>
<td>4.35±0.42</td>
<td>4.36±0.41</td>
<td>0.56±0.30</td>
<td>0.26±0.29</td>
</tr>
<tr>
<td>Week 6</td>
<td>3.96±0.43</td>
<td>4.11±0.41</td>
<td>0.18±0.30</td>
<td>0.01±0.29</td>
</tr>
<tr>
<td><strong>DS scaled total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.81±0.58</td>
<td>8.54±0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>8.09±0.58</td>
<td>8.26±0.56</td>
<td>0.28±0.32</td>
<td>-0.27±0.32</td>
</tr>
<tr>
<td>Week 4</td>
<td>8.45±0.58</td>
<td>8.88±0.57</td>
<td>0.64±0.32</td>
<td>0.34±0.32</td>
</tr>
<tr>
<td>Week 6</td>
<td>8.70±0.58</td>
<td>8.42±0.57</td>
<td>0.89±0.33</td>
<td>-0.12±0.32</td>
</tr>
<tr>
<td><strong>MMSE attention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.15±0.34</td>
<td>3.55±0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>2.97±0.34</td>
<td>3.76±0.33</td>
<td>-0.18±0.27</td>
<td>0.21±0.26</td>
</tr>
<tr>
<td>Week 4</td>
<td>3.25±0.34</td>
<td>3.48±0.33</td>
<td>0.10±0.27</td>
<td>-0.06±0.26</td>
</tr>
<tr>
<td>Week 6</td>
<td>3.47±0.34</td>
<td>3.42±0.33</td>
<td>0.32±0.27</td>
<td>-0.13±0.26</td>
</tr>
</tbody>
</table>

Abbreviations: MPH=methylphenidate, PLB=placebo, DS=digit span, MMSE=mini-mental status examination
*p<0.05 significance
Figure V: Estimated change scores for attention scores over time for MPH (n=29) and PLB (n=31). Positive values indicate improvement on test scores. A) Digit Span backward, B) Digit Span scaled total C) MMSE attention. Error bars indicate standard error.
3.4.2 Association between Attention and Apathy

2) Change in attention from baseline to week 6, measured by Digit Span backward, scaled total and Mini-Mental Status Examination attention, will be associated with change in apathy scores from baseline to week 6, measured by the Apathy Evaluation Scale and Neuropsychiatric Inventory apathy.

Similar to the findings in the secondary analyses, Pearson correlation coefficients were not significantly different from zero for DS forward and NPI apathy ($r = -0.06$, $p = 0.64$). Additionally, AES change scores did not correlate with any of the attention outcomes (DS backward, scaled total, MMSE attention). However, AES did correlate with NPI apathy in all patients ($r = 0.33$, $p = 0.01$). As expected, significant correlations existed for subscores and total scores for the same test in all patients. For example, NPI apathy correlated with NPI total ($r = 0.38$, $p < 0.01$) and MMSE attention correlated with MMSE total ($r = 0.60$, $p < 0.01$). For the digit span test, DS scaled total correlated with both DS forward ($r = 0.71$, $p < 0.01$) and DS backward ($r = 0.67$, $p < 0.01$). However, DS forward and backward were not correlated ($r = 0.01$, $p = 0.90$). Similar associations were observed in MPH and PLB, analyzed separately. Overall, changes in attention and changes in apathy did not correlate in any of the treatment groups (Table 11).
Table 11: Pearson correlation coefficients of attention and apathy change scores for all participants. Shaded values specifically point out correlations between attention and apathy measures. P-values are in parenthesis.

<table>
<thead>
<tr>
<th>Test Scores</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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</thead>
<tbody>
<tr>
<td>ALL</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. NPI</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. NPI apathy</td>
<td>0.38* (&lt;0.01)</td>
<td>-</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. AES</td>
<td>0.07 (0.58)</td>
<td>0.33* (0.01)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4. MMSE total</td>
<td>0.02 (0.90)</td>
<td>-0.17 (0.22)</td>
<td>-0.11 (0.40)</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>5. MMSE attention</td>
<td>0.03 (0.83)</td>
<td>-0.03 (0.83)</td>
<td>-0.09 (0.53)</td>
<td>0.60* (&lt;0.01)</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>6. DS forward</td>
<td>0.02 (0.88)</td>
<td>-0.06 (0.64)</td>
<td>-0.08 (0.54)</td>
<td>0.28* (0.04)</td>
<td>0.14 (0.29)</td>
<td>-</td>
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<tr>
<td>7. DS backward</td>
<td>0.24 (0.82)</td>
<td>-0.20 (0.14)</td>
<td>0.02 (0.14)</td>
<td>0.10 (0.44)</td>
<td>-0.20 (0.13)</td>
<td>0.01 (0.92)</td>
<td>-</td>
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</tr>
<tr>
<td>8. DS scaled total</td>
<td>0.19 (0.16)</td>
<td>-0.20 (0.14)</td>
<td>-0.07 (0.53)</td>
<td>0.26 (0.06)</td>
<td>0.01 (0.60)</td>
<td>0.71* (&lt;0.01)</td>
<td>0.67* (&lt;0.01)</td>
<td>-</td>
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<tr>
<td>MPH</td>
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<td></td>
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<tr>
<td>1. NPI</td>
<td>-</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. NPI apathy</td>
<td>0.17 (0.32)</td>
<td>-</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3. AES</td>
<td>-0.01 (0.97)</td>
<td>0.47* (0.01)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. MMSE total</td>
<td>-0.003 (0.98)</td>
<td>-0.20 (0.31)</td>
<td>-0.02 (0.92)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. MMSE attention</td>
<td>-0.05 (0.80)</td>
<td>-0.01 (0.96)</td>
<td>-0.04 (0.83)</td>
<td>0.67* (&lt;0.01)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. DS forward</td>
<td>0.03 (0.86)</td>
<td>0.08 (0.68)</td>
<td>0.07 (0.72)</td>
<td>0.07 (0.72)</td>
<td>0.01 (0.96)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. DS backward</td>
<td>0.17 (0.39)</td>
<td>-0.45 (0.20)</td>
<td>0.01 (0.94)</td>
<td>-0.03 (0.86)</td>
<td>-0.31 (0.11)</td>
<td>-0.07 (0.74)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>8. DS scaled total</td>
<td>0.21 (0.31)</td>
<td>-0.27 (0.18)</td>
<td>0.02 (0.94)</td>
<td>0.07 (0.73)</td>
<td>-0.21 (0.28)</td>
<td>0.66* (&lt;0.01)</td>
<td>0.69* (&lt;0.01)</td>
<td>-</td>
</tr>
<tr>
<td>PLB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. NPI</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. NPI apathy</td>
<td>0.57* (&lt;0.01)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. AES</td>
<td>0.18 (0.36)</td>
<td>0.13 (0.49)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. MMSE total</td>
<td>0.04 (0.84)</td>
<td>-0.04 (0.83)</td>
<td>-0.16 (0.42)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. MMSE attention</td>
<td>0.15 (0.45)</td>
<td>0.04 (0.82)</td>
<td>-0.10 (0.59)</td>
<td>0.59* (&lt;0.01)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. DS forward</td>
<td>7. DS backward</td>
<td>8. DS scaled total</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>0.02 (0.92)</td>
<td>0.32 (0.10)</td>
<td>0.22 (0.26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0.99)</td>
<td>0.05 (0.79)</td>
<td>0.06 (0.77)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.19 (0.33)</td>
<td>0.05 (0.79)</td>
<td>-0.08 (0.69)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.41* (0.03)</td>
<td>0.24 (0.21)</td>
<td>0.38* (0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.27 (0.17)</td>
<td>-0.06 (0.74)</td>
<td>0.05 (0.81)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.09 (0.66)</td>
<td>0.72* (0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.05 (0.79)</td>
<td>0.68* (0.01)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: NPI=neuropsychiatric inventory, AES=apathy evaluation scale, MMSE=mini-mental status examination, DS=digit span
*p<0.05 significance

### 3.4.3 Baseline Attention as Predictors of Outcome

3) Higher baseline attention scores, measured by Digit Span forward, backward, scaled total and Mini-Mental Status Examination attention tests, will predict better response to treatment, as indicated by improved scores on Apathy Evaluation Scale, Neuropsychiatric Inventory apathy and Clinical Global Impression of Change apathy.

Regression analyses were conducted to determine whether attention scores at baseline could predict treatment response using the AES as a primary outcome. Additionally, sensitivity analyses with NPI and CGIC as apathy outcomes were also performed to explore whether the definition of responder had an effect on the association with baseline attention. Linear regressions were used to examine attention scores as predictors of change in AES and NPI apathy scores (week 6 - baseline). This regression model was not performed for CGIC as the categorical values of this measure did not allow for the calculation of change scores. A logistic regression was conducted for baseline attention scores as potential predictors of apathy outcome. For this analysis, patients were classified as responders or non-responders to treatment based on AES, NPI apathy and CGIC apathy (week 6 changes from baseline).
AES

For the linear regression, slopes were determined using AES change scores as the outcome and the different measures of attention as predictors. The difference in slopes for MPH and PLB groups were used to additionally observe the effect of MPH treatment by each attention measure. The regression model (summarized in Table 12) indicated that none of the baseline attention scores mediated the change in AES scores. Figure VI demonstrates the opposing directions of the MPH and PLB slopes for the DS forward component. In the MPH group, the positive slope trending towards significance (B = 0.90, t = 1.43, 95% CIs: -0.4 to 2.1, p = 0.16) indicates that lower DS forward was associated with greater improvement in AES scores.

Table 12: Linear slope of AES change scores by baseline attention scores and treatment group. Negative difference in slopes (MPH-PLB) favours methylphenidate.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>MPH slope B (95% CI)</th>
<th>t</th>
<th>P</th>
<th>PLB slope B (95% CI)</th>
<th>t</th>
<th>P</th>
<th>MPH - PLB B (95% CI)</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS forward</td>
<td>0.9 (-0.4, 2.1)</td>
<td>1.43</td>
<td>0.16</td>
<td>-0.3 (-1.8, 1.2)</td>
<td>-0.39</td>
<td>0.69</td>
<td>1.2 (-0.8, 3.1)</td>
<td>1.22</td>
<td>0.23</td>
</tr>
<tr>
<td>DS backward</td>
<td>0.1 (-1.1, 1.4)</td>
<td>0.23</td>
<td>0.82</td>
<td>0 (-1.3, 1.4)</td>
<td>0.07</td>
<td>0.95</td>
<td>0.1 (-1.7, 2.0)</td>
<td>0.11</td>
<td>0.91</td>
</tr>
<tr>
<td>DS scaled total</td>
<td>0.3 (-0.6, 1.3)</td>
<td>0.72</td>
<td>0.47</td>
<td>-0.2 (-1.3, 0.9)</td>
<td>-0.36</td>
<td>0.72</td>
<td>0.5 (-0.9, 2.0)</td>
<td>0.74</td>
<td>0.46</td>
</tr>
<tr>
<td>MMSE attention</td>
<td>-0.1 (-1.7, 1.4)</td>
<td>-0.18</td>
<td>0.86</td>
<td>0.3 (-1.4, 2.0)</td>
<td>0.39</td>
<td>0.70</td>
<td>-0.5 (-2.8, 1.8)</td>
<td>-0.41</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Abbreviations: MPH=methylphenidate, PLB=placebo, DS=digit span, MMSE=mini-mental status examination
*p<0.05 significance
Figure VI: Relationship between baseline DS forward score and AES change scores, as analyzed by a linear regression model.

Using the AES as a measure of treatment response, 17 patients had improved apathy (improvement of at least 3.3 points) and 40 did not. Table 13 shows that responders and non-responders were comparable on baseline characteristics except AES. Responders had close to significantly higher baseline AES scores ($K = 3.76$, $p = 0.06$), suggesting that patients with higher initial apathy may be more likely to improve later on. Logistic regression, as well, showed that baseline attention measures did not mediate response on the AES for both MPH and PLB groups. However, there was a treatment by attention interaction for DS forward ($\beta = -0.67$, $p = 0.04$) and scaled total ($\beta = -0.45$, $p = 0.05$), which was near significance. The negative $\beta$ values indicate that MPH decreased the likelihood of improving due to higher baseline attention scores, consistent with results from linear regression analyses. Trends were observed in both treatment groups for DS forward as predictor. In the MPH group, higher baseline DS forward decreased the likelihood of responding on the AES ($OR = 0.8$, $p = 0.18$),
whereas in the PLB group, higher baseline DS forward increased the odds of responding (OR = 1.5, p = 0.11). Table 14 shows the odds ratios for each baseline attention measure.

Table 13: Baseline characteristics by AES responders. Values are mean ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=57)</th>
<th>Responder (n=17)</th>
<th>Non-responder (n=40)</th>
<th>K or χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>77±8</td>
<td>76±10</td>
<td>77±7</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td>Women, (%)</td>
<td>60</td>
<td>53</td>
<td>63</td>
<td>0.45</td>
<td>0.56</td>
</tr>
<tr>
<td>Racial / ethnic group, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>91</td>
<td>94</td>
<td>90</td>
<td>-</td>
<td>0.61†</td>
</tr>
<tr>
<td>African-American, non-Hispanic</td>
<td>9</td>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, non-Hispanic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No High school diploma</td>
<td>12</td>
<td>6</td>
<td>15</td>
<td>-</td>
<td>0.20†</td>
</tr>
<tr>
<td>High school diploma</td>
<td>26</td>
<td>18</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college/associates degree</td>
<td>21</td>
<td>47</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor's degree</td>
<td>23</td>
<td>6</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional/graduate degree</td>
<td>16</td>
<td>18</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure in mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>132±17</td>
<td>133±17</td>
<td>133±17</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75±10</td>
<td>76±12</td>
<td>74±10</td>
<td>0.02</td>
<td>0.88</td>
</tr>
<tr>
<td>Abnormal ECG results, (%)</td>
<td>61</td>
<td>53</td>
<td>65</td>
<td>0.73</td>
<td>0.39</td>
</tr>
<tr>
<td>Duration of dementia in years</td>
<td>3±3</td>
<td>3±3</td>
<td>3±2</td>
<td>0.01</td>
<td>0.92</td>
</tr>
<tr>
<td>Concomitant medications, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>32</td>
<td>29</td>
<td>33</td>
<td>0.05</td>
<td>0.81</td>
</tr>
<tr>
<td>ChEls</td>
<td>72</td>
<td>71</td>
<td>72</td>
<td>0.02</td>
<td>0.88</td>
</tr>
<tr>
<td>Memantine</td>
<td>61</td>
<td>65</td>
<td>60</td>
<td>0.74</td>
<td>0.77</td>
</tr>
<tr>
<td>History of mood disorder before AD, (%)</td>
<td>10</td>
<td>6</td>
<td>12</td>
<td>-</td>
<td>0.66†</td>
</tr>
<tr>
<td>AES</td>
<td>51±12</td>
<td>55±11</td>
<td>49±12</td>
<td>3.76</td>
<td>0.06</td>
</tr>
<tr>
<td>NPI Total score</td>
<td>16±8</td>
<td>18±9</td>
<td>15±7</td>
<td>0.79</td>
<td>0.38</td>
</tr>
<tr>
<td>Apathy subscore</td>
<td>7±2</td>
<td>8±2</td>
<td>7±2</td>
<td>0.12</td>
<td>0.73</td>
</tr>
<tr>
<td>Depression subscore</td>
<td>1±2</td>
<td>2±3</td>
<td>1±2</td>
<td>3.98</td>
<td>0.14</td>
</tr>
<tr>
<td>MMSE Total score</td>
<td>20±5</td>
<td>20±5</td>
<td>20±5</td>
<td>0.07</td>
<td>0.79</td>
</tr>
<tr>
<td>Attention subscore</td>
<td>3±2</td>
<td>3±2</td>
<td>3±2</td>
<td>0.45</td>
<td>0.51</td>
</tr>
</tbody>
</table>

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### Abbreviations:
- SSRI = selective serotonin reuptake inhibitor
- ChEI = cholinesterase inhibitor
- AES = apathy evaluation scale
- NPI = neuropsychiatric inventory
- MMSE = mini-mental status examination
- DS = digit span
- ECG = electrocardiogram

### Table 14: Odds ratios for baseline attention as predictors of AES response, based on logistic regression.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>MPH</th>
<th>PLB</th>
<th>Treatment X Attention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>DS forward</td>
<td>0.8 (0.5-1.1)</td>
<td>0.18</td>
<td>1.5 (0.9-2.5)</td>
</tr>
<tr>
<td>DS backward</td>
<td>0.8 (0.6-1.2)</td>
<td>0.38</td>
<td>1.2 (0.8-1.9)</td>
</tr>
<tr>
<td>DS scaled total</td>
<td>0.8 (0.6-1.1)</td>
<td>0.23</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td>MMSE attention</td>
<td>0.9 (0.6-1.4)</td>
<td>0.79</td>
<td>0.9 (0.2-1.5)</td>
</tr>
</tbody>
</table>

### NPI

The linear regression model used for the AES was applied to the NPI to assess whether baseline attention predicted outcomes on the NPI apathy item (Table 15). In the PLB group, baseline DS backward was a significant predictor of NPI change scores (B = -0.6, t = -2.31, 95% CIs: -1.1 to -0.1, p = 0.02) while DS scaled total was near significance (B = -0.4, t = -2.0, 95% CIs: -0.8 to 0.0, p = 0.05). The negative slope values indicate that higher baseline DS backward and scaled total was associated with better improvements on NPI scores in the placebo group only. There was an additional significant difference in MPH and PLB slopes for
baseline DS backward scores as a predictor (B = 0.7, t = 2.14, 95% CIs: 0.0 to 1.4, p = 0.04), indicating a treatment group effect.

**Table 15: Linear slope of NPI apathy change scores by baseline attention scores and treatment group.** Negative difference in slopes (MPH-PLB) favours methylphenidate.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>MPH slope</th>
<th>PLB slope</th>
<th>MPH - PLB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td>DS forward</td>
<td>0.1 (-0.4, 0.6)</td>
<td>0.36</td>
<td>0.72</td>
</tr>
<tr>
<td>DS backward</td>
<td>0.2 (-0.3, 0.6)</td>
<td>0.68</td>
<td>0.50</td>
</tr>
<tr>
<td>DS scaled total</td>
<td>0.1 (-0.3, 0.4)</td>
<td>0.44</td>
<td>0.66</td>
</tr>
<tr>
<td>MMSE attention</td>
<td>-0.2 (-0.8, 0.4)</td>
<td>-0.58</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Abbreviations: MPH=methylphenidate, PLB=placebo, DS=digit span, MMSE=mini-mental status examination
*p<0.05 significance

Response on the NPI apathy item was defined as a 1 point improvement. With this definition, more responders were identified compared with the AES - 42 responders and 15 non-responders of the 57 patients analyzed. Baseline characteristics were comparable between groups, including the AES (Table 16). The logistic regression model showed that baseline attention measures did not reliably distinguish between NPI apathy responders and non-responders, as well, no interactions were observed between treatment group and attention scores (Table 17).
Table 16: Baseline characteristics by NPI apathy responders. Values are mean ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Responder (n=42)</th>
<th>Non-responder (n=15)</th>
<th>K or χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>78±10</td>
<td>78±7</td>
<td>0.01</td>
<td>0.90</td>
</tr>
<tr>
<td>Women, (%)</td>
<td>62</td>
<td>53</td>
<td>0.34</td>
<td>0.56</td>
</tr>
<tr>
<td>Racial / ethnic group, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>91</td>
<td>93</td>
<td>-</td>
<td>1.00†</td>
</tr>
<tr>
<td>African-American, non-Hispanic</td>
<td>9</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, non-Hispanic</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No High school diploma</td>
<td>12</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>29</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some college/associates degree</td>
<td>17</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bachelor's degree</td>
<td>17</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional/graduate degree</td>
<td>19</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure in mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>134±17</td>
<td>129±18</td>
<td>0.89</td>
<td>0.35</td>
</tr>
<tr>
<td>Diastolic</td>
<td>75±11</td>
<td>75±10</td>
<td>0.13</td>
<td>0.72</td>
</tr>
<tr>
<td>Abnormal ECG results, (%)</td>
<td>69 (60?)</td>
<td>67</td>
<td>0.24</td>
<td>0.63</td>
</tr>
<tr>
<td>Duration of dementia in years</td>
<td>3±2</td>
<td>4±3</td>
<td>1.39</td>
<td>0.24</td>
</tr>
<tr>
<td>Concomitant medications, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>29</td>
<td>40</td>
<td>0.67</td>
<td>0.41</td>
</tr>
<tr>
<td>ChEIs</td>
<td>69</td>
<td>80</td>
<td>0.66</td>
<td>0.42</td>
</tr>
<tr>
<td>Memantine</td>
<td>57</td>
<td>73</td>
<td>1.22</td>
<td>0.27</td>
</tr>
<tr>
<td>History of mood disorder before AD, (%)</td>
<td>12</td>
<td>7</td>
<td>-</td>
<td>1.00†</td>
</tr>
<tr>
<td>AES</td>
<td>50±12</td>
<td>54±11</td>
<td>1.05</td>
<td>0.27</td>
</tr>
<tr>
<td>NPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>16±8</td>
<td>17±8</td>
<td>0.86</td>
<td>0.35</td>
</tr>
<tr>
<td>Apathy subscore</td>
<td>8±3</td>
<td>6±2</td>
<td>2.95</td>
<td>0.08</td>
</tr>
<tr>
<td>Depression subscore</td>
<td>1±2</td>
<td>2±3</td>
<td>1.18</td>
<td>0.28</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>20±5</td>
<td>19±5</td>
<td>0.15</td>
<td>0.70</td>
</tr>
<tr>
<td>Attention subscore</td>
<td>3±2</td>
<td>3±2</td>
<td>0.11</td>
<td>0.74</td>
</tr>
<tr>
<td>DS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward score</td>
<td>8±2</td>
<td>8±1</td>
<td>1.35</td>
<td>0.25</td>
</tr>
<tr>
<td>Backward score</td>
<td>4±2</td>
<td>3±2</td>
<td>1.31</td>
<td>0.25</td>
</tr>
<tr>
<td>Raw total score</td>
<td>13±4</td>
<td>11±3</td>
<td>1.57</td>
<td>0.21</td>
</tr>
<tr>
<td>Scaled total score</td>
<td>9±3</td>
<td>8±2</td>
<td>1.16</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Table 17: Odds ratios for baseline attention as predictors of NPI apathy response, based on logistic regression.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>MPH</th>
<th></th>
<th>PLB</th>
<th></th>
<th>Treatment X Attention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>β</td>
</tr>
<tr>
<td>DS forward</td>
<td>1.2 (0.8, 1.7)</td>
<td>0.70</td>
<td>1.1 (0.7, 1.7)</td>
<td>0.27</td>
<td>0.06</td>
</tr>
<tr>
<td>DS backward</td>
<td>1.1 (0.7, 1.6)</td>
<td>0.75</td>
<td>1.2 (0.9, 1.8)</td>
<td>0.23</td>
<td>-0.16</td>
</tr>
<tr>
<td>DS scaled total</td>
<td>1.1 (0.8, 1.6)</td>
<td>0.41</td>
<td>1.1 (0.8, 1.5)</td>
<td>0.38</td>
<td>0.01</td>
</tr>
<tr>
<td>MMSE attention</td>
<td>1.3 (0.8, 2.2)</td>
<td>0.28</td>
<td>0.9 (0.6, 1.5)</td>
<td>0.79</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Abbreviations: MPH=methylphenidate, PLB=placebo, DS=digit span, MMSE=mini-mental status examination
*p<0.05 significance

CGIC

For the CGIC, responders were defined as having “marked improvement”, “moderate improvement” and “minimal improvement” at the week 6 evaluation. Twenty-four responders and 33 non-responders, with comparable baseline characteristics, were identified under this definition (Table 18). The logistic regression results revealed that baseline attention scores were not significant predictors of improvement on this neuropsychological test (Table 19).
Table 18: Baseline characteristics by CGIC responders. Values are mean ± standard deviation.

<table>
<thead>
<tr>
<th></th>
<th>Responder (n=24)</th>
<th>Non-responder (n=33)</th>
<th>K or χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>76±9</td>
<td>77±8</td>
<td>0.01</td>
<td>0.90</td>
</tr>
<tr>
<td>Women, (%)</td>
<td>58</td>
<td>61</td>
<td>0.30</td>
<td>0.86</td>
</tr>
<tr>
<td>Racial / ethnic group, (%)</td>
<td></td>
<td></td>
<td>-</td>
<td>1.00†</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>92</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American, non-Hispanic</td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, non-Hispanic</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education, (%)</td>
<td></td>
<td></td>
<td>-</td>
<td>0.32†</td>
</tr>
<tr>
<td>No High school diploma</td>
<td>4</td>
<td>18</td>
<td>0.11</td>
<td>0.74</td>
</tr>
<tr>
<td>High school diploma</td>
<td>25</td>
<td>27</td>
<td>0.25</td>
<td>0.87</td>
</tr>
<tr>
<td>Some college/associates degree</td>
<td>17</td>
<td>24</td>
<td>5.52</td>
<td>0.02</td>
</tr>
<tr>
<td>Bachelor's degree</td>
<td>25</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional/graduate degree</td>
<td>25</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure in mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133±17</td>
<td>132±17</td>
<td>0.21</td>
<td>0.64</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76±12</td>
<td>74±10</td>
<td>0.02</td>
<td>0.89</td>
</tr>
<tr>
<td>Abnormal ECG results, (%)</td>
<td>63</td>
<td>61</td>
<td>0.02</td>
<td>0.88</td>
</tr>
<tr>
<td>Duration of dementia in years</td>
<td>3±2</td>
<td>3±3</td>
<td>0.01</td>
<td>0.93</td>
</tr>
<tr>
<td>Concomitant medications, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>29</td>
<td>33</td>
<td>0.11</td>
<td>0.74</td>
</tr>
<tr>
<td>ChEIs</td>
<td>71</td>
<td>73</td>
<td>0.25</td>
<td>0.87</td>
</tr>
<tr>
<td>Memantine</td>
<td>46</td>
<td>73</td>
<td>5.52</td>
<td>0.02</td>
</tr>
<tr>
<td>History of mood disorder before AD, (%)</td>
<td>8</td>
<td>12</td>
<td>-</td>
<td>1.00†</td>
</tr>
<tr>
<td>AES</td>
<td>49±12</td>
<td>52±12</td>
<td>1.20</td>
<td>0.27</td>
</tr>
<tr>
<td>NPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>15±7</td>
<td>17±8</td>
<td>1.50</td>
<td>0.22</td>
</tr>
<tr>
<td>Apathy subscore</td>
<td>7±2</td>
<td>7±2</td>
<td>2.80</td>
<td>0.09</td>
</tr>
<tr>
<td>Depression subscore</td>
<td>2±3</td>
<td>1±2</td>
<td>0.27</td>
<td>0.60</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>19±5</td>
<td>20±5</td>
<td>0.48</td>
<td>0.49</td>
</tr>
<tr>
<td>Attention subscore</td>
<td>3±2</td>
<td>3±2</td>
<td>0.23</td>
<td>0.63</td>
</tr>
<tr>
<td>DS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward score</td>
<td>8±3</td>
<td>8±2</td>
<td>0.30</td>
<td>0.58</td>
</tr>
<tr>
<td>Backward score</td>
<td>4±2</td>
<td>4±2</td>
<td>0.002</td>
<td>0.92</td>
</tr>
<tr>
<td>Raw total score</td>
<td>12±4</td>
<td>12±4</td>
<td>0.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Scaled total score</td>
<td>8±3</td>
<td>8±3</td>
<td>0.07</td>
<td>0.79</td>
</tr>
</tbody>
</table>
Abbreviations: SSRI=selective serotonin reuptake inhibitor, ChEI=cholinesterase inhibitor, AES=apathy evaluation scale, NPI=neuropsychiatric inventory, MMSE=mini-mental status examination, DS=digit span, ECG=electrocardiogram
*p<0.05 significance † P-value for Fisher’s exact test

Table 19: Odds ratios for baseline attention as predictors of CGIC apathy response, based on logistic regression.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>MPH</th>
<th>PLB</th>
<th>Treatment X Attention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>DS forward</td>
<td>0.9 (0.7, 1.3)</td>
<td>0.62</td>
<td>1.4 (0.8, 2.1)</td>
</tr>
<tr>
<td>DS backward</td>
<td>1.1 (0.8, 1.5)</td>
<td>0.65</td>
<td>1.9 (0.6, 1.3)</td>
</tr>
<tr>
<td>DS scaled total</td>
<td>1.0 (0.8, 1.5)</td>
<td>0.94</td>
<td>1.1 (0.8, 1.5)</td>
</tr>
<tr>
<td>MMSE attention</td>
<td>1.2 (0.8, 1.8)</td>
<td>0.42</td>
<td>0.8 (0.5, 1.2)</td>
</tr>
</tbody>
</table>

Abbreviations: MPH=methylphenidate, PLB=placebo, DS=digit span, MMSE=mini-mental status examination
*p<0.05 significance
4 GENERAL DISCUSSION AND CONCLUSIONS

Using data from a clinical trial of methylphenidate for the treatment of apathy in AD, this study explored attention in this patient population and possible interactions with apathy. The results suggest that methylphenidate, compared with placebo, improved selective attention on the DS forward (δ = 0.87, 95% CIs: 0.06 to 1.08, p = 0.03; Table 8) in an elderly dementia population with apathy. In support of the primary hypothesis, selective attention measured by the DS scaled total was also significantly improved in the methylphenidate versus placebo groups (δ = 1.01, 95% CIs: 0.09 to 1.93, p = 0.03; Table 10). As there were no correlations found between change scores on apathy and attention tests throughout the trial (Table 9 and Table 11), the data also suggest that apathy and attention may respond independently to psychostimulants in this cohort. Additionally, attention scores at baseline did not predict improvements in apathy symptoms in response to treatment. Overall, the finding of modest benefits for attention and apathy provide support for the use of methylphenidate in elderly populations with mild to moderate AD.

4.1 MPH and Attention in AD

In children and young adults with ADHD, psychostimulants have been shown to improve performance on tasks of divided, sustained, focused and selective attention (Lopez et al, 2004; Tucha et al, 2006a; Tucha et al, 2006b). However, in a group of healthy elderly male volunteers, the cognitively enhancing effects of MPH were attenuated (Turner et al, 2003). In particular, subjects did not improve on tests of sustained and selective attention, including the Digit Span. This appears to contradict the finding of significant improvements on the Digit Span forward with corroboration by the DS scaled total in the present study in diseased elderly patients. These conflicting findings may be rationalized through closer examination of the
different study designs. Specifically, the present study evaluated attention over a duration of 6 weeks and not in response to a single dose of drug. It may be that measurable responses to MPH might require a longer duration to be detected by the Digit Span due to age-related decline in DA activity (Li and Sikstrom, 2002; Roth et al., 1995; Volkow et al., 2000). The gradual improvements in DS forward and scaled total scores over the 6 weeks of treatment in the MPH but not PLB group also suggest progressive sensitization to the effects of the drug in our patients. In children and young adults with ADHD, the effects of MPH can be detected 1.5-2 hours following administration (Hood et al., 2005; Lopez et al., 2004; Tucha et al., 2006a; Tucha et al., 2006b). In the elderly, as a result of decline in DAergic function, neurochemical changes produced by MPH may require a longer duration to take effect.

However, other single dose studies in diseased elderly populations contradict the results found in healthy elderly following a single dose of drug. A study of methylphenidate use in PD patients produced results consistent with the present findings (Auriel et al., 2006). Attention measured by a cognitive assessment battery significantly improved 2 hours following a dose of MPH, along with enhanced gait mobility. It has been suggested that in PD, control of posture and gait during movement is attention-demanding and thus, treatment with MPH might reduce fall risk by improving attention (YogeV et al., 2005). Similarly, in a sample of non-demented older adults with reports of memory problems, MPH had positive effects on attention, gait and mobility (Ben-Itzhak et al., 2008), suggesting that MPH may be increasing DA levels in both mesocorticolimbic and nigrostriatal pathways in elderly with high fall risk. It may be that the assessments used by Ben-Itzhak et al (2008) and Auriel et al (2006) were more sensitive to changes in attention. The presence of disease pathology in the brain of dementia patients may also contribute to the response to MPH treatment observed in the present investigation. In dementia patients, due to dysfunction in various neurotransmitter systems in addition to DA,
MPH may be operating under different mechanisms to modulate attention, producing effects even with a single dose. Thus, our AD patients might have responded similar to those in the Ben-Itzhak et al (2008) and Auriel et al (2006) studies following a single dose of MPH. Overall, the effect of disease and repeated exposure may mediate the attention improvements observed in apathetic AD patients.

As each study described above utilized different tests to measure attention, a caveat is attached when comparing results across these studies. The neuropsychological assessments used may be conceptually different and therefore tapping into various components of attention. The findings in the present study suggest that selective attention, measured by the DS forward, is modulated by MPH treatment in AD patients. Alternatively, DS backward score did not improve in the MPH group compared with placebo. The DS backward subtest does require some attention abilities but predominantly recruits neural resources for executive function and working memory (Colom et al, 2005; Gathercole et al, 2004; Groeger et al, 1999; St Clair-Thompson, 2010). The correlation analysis indicating no significant associations between DS forward and backward change scores (r = 0.01, p = 0.92) provides further support for the notion that these subtests are evaluating different cognitive processes. In the studies of Ben-Itzhak et al (2008) and Auriel et al (2006), attention on the Mindstreams cognitive assessment battery (NeuroTrax Corporation, Bellaire, United States of America), a test comparable to the Conners’ Continuous Performance Test (CPT) for attention deficits (Schweiger et al, 2007), demonstrated improvements following MPH treatment, corroborating with findings from the present study. Additionally, results from a study of MPH in frontotemporal dementia patients were also largely consistent with outcomes on the DS backward. Patients did not demonstrate improvements on attentional set shifting and spatial span tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, Cambridge,
United Kingdom) - assessments of executive function - after administration of a single dose of MPH (Rahman et al, 2006). Results of no improvement with MPH on the MMSE attention subscore were consistent with findings for the DS backward. Intuitively, the task of spelling “WORLD” backwards is similar to repeating digits in reverse as they both require mental manipulation and thus, more closely associated with executive function and working memory than selective attention. However, no correlations between MMSE attention and DS backward changes scores (r = -0.20, p = 0.13) were observed and the trend appears to be in the opposite direction, indicating that studies aimed at exploring the cognitive processes involved in these two subtests are necessary in order to draw more definitive conclusions. Improvements observed on the DS scaled total score might be due to the additive effect of the DS forward and the attention component of the DS backward. Correlations between change scores for DS scaled total and forward (r = 0.66, p < 0.01), as well as DS scaled total and backward (r = 0.69, p <0.01) support this interpretation. Taken together, these results provide evidence for the positive effects of MPH on selective attention in an apathetic AD sample.

4.2 Apathy and Attention in AD

Evidence for the use of MPH in the treatment of apathy in AD was found in the ADMET study (Rosenberg et al, under review), as well as earlier studies (Galynker et al, 1997; Herrmann et al, 2008; Padala et al, 2007b; Padala et al, 2010). The present study also found benefits for selective attention. However, there were no significant correlations between change scores on apathy and attention tests (Table 9 and Table 11), suggesting that these two processes may be independently modulated by MPH. As a result of interactions with the DAergic and NE systems, psychostimulants can have various effects on the brain, which may explain the dissociation between two processes which are thought to share similar neural
pathways. Evidence indicates that low and therapeutically relevant doses of psychostimulants, such as those administered in this study, are cognitively enhancing via preferential stimulation of the prefrontal cortex (Arnsten and Dudley, 2005; Berridge and Devilbiss, 2010; Gronier, 2011; Mehta et al, 2000). In contrast, higher doses, by amplifying catecholaminergic tone more globally throughout the brain, are behaviourally activating (Kuczenski and Segal, 1992; Kuczenski et al, 1995). In previous studies of MPH for the treatment of apathy, patients showed increases in irritability, agitation and psychosis (Galynker et al, 1997; Herrmann et al, 2008; Padala et al, 2010). Similarly, results from ADMET indicated a trend towards increased anxiety in patients taking MPH (Rosenberg et al, under review). These observations may be reflecting the presence of behavioural effects in dementia patients even at low doses. The relevance of this to apathy may be that in the population under study, psychostimulants can simultaneously drive both cognitively enhancing and behaviourally activating pathways, modulating different components of apathy and attention.

Disease-related neurochemical alterations in the brain may be at the root of the diverse and unconnected changes produced by MPH in dementia patients. The heterogeneous nature of AD can be perceived through the BPSD present in our patient sample. While we successfully separated apathy from depression, a mean NPI total of 16±8 of all patients at baseline imply dysfunction in many different neurotransmitter systems.

The action of psychostimulants on the dopamine mesocorticolimbic reward pathway, the major system thought to be compromised in apathy (Mitchell et al, 2010), may be limited in AD patients. DA neurotransmission is dysfunctional in AD brains (Arai et al, 1984; Cross et al, 1984b; Kumar and Patel, 2007; Mitchell et al, 2010; Murray et al, 1995; Reinikainen et al, 1988; Storga et al, 1996; Sweet et al, 2001) and specifically, disruption in DAT uptake is associated with apathy (David et al, 2008). NE activity, closely related to DA, is also
dysfunctional in AD brains (Bierer et al, 1995; Bondareff et al, 1982; Mann et al, 1982; Mann et al, 1984; Nyberg et al, 1985) and has been linked with BPSD (Forstl et al, 1992; Perry et al, 1981; Russo-Neustadt and Cotman, 1997; Zubenko and Moossy, 1988). Given that NET is another substrate of psychostimulant compounds, aberrations in this system could influence the action of MPH. In regards to behaviour, apathetic AD patients also demonstrate a blunted response to the subjective rewarding effects of dextroamphetamine (Lanctôt et al, 2008). These findings of aberrations in the DAergic system may be a factor in driving MPH to have independent effects on different processes such as apathy and attention.

While MPH does not appear to exhibit effects on extracellular serotonin (Kuczenski and Segal, 1997) in the therapeutic dose range, dysfunction of this system in dementia may nonetheless play a role in the changes in attention and apathy observed in ADMET patients due to interactions with the DA and NE systems. Anatomically, the 5-HT neurons of the raphe nucleus innervate DAergic ventral tegmental and prefrontal cortex neurons (Azmitia and Segal, 1978; Beart and McDonald, 1982), suggesting that the 5-HT system can modulate DA neurotransmission. However, the nature of this modulating action remains unclear. Serotonin has been shown to inhibit (Kapur and Remington, 1996; Westfall and Tittermary, 1982) and facilitate (Benloucif et al, 1993; Blandina et al, 1989; Pehek et al, 2006) DA activity. Additionally, different 5-HT receptor families have been shown to regulate NE release in the locus coeruleus (Clement et al, 1992; Ortega et al, 2012). Thus dysfunction in serotonin neurotransmission, such as that associated with BPSD (Chen et al, 1996; Hoogendijk et al, 1999; Lanctôt et al, 2001; Zweig et al, 1988), can affect the action of MPH on DA and NE activity. Also, though MPH does not have affinity for the 5-HT transporter, age- and disease-related changes in the brain may cause MPH to interact with other catecholaminergic systems.
including serotonin, thereby mimicking the behaviourally activating effects normally observed at higher doses (Berridge and Devilbiss, 2010; Spencer et al, 2012).

Possible interactions with the concomitant use of ChEIs might also account for the differential effects of MPH on apathy and attention, particularly in this study as the majority of participants were stable on ChEIs. The interaction between the DA and ACh system has been established in early studies looking specifically at the cholinergic interneurons located within the striatum (Bertorelli and Consolo, 1990; Stoof et al, 1992). The data consistently indicate that D1 receptor stimulation is associated with increased striatal ACh release (Anderson et al, 1994; DeBoer and Abercrombie, 1996) while D2 agonists mediates reduction in ACh levels (DeBoer et al, 1996; Ikarashi et al, 1997). One study found that dopaminergic modulation of ACh release is influenced by the concentration of ChEIs (Acquas and Fibiger, 1998). In particular, under conditions of high ChEI concentrations, d-AMPH administration further increased ACh output. Thus, this represents another pathway in which MPH can modulate either apathy or attention or different components of both. Again, the effect of disease on the cholinergic system may also alter the mechanisms which connect DA and ACh neurotransmission. Taken together, depletion and imbalances in the neurotransmitter systems in AD may cause MPH to have a more widespread - and behaviourally activating - effect on the brain, producing the independent drug responses observed in this study.

4.3 Attention and Prediction of Response

Exploratory analyses revealed that baseline attention subscores (DS forward, backward, scaled total and MMSE attention) did not predict response to MPH for apathy treatment, as measured by the AES and NPI apathy. This appears to contradict results of the drug challenge study conducted by our lab (Herrmann et al, 2008), where inattention on d-AMPH was
predictive of positive response to MPH medication later on. Conceptual differences, including the use of a different psychostimulant, may account for the contradictory findings. d-AMPH has a more widespread effect on the brain, interacting with DAT, NET, SERT (Heal et al., 1998b; Richelson and Pfenning, 1984; Rothman et al., 2001) and MAO inhibitors (Miller et al., 1980; Robinson, 1985). Additionally, d-AMPH can induce release of catecholamines from the presynapse even at low therapeutic doses (Floor and Meng, 1996a, b; Sulzer and Rayport, 1990). MPH, on the other hand, does not bind SERT (Andersen, 1989; Richelson and Pfenning, 1984) nor does it potentiate DA or NE release (Easton et al., 2007; Heal et al., 2009; Kuczenski and Segal, 1997; Patrick et al., 1987). Thus, the differing pharmacology of each drug may produce subtle dissimilarities in response. Ultimately, the purpose of the drug challenge was to probe the functional integrity of the DA reward system using a single dose of d-AMPH rather than testing whether MPH-naive attention abilities could predict response. Inattention may be an indication of the ability to respond to a single dose of a stimulant drug due to a functional DA system, which might increase the likelihood of improving in the trial. In fact, the authors suggested that the behaviourally activating mechanisms of psychostimulants which caused distractibility and subsequently inattention might also be involved in ameliorating apathetic symptoms. This is consistent with the interpretations of results as discussed above. In the present study, baseline attention levels were used as an indicator of better DA function, and thus better ability to respond to treatment. However, the non-significant results suggest that these attention tests may not be an appropriate probe of DA function.

Though attention predictors were not significant in the MPH group, a significant treatment by baseline attention interaction was found for DS forward subscores in the logistic regression for predictors of AES response. This indicates an effect of treatment on the odds of
responding on the AES due to higher DS forward scores. The odds ratio (OR = 1.5, CI: 0.9-2.5, p = 0.11), though not significant, suggest that in the PLB group, higher baseline DS forward was associated with increased likelihood of responding. The odds ratio in the MPH group suggests lower DS forward score was associated with response. This is consistent with the non-significant trend for lower baseline DS forward as predictor of improvements on the AES, found in the linear regression analysis (B = 0.90, t = 1.43, 95% CIs: -0.4 to 2.1, p = 0.16).

Contradictory to the hypothesis, higher attention scores were not predictors of response but rather, lower initial attention was more closely linked with better apathy outcomes in the MPH group. The opposite was true in the PLB group. This suggests that those with worse selective attention at baseline were more likely to improve on psychostimulant medication. Comparison of baseline characteristics of AES responders versus non-responders revealed that responders had higher initial apathy, measured by the AES. Thus, more disordered attention and apathy may be associated with better treatment response, however, these changes were not correlated. This is consistent with the premise that MPH may be working through different mechanisms to modulate these processes. It should be noted that these interpretations were based on observations of trends and must be interpreted with caution.

Linear regression analysis also revealed that higher DS backward and scaled total scores at baseline was a predictor of improvements on the NPI in the PLB group only, with a significant attention by treatment interaction. Again, the effect of active treatment was not observed. However, it is interesting to consider why associations were found for the NPI and not AES on this specific subscore. Significance on the DS backward, a test of working memory, short-term memory and executive function (Colom et al, 2005; Gathercole et al, 2004; Groeger et al, 1999; St Clair-Thompson, 2010), and not the selective attention test may be due to the nature of the NPI. Apathy items of the NPI refer to observable behaviours which
relate to functioning. For example, items such as “contribution to household chores”, and “enthusiasm about usual interests” are similar to items on the ADCS-Activities of Daily Living (ADL) inventory (Galasko et al., 1997), which is a measure of function in AD patients. The AES, in contrast, include items associated with internal states such as “initiative” and “motivation”. This might explain why a test of executive function (DS backward) was a better predictor of response on the NPI apathy.

4.4 Limitations

There are many factors to take into account when interpreting the results of this study. Mainly, the sample size of 60 patients was originally based on power calculations performed to evaluate efficacy of MPH for apathy and not attention as the primary outcome in the clinical trial. Calculations for the primary hypothesis of the present study indicated that a sample size of 60 was sufficiently powered to detect large effect sizes for a linear regression with 3 covariates. However, this value may not have the ability to detect significant correlations between the attention (DS forward) and apathy (AES) change scores in the secondary hypothesis. More robust findings might be possible with a larger sample size.

The value used to determine responders on the AES for logistic regression analyses was derived from statistical power calculations for the clinical trial (Drye et al., 2012). Using information from the first randomized cross-over RCT of methylphenidate for the treatment of apathy in AD (Herrmann et al., 2008), it was determined that a sample size of 60 was sufficiently powered (80%) to detect a minimum difference of 3.3 points on the AES between MPH and PLB. Thus, this value has not been validated in any other study and may not be clinically relevant. However, a small non-significant difference between MPH and PLB (2.5 points) was found on the AES in ADMET. High variance in the caregiver reports on this test
may account for the lack of significance. Additionally, clinical impression of change in apathy (CGIC), assessed by clinicians, significantly favoured MPH compared to PLB. These are encouraging results in support of the clinical relevance of the 3.3 points change on the AES. In the same vein, definition of response on the NPI apathy item (1 point improvement) is also not supported by concrete evidence and is likely not clinically relevant. It has been suggested by NPI test developers and studies of neuropsychiatric symptoms in AD that a 30% reduction in total NPI scores is clinically meaningful, based on comparability to changes observed with antipsychotic agents (Cummings, 2000; Cummings et al, 2000; Finkel, 2004). This might be applied to domain scores such as apathy. Further studies are needed to establish a change score on the AES and NPI that correlates with clinically significant improvements in apathetic symptoms.

The neuropsychological tests used in this study were administered by several research staff, which may introduce confounding factors due to inter-rater variability. The Digit Span required administrators to read aloud a series of digits, adhering to a rhythm of 1 digit per second. Tempo may differ between raters and may even differ within each rater at different time points in the study. This may influence patient performance: random short and long delays between clusters of digits might facilitate better attention and memory for a select cluster. However, it should be noted that in this study, all research staff received training and practice on administering this test in a standardized manner. Additionally, within an elderly population, auditory perception may not be optimal, resulting in difficulty hearing and concentration on the task. Thus, poor performance might be due to physical disability and would not truly reflect attention deficits.

As this study involved repeating neuropsychological assessments at several follow-up visits, learning effects associated with improvements on the primary attention outcome should
be considered. As these were patients with marked memory deficits, it is unlikely that participants were able to recall prior testing sessions in order improve their performance. Moreover, results indicate that the MPH group improved on DS forward scores throughout the trial while the PLB group did not, favouring a drug effect over a learning effect. While it is possible that a drug-learning interaction existed, our conclusion is nevertheless warranted given that learning occurred only in the MPH group.

In this study, compliance to medication was assessed through pill counts and follow-up with caregivers during every study visit after randomization. Based on these evaluations compliance was not reported to be an issue. However, patients with memory impairments may neglect to follow the dose schedule, particularly if they are not aided by the caregivers. Patients may fail to properly store drugs in dry and room temperature conditions, degrading the drugs and rendering them less effective. These events would confound results as the true effect of MPH would not be measured in each case.

The Digit Span test and MMSE attention used in this study may not be tapping into the attention domains which might be more relevant to both apathy and AD. Selective attention measured by the DS forward, which significantly improved on MPH in this study, could be measuring a component of attention which does not interact with the mechanisms which modulate apathy in the AD brain. Additionally, in terms of response prediction, using a baseline attention test to probe the integrity of the DAergic system does not appear to be sufficient. Different measures of attention and methods which more directly reflect neurochemical activity in the brain is needed in order to better explore attention-associated predictors.
4.5 Recommendations for Future Studies

This study found that MPH had modest benefits for selective attention, measured by the DS forward. While the short length and ease of administration of the Digit Span is a benefit in studies with cognitively impaired patients, it would be interesting to explore more comprehensive assessments which target other types of attention. The Conners’ CPT (MHS Inc., North Tonawanda, NY, USA), used in the d-AMPH drug challenge study conducted by our group previously (Herrmann et al. 2008), would be a good choice. The CPT is a computerized research instrument used for the assessment of attention, vigilance and impulsivity. Test-takers are required to press a space bar whenever letters other than X appears on the screen (Conners, 2000). The software reports scores for errors and response times based on patterns of performance. This attention test is widely used for research in ADHD and other psychiatric populations (Cohen and Shapiro, 2007; Lundervold et al., 2012; Sanz et al., 2012; Shang and Gau, 2012). Studies indicate that the CPT can detect changes in attention following treatment for ADHD (Fernandez-Jaen et al., 2009; Levin et al., 2001; Shang and Gau, 2012; Solanto et al., 2009). An added strength of a computerized test is the elimination of inter-rater variability as a confounder. Furthermore, a drug challenge such as the one used in Herrmann et al. (2008) to find a clinically useful instrument for the assessment of MPH response, can be implemented into this protocol to investigate whether response immediately following a single dose of psychostimulant can predict apathy outcome in the clinical trial. This would also allow results to be more comparable between these two studies. More importantly, this may be a better approach to speculating status of neurotransmitter systems and underlying neurobiological mechanisms than simple assessments of baseline attention abilities.

In the present study, the AES-I was used as the apathy outcome measure. Variability leading to confounders might exist due to differences in each informant’s interpretation of
questions on the AES, which may be ambiguous. The higher recommended cut-off score for the caregiver version (41.5) suggests that compared to self (36.5) and clinician (40.5) reports, informants might be overestimating apathy symptoms in patients (Clarke et al, 2007a). In order to standardize this method of assessment, the AES-C can be used. This version of the AES is administered as a semi-structured interview in which a trained rater utilizes both verbal and non-verbal data to determine the patient’s apathy level on each item of the test. The AES-C, though a reliable and valid scale for apathy (Clarke et al, 2007b; Marin et al, 1991), is psychometrically less robust in regards to diagnostic performance than the AES-I, according to Clarke et al (2007a). The researchers proposed that the AES-I was a better quick screen of apathy symptoms and training level of raters used in the study may have lowered performance ability of the clinician version. The 4-6 hours experience with the scale suggested by Marin et al (1991) might not be sufficient for reliability. Thus, a caveat to using the AES-C in future studies is that it should be administered by a trained clinician who knows the patients well, such as a physician, and who has had opportunities to observe their behaviours.

In this study, cognitive status was assessed using the MMSE and the WORLD backwards task on this test was additionally used to examine changes in attention. While the MMSE is a widely used screen for cognitive impairments (Galasko et al, 1990; Pezzotti et al, 2008), it is not a test of cognition per se due to the presence of ceiling and floor effects (Galasko et al, 2000; Tombaugh and McIntyre, 1992). Typically, floor effects are associated with lower education (Ostrosky-Solis et al, 2000) and gender (Rosselli et al, 2006) while ceiling effects are observed in MCI (van Gorp et al, 1999; Xu et al, 2002) and highly educated individuals (Crum et al, 1993). Additionally, variability of scores within patients represents another confounder (Clark et al, 1999). Given that the MPH is thought to enhance cognition by preferentially inducing DA release in the prefrontal cortex (Berridge and Devilbiss, 2010), a
more extensive cognitive battery would be an interesting next step in this line of research. Thus, the ADAS-cognition (ADAS-cog) (Rosen et al, 1984), the standard outcome measure in clinical trials of AD treatment, should be considered. However, because of recent failures of drugs to improve ADAS-cog scores in RCTs, researchers have questioned whether this scale is sensitive to subtle changes in the mild range disease severity. Indeed, studies have demonstrated ceiling effects in MCI and mild AD patients (Benge et al, 2009; Cano et al, 2010). This is relevant as the population under study is AD patients with mild to moderate disease severity. Thus, more difficult tests such as the CANTAB can also be included. The CANTAB is a computerized visual cognitive battery which assesses domains such as reaction time, spatial working memory and rapid visual information processing. There are batteries assessing core cognition, in addition to ones specific for AD, MCI and ADHD. The overall battery and its subtests are sensitive to age-related decline (Robbins et al, 1994) and has been shown to differentiate MCI and mild AD (Egerhazi et al, 2007; Owen et al, 1995). In the ADMET study, a near significant positive effect of MPH on MMSE scores were observed, suggesting that with a more sensitive cognitive test, stronger effects will be detected.

4.6 Clinical Implications

The negative factors associated with apathy in AD, including increase caregiver burden (Banerjee et al, 2006; Coen et al, 1997), diminished global functioning (Boyle et al, 2003; Senanarong et al, 2012; Wadsworth et al, 2012) and more rapid decline in cognition and function (Lechowski et al, 2009; Starkstein et al, 2006), necessitates a better understanding of its neurobiology and relevant pharmacotherapies. There is evidence to support the use of methylphenidate for treatment apathetic symptoms in AD patients (Galynker et al, 1997; Herrmann et al, 2008; Padala et al, 2007a; Padala et al, 2007b; Padala et al, 2010). The
additional benefit for selective attention found in this study adds to the limited knowledge of MPH effects on elderly populations with AD. It is clear that benefits for attention and cognition are of particular relevance in patients with severe cognitive deterioration. Furthermore, use of MPH to improve attention in other elderly psychiatric populations, such as adult attention deficit/hyperactive disorder, frontotemporal dementia and Parkinson’s disease, may be warranted. This might also be applicable to non-psychiatric older adults experiencing frequent falls. Ben-Itzhak (2008) proposed that MPH, by increasing focus and concentration, can reduce fall risk in the elderly.

Since drug-mediated changes on the attention and apathy tests were not associated, it is hypothesized that MPH may exert a more wide-spread and consequently behaviourally activating effect, which differentially modulated attention and apathy. This provides a glimpse of the neurobiological workings of the AD brain. However, further studies are needed to provide a clearer picture of the underlying mechanisms. From the clinical perspective, emerging behaviourally activating effects indicates that implementing high doses of psychostimulants may be detrimental in these patients. The trend towards elevated anxiety in patients taking MPH in the ADMET study, in addition to evidence of increases in irritability, agitation and psychosis found in previous studies (Galynker et al., 1997; Herrmann et al., 2008; Padala et al., 2010) suggests that adjustments to higher doses might tip the balance away from efficacy and towards side effects.

Though baseline attention did not predict response to apathy treatment in this study, it may be worthwhile to consider exploring other attention measures as potential predictors. In frail populations where concurrent medical conditions and polypharmacy are common, identifying reliable predictors is of value toward guiding treatment decisions in clinical settings. Given that psychostimulants have been associated with cardiovascular events
(Schelleman et al, 2012) in addition to behaviourally activating effects discussed above, information on a patient’s response likelihood will help physicians make better risk-benefit assessments for treatment options.

4.7 Conclusions

In summary, MPH improved scores on a test of selective attention in AD patients participating in a clinical trial for treatment of apathetic symptoms. Additionally, the effects of MPH on attention and apathy scores were not correlated, suggesting diverging mechanistic pathways associated with their modulation. It may be that AD specific disruptions in neurotransmitter systems such as DA, NE, 5-HT and ACh propelled MPH to exert a more widespread and diverse action on the brain, leading to the activation of many different neuronal pathways. This study provides some insight into the different effects MPH can produce in a heterogeneous disease such as AD, thereby increase understanding of apathy and how different pharmacotherapies might work to ameliorate symptoms.
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LIST OF PUBLICATIONS AND ABSTRACTS

Refereed Journals


Book Chapters

Abstracts

Manuscripts
APPENDICES

Appendix A - REB Approval
To: K. Lanctot, PhD.
Psychiatry
Room FC005

From: Dr. Philip Hébert

Date: March 4, 2010

Subject: Apathy in Dementia Methylphenidate Trial (ADMET)

Project Identification Number: 288-2009
Approval Date: March 4, 2010
Expiry date: March 4, 2011

The Research Ethics Board of Sunnybrook Health Sciences Centre has conducted a Full Board review of the research protocol referenced above and approved the involvement of human subjects as specified in the protocol on the above captioned date. The quorum for approval did not involve any member associated with this project.

The approval of this study includes the following documents:

- Information sheet/consent form Version 1.2 dated February 10, 2010
- Caregiver Information sheet/consent form version 1.0 dated December 10, 2009
- ADMET Protocol Version 1.2 dated March 2, 2010 including document history
- Product Monograph Apo-Methylphenidate SR dated March 31, 2005

The above Project Identification Number has been assigned to your project. Please use this number on all future correspondence. Should your study continue for more than one year you must request a renewal on or before one year from the approval date. Please advise the Board of the progress of your research annually and/or any adverse reactions or deviations which may occur in the future.

The Research Ethics Board of Sunnybrook Health Sciences Centre Operates in Compliance with the Tri-Council Policy Statement, ICH GCP Guidelines, Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, and the Medical Devices Regulations. All Health Canada regulated trials at Sunnybrook are conducted by a Qualified Investigator.

Fully affiliated with the University of Toronto
Approval of this study by the Sunnybrook REB entails that this study complies with current legislation as outlined in the Ontario Personal Health Information Protection Act (PHIPA) and all policies and guidelines established by Sunnybrook Health Sciences Centre. All applicable contracts and agreements must be submitted to Sunnybrook Research Administration before this research may be initiated.

[Signature]

Philip C. Hébert, MD PhD FCFPC
Chair, Research Ethics Board

OR

Blair Henry,
Vice-Chair, Research Ethics Board
APPENDICES

Appendix B - Study Consent Forms
INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY: PATIENT

Title: APATHY IN DEMENTIA METHYLPHENIDATE TRIAL (ADMET)

Investigators:  
K.L. Lanctôt, PhD Sunnybrook Health Sciences Centre  
N. Herrmann, MD FRCPC Sunnybrook Health Sciences Centre  
S.E. Black, MD FRCPC Sunnybrook Health Sciences Centre

Sponsor: This study is being funded by National Institutes of Health (NIH).

INFORMED CONSENT
You are being asked to consider participating in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood.

This form explains the purpose of this research study, provides information about the study drug, methylphenidate, the tests and procedures involved, possible risks and benefits, and the rights of participants.

Please read this form carefully and ask any questions you may have. You may take as much time as you wish to decide whether or not to participate. Feel free to discuss it with your friends and family, or your family doctor. Please ask the study staff or one of the investigators to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

INTRODUCTION
You are being asked to consider participating in this study because you have a condition called Alzheimer’s disease, which involves a disturbance in memory and learning. You may also be experiencing some changes called “apathy” (a lack of interest in activities). The purpose of this study is to assess a drug called methylphenidate to see if it is safe and if it works as a treatment for apathy in Alzheimer’s disease when compared to placebo. Placebo is a tablet that looks like methylphenidate but has no active ingredient.
Methylphenidate is a man-made drug that is approved for the treatment of Attention-Deficit Hyperactive Disorder (ADHD). It has also been shown to improve initiative, interest in activities and overall mood responses in people with Alzheimer’s disease.

**WHAT IS THE USUAL TREATMENT?**
The usual treatment for Alzheimer’s disease is treatment with either a type of drug called a cholinesterase inhibitor or a drug called memantine. However, there is currently no standard treatment for apathy in Alzheimer’s patients.

**WHY IS THIS STUDY BEING DONE?**
This research is being done because the researchers want to see what effects (good and bad) methylphenidate has on your feelings of apathy.

**WHAT WILL HAPPEN DURING THIS STUDY?**
This is a placebo-controlled study. The placebo in this study will be the same shape, size and colour of methylphenidate but is not expected to have any effect on your apathy. A placebo is used to decrease expectations in the study, making the results of the study more reliable. Participants in this study will be randomly placed in one of two study groups (methylphenidate or placebo). Neither you, nor the study staff nor investigators will know which group you are in. However, in a case of an emergency the study treatment can be identified. You will have a 50% chance of getting placebo during the entire study.

You will be asked to take the study drug twice a day for 6 weeks. You will take 2 capsules a day for the first 3 days (1 capsule in the morning and 1 capsule in the afternoon [before 6pm]). Starting in on the fourth day and until the end of the study, you will take 4 capsules a day (2 capsules in the morning and 2 capsules in the afternoon [before 6pm]).

**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**
It is anticipated that about 60 people that will take part in this study at three centres throughout North America. About 20 people will be recruited from Sunnybrook Health Sciences Centre. The length of this study for participants is 6 weeks. The entire study is expected to take about one and a half years to complete and the results should be known in two years.

**WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?**
If you decide to participate in the study, you will be asked to do the following:

- Take the prescribed pill(s) (either methylphenidate or placebo)
- Answer questions about your health, your medication history and the medications you take.
- Answer questions about your mood and your behaviour
- Activities to assess your memory and thinking. The study doctor can tell you more about this test.
- Have your blood pressure taken and make sure that you are feeling good
- Check your heart rate
- Have your blood taken

You will be asked to return to Sunnybrook Health Sciences Centre 4 times over the next 6 weeks (Baseline, Week 2, Week 4, and Week 6). Each visit will last anywhere from 1.5 to 2 hours. The collection of blood is a necessary part of this research study to make
sure that your body’s chemicals are balanced. You will be asked to fast before the blood is taken. You may drink water while you are fasting.

You will be contacted via telephone by the study staff three times over the six weeks to make sure that everything is going well with the study. See end of this document for a detailed schedule of visits.

**WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?**

You should not take any other medicines for fear or tremors when you are taking the study drug. If you are taking medicine for sadness, please discuss this with your doctor.

You may experience side effects from participating in this study. Some side effects are known and are listed below.

The most common risks or side effects seen with methylphenidate for the treatment of ADHD in young adults are:

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency Expected (30-100%)</th>
<th>Frequency Likely (10-30%)</th>
<th>Frequency Less Likely (1-10%)</th>
<th>Frequency Rare (0-1%)</th>
<th>Long Term Impact Temporary</th>
<th>Permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervousness</td>
<td>X</td>
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<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Insomnia</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Decreased Appetite</td>
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<tr>
<td>Dizziness</td>
<td>X</td>
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<td>X</td>
<td></td>
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<tr>
<td>Drowsiness</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Nausea/Vomiting</td>
<td>X</td>
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<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Abdominal Pain</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>X</td>
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<tr>
<td>Fever</td>
<td>X</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Changes in Blood Pressure and Heart Rate</td>
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<td>X</td>
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</tr>
</tbody>
</table>

In a study that we conducted on methylphenidate for the treatment of apathy in Alzheimer’s disease 3/13 participants experienced some form of side effect on methylphenidate. These were:
- Delusions/delirium
- Flushing of face
- Agitation/anger/irritability
- Physical aggression
- Restlessness
- Insomnia
- Nightmares
- Decreased appetite
- Irregular heart beat
- Dry Mouth

Two of these participants experienced severe side effects that resulted in dropping out of the study. One participant experienced severe delusions/delirium, flushing of face,
agitation/anger and physical aggression. The other participant experienced severe restlessness, insomnia, nightmares, delusional episodes, decreased appetite and irritability towards spouse.

You should discuss these risks with the study doctor or if they happen to you during the study you should tell the study staff right away. Ask the study doctor if you have questions about the signs or symptoms of any side effects you read about in this consent form.

For more information about risks and side effects, ask the study doctor.

You could have an allergic reaction. Sometimes people have allergic reactions to drugs. Some things that happen during an allergic reaction are:
- a rash
- having a hard time breathing
- wheezing when you breathe
- sudden drop in blood pressure
- swelling around the mouth, throat or eyes
- fast pulse
- sweating

You should get medical help and contact the study doctor or study staff if you have any of these symptoms of allergic reaction during the study.

The study doctor or study staff will take your blood by inserting a needle in your arm. Some problems you might have from this are:
- It may hurt
- You may get a bruise
- You may feel dizzy
- You may get an infection

It is possible that you could have problems and side effects of methylphenidate that nobody knows about yet. If the study investigator learns any new information, you will be told about it or any other finding or change to the study that might affect your willingness to continue in this study.

**WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?**
If you agree to take part in this study, there may or may not be direct benefit to you in terms of your interest in activities, motivation and overall mood. We hope the information learned from this study will benefit people with Alzheimer’s disease in the future.

**CAN PARTICIPATION IN THIS STUDY END EARLY?**
The investigators can remove you from the study at any time, even if you want to stay in the study. This could happen if:

- The study investigator believes it is best for you to stop being in the study
- You do not follow the study directions
- The sponsor stops funding the study for any reason
You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study team. To help you leave the study safely, the study doctor may ask you to participate in more tests.

**WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?**
There is no cost to you for the study visits or tests that are part of the study. In addition, you do not have to pay for study drug.

**ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?**
You will not be compensated for your participation in this study. However, you and your caregiver will be reimbursed for parking expenses for each study visit.

**DO THE INVESTIGATORS HAVE ANY CONFLICTS OF INTEREST?**
The investigators do not have any conflicts of interest.

**WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?**
All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish translated into your preferred language.

2. Participating in this study is your choice (voluntary). You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, it will not have any effect on your future medical treatment or health care. Should you choose to withdraw from the study you are encouraged to contact Jaclyn Cappell, Neuropsychopharmacology at 416-480-6100 ext. 3185 immediately.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the person in charge of this study (Principal Investigator) Dr. Lancot at 416-480-6100 ext.2241 or the study physician Dr Herrmann at 416 480-6133. If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call Dr. Philip C. Hébert, Chair of the Sunnybrook Research Ethics Board at (416) 480-4276.

4. By signing this consent form, you do not give up any of your legal rights.

5. You have the right to receive a copy of this signed and dated informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. If you become sick or injured as a direct result of your participation in this study, your medical care will be provided.
8. Any of your personal information (information about you and your health that identifies you as an individual) collected or obtained, whether you choose to participate or not, will be kept confidential and protected to the fullest extent of the law. All personal information collected will be kept in a secure location. The study staff, the Sunnybrook Research Ethics Board, NIH, the monitor(s), and the regulatory authority(ies) (Health Canada and/or FDA) will have access to your personal information for purposes associated with the study, but will only be allowed to access your records under the supervision of the Principal Investigator and will be obligated to protect your privacy and not disclose your personal information. None of your personal information will be given to anyone without your permission unless required by law. When the results of this study are published, your identity will not be disclosed. The data for this study will be retained for 25 years. All computers used to hold information will be encrypted as per Sunnybrook policy.

9. If, as a result of your participation in this study, any new clinically important medical information about your health is obtained, you will be given the opportunity to decide whether you wish to be made aware of that information.

10. You have the right to access, review and request changes to your personal information (i.e. address, date of birth).

11. You have the right to be informed of the results of this study once the entire study is complete.
DOCUMENTATION OF INFORMED CONSENT

Full Study Title: APATHY IN DEMENTIA METHYLPHENIDATE TRIAL

Name of Participant: ____________________________________________

Participant/Substitute decision-maker
By signing this form, I confirm that:
• This research study has been fully explained to me and all of my questions answered to my satisfaction
• I understand the requirements of participating in this research study
• I have been informed of the risks and benefits, if any, of participating in this research study
• I have been informed of any alternatives to participating in this research study
• I have been informed of the rights of research participants
• I have read each page of this form
• I authorize access to my personal health information (medical record) and research study data as explained in this form
• I have agreed to participate in this study or agree to allow the person I am responsible for to participate in this study

_________________________________  ___________________________  __________
Name of participant/Substitute decision-maker (print)  Signature  Date

Person obtaining consent
By signing this form, I confirm that:
• I have explained this study and its purpose to the participant named above
• I have answered all questions asked by the participant
• I will give a copy of this signed and dated document to the participant

_________________________________  ___________________________  __________
Name of person obtaining consent (print)  Signature  Date

Statement of Investigator
I acknowledge my responsibility for the care and well being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research.

Dr. Krista L. Lanctôt  ___________________________  ___________________________
Name of investigator (print)  Signature  Date
### Detailed Schedule of Visits

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INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY:
CAREGIVER

Title: APATHY IN DEMENTIA METHYLPHENIDATE TRIAL (ADMET)

Investigators:  K.L. Lanctôt, PhD  Sunnybrook Health Sciences Centre
              N. Herrmann, MD FRCPC  Sunnybrook Health Sciences Centre
              S.E. Black, MD FRCPC  Sunnybrook Health Sciences Centre

Sponsor: This study is being funded by National Institutes of Health (NIH).

INFORMED CONSENT
You are being asked to consider participating in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood.

This form explains the purpose of this research study, provides information about the tests and procedures involved, possible risks and benefits, and the rights of participants.

Please read this form carefully and ask any questions you may have. You may take as much time as you wish to decide whether or not to participate. Feel free to discuss it with your friends and family, or your family doctor. Please ask the study staff or one of the investigators to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study. As a caregiver for someone with Alzheimer’s disease, your role in this study will be referred as “caregiver” in this document and the person that you care for with Alzheimer’s disease will be referred to as the “patient”.

INTRODUCTION
You are being asked to consider participating in this study because you are caring for someone with a condition called Alzheimer’s disease, which involves a disturbance in memory and learning. The patient may also be experiencing some changes called “apathy” (a lack of interest in activities). The purpose of this study is to assess a drug called methylphenidate to see if it is safe and if it works as a treatment for apathy in Alzheimer’s disease when compared to placebo. Placebo is a tablet that looks like methylphenidate but has no active ingredient. The purpose of this study is also to see if methylphenidate makes caring for this person easier.
WHAT IS THE USUAL TREATMENT?
The usual treatment for Alzheimer’s disease is treatment with either a type of drug called a cholinesterase inhibitor or a drug called memantine. However, there is currently no standard treatment for apathy in Alzheimer’s patients.

WHY IS THIS STUDY BEING DONE?
This research is being done because the researchers want to see what effects (good and bad) methylphenidate has on the patient’s feelings of apathy. The researchers also want to see if this drug makes caring for a person with Alzheimer’s disease easier.

WHAT WILL HAPPEN DURING THIS STUDY?
This is a placebo-controlled study. The placebo in this study will be the same shape, size and colour of methylphenidate but is not expected to have any effect on apathy. A placebo is used to decrease expectations in the study, making the results of the study more reliable. Patients in this study will be randomly placed in one of two study groups (methylphenidate or placebo). Neither you, nor the study staff nor investigators will know which group they are in. However, in a case of an emergency the study treatment can be identified. They will have a 50% chance of getting placebo during the entire study.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
It is anticipated that about 60 people that will take part in this study at three centres throughout North America. About 20 people will be recruited from Sunnybrook Health Sciences Centre. The length of this study for participants is 6 weeks. The entire study is expected to take about one and a half years to complete and the results should be known in two years.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANT CAREGIVERS?
If you decide to participate in the study, as a caregiver you will be asked to do the following:

- Answer questions about the patient’s health, their medication history and the medications they take.
- Answer questions about the patient’s mood and behaviour, and its impact on you

You will be asked to help remind the patient member to the study drug (either methylphenidate or a placebo) twice a day for 6 weeks.

You will receive one-on-one counseling, no matter which drug the patient. You will be provided with materials about how to care for someone who has Alzheimer’s disease with apathy.

You and the patient will be asked to come into the clinic 3 more times and will be asked to be available for phone calls 3 times. You and the patient will come to the clinic for visits 2 weeks, 4 weeks, and 6 weeks after the first visit. The study staff will call you in the weeks that you don’t come to the clinic. You will receive a phone call at 1 week, 3 weeks, and 5 weeks after you start the study. Each visit at the clinic will last about 1 to 2 hours, and each phone call will last about 10 minutes.

You will be asked to return all study medicines and bottles used and unused at each visit.
WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?
There are few risks to you being in the study. This will require some of your time. Also, some people may not like to answer questions about another person. If you are such a person, you may feel uncomfortable.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?
If you agree to take part in this study, there may or may not be direct benefit to you in terms of reducing the burden of caring for a person with Alzheimer’s disease.

CAN PARTICIPATION IN THIS STUDY END EARLY?
The investigators can remove you and the patient from the study at any time, even if you want to stay in the study. This could happen if:

- The study investigator believes it is best for you and/or the patient to stop being in the study
- You and/or the patient do not follow the study directions
- The sponsor stops funding the study for any reason

You and the patient can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study team. To help you leave the study safely, the study doctor may ask you to participate in more tests.

WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?
There is no cost to you for the study visits or tests that are part of the study. In addition, you do not have to pay for study drug.

ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?
You will not be compensated for your participation in this study. However, you will be reimbursed for parking expenses for each study visit.

WHAT OTHER CHOICES ARE THERE?
If you decide not to participate in this study, other treatment choices, that do not involve medication, may be available. You may choose to receive counseling from a trained professional. There are currently no safe and effective treatments for apathy in AD that involve medication.

DO THE INVESTIGATORS HAVE ANY CONFLICTS OF INTEREST?
The investigators do not have any conflicts of interest.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?
All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish translated into your preferred language.

2. Participating in this study is your choice (voluntary). You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, it will not have any effect on your future medical treatment or health care. Should you choose to withdraw from the study you are encouraged to contact Jaclyn Cappell, Neuropsychopharmacology at 416-480-6100 ext. 3185 immediately.
3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the person in charge of this study (Principal Investigator) Dr. Lanctôt at 416-480-6100 ext.2241 or the study physician Dr Herrmann at 416 480-6133. If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call Dr. Philip C. Hébert, Chair of the Sunnybrook Research Ethics Board at (416) 480-4276.

4. By signing this consent form, you do not give up any of your legal rights.

5. You have the right to receive a copy of this signed and dated informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. If you become sick or injured as a direct result of your participation in this study, your medical care will be provided.

8. Any of your personal information (information about you and your health that identifies you as an individual) collected or obtained, whether you choose to participate or not, will be kept confidential and protected to the fullest extent of the law. All personal information collected will be kept in a secure location. The study staff, the Sunnybrook Research Ethics Board, NIH, the monitor(s), and the regulatory authority(ies) (Health Canada and/or FDA) will have access to your personal information for purposes associated with the study, but will only be allowed to access your records under the supervision of the Principal Investigator and will be obligated to protect your privacy and not disclose your personal information. None of your personal information will be given to anyone without your permission unless required by law. When the results of this study are published, your identity will not be disclosed. The data for this study will be retained for 25 years. All computers used to hold information will be encrypted as per Sunnybrook policy.

9. If, as a result of your participation in this study, any new clinically important medical information about your health is obtained, you will be given the opportunity to decide whether you wish to be made aware of that information.

10. You have the right to access, review and request changes to your personal information (i.e. address, date of birth).

11. You have the right to be informed of the results of this study once the entire study is complete.
DOCUMENTATION OF INFORMED CONSENT

Full Study Title: APATHY IN DEMENTIA METHYLPHENIDATE TRIAL

Name of Participant: ________________________________________

Participant/Substitute decision-maker
By signing this form, I confirm that:
• This research study has been fully explained to me and all of my questions answered to my satisfaction
• I understand the requirements of participating in this research study
• I have been informed of the risks and benefits, if any, of participating in this research study
• I have been informed of any alternatives to participating in this research study
• I have been informed of the rights of research participants
• I have read each page of this form
• I authorize access to my personal health information (medical record) and research study data as explained in this form
• I have agreed to participate in this study or agree to allow the person I am responsible for to participate in this study

________________________  ______________________   __________
Name of participant/Substitute decision-maker (print)  Signature  Date

Person obtaining consent
By signing this form, I confirm that:
• I have explained this study and its purpose to the participant named above
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Dr. Krista L. Lanctôt  ______________________  ______________________
Name of investigator (print)  Signature  Date