

# Pharmacological Therapy for Apathy in Alzheimer's Disease: A Systematic Review and Meta-Analysis

Amir A. Sepehry, Michael Sarai, Ging-Yuek R. Hsiung

**ABSTRACT:** *Introduction:* Apathy is highly prevalent in Alzheimer's disease (AD), but whether pharmacotherapy is effective in managing apathy is unclear. *Methods:* To assess the efficacy of pharmacotherapy for apathy in AD we searched for randomized controlled trials (RCT) and aggregate data reporting on apathy in several search engines, reference lists of articles, and reviews. Demographic characteristics and relevant data were extracted to assess apathy. *Results:* Fifteen RCTs were examined, and 11 were used in aggregate meta-analytic statistics. Drugs included were cholinesterase inhibitors, memantine, and psycho-stimulants. We found no significant treatment effect in favour of any of the drugs, and the effect-size estimates under a random effect model were heterogeneous. Most RCTs had a high attrition rate and used the NPI apathy subscale to measure apathy. *Conclusion:* The lack of an effect could be explained by methodological limitations, publication bias, and heterogeneity.

**RÉSUMÉ:** *Traitement pharmacologique de l'apathie liée à la maladie d'Alzheimer: revue systématique et méta-analyse.* *Introduction:* L'apathie est un état très courant chez les patients atteints de la maladie d'Alzheimer. Cela dit, on ignore encore dans quelle mesure la pharmacothérapie permet de le traiter de façon efficace. *Méthodes:* Afin d'évaluer l'efficacité des traitements pharmacologiques de l'apathie liée à la maladie d'Alzheimer, nous avons effectué une recension d'essais cliniques randomisés (ECR) et rassemblé, au moyen de plusieurs moteurs de recherche, de listes de référence d'articles clés et de recensions, des données concernant cet état. Des caractéristiques démographiques et d'autres données jugées pertinentes ont ensuite été extraites afin de mieux l'évaluer. *Résultats:* Au total, nous avons passé en revue quinze ECR ; onze d'entre eux ont été utilisés dans le cadre d'une méta-analyse agrégée. Parmi les médicaments inclus, on peut mentionner les inhibiteurs de cholinestérase, la mémantine et un certain nombre de psychostimulants. En gros, nous n'avons relevé aucun effet notable associé à la prise de ces médicaments. De plus, les estimations de l'ampleur des effets en vertu d'un modèle à effets aléatoires se sont révélées hétérogènes. Fait à noter, la plupart des ECR ont dû composer avec un taux d'abandon élevé et ont utilisé le *Neuropsychiatric Inventory* (NPI) pour mesurer l'apathie. *Conclusions:* L'absence d'effet pourrait s'expliquer par des contraintes méthodologiques, des biais de publication et une hétérogénéité statistique.

**Keywords:** Apathy, Pharmacological treatment, Alzheimer's disease, Review, Clinical trials

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## INTRODUCTION

Apathy, defined as the absence or lack of feeling, emotion, interest, concern, or motivation not attributable to cognitive impairment, emotional distress, or a decreased level of consciousness, is a common neuropsychiatric syndrome in Alzheimer's disease (AD).<sup>1</sup> Apathy is seen to occur early in the clinical course of the illness and progresses in concert with declining cognitive function.<sup>2</sup> Apathetic AD patients often have more rapid cognitive decline,<sup>3</sup> and are more impaired on activities of daily living.<sup>4</sup> Up to 80% of AD patients experience some degree of apathy during the course of their illness,<sup>2</sup> depending on the assessment scale, type of population studied, diagnostic criteria, and by type and severity of AD.<sup>5</sup> Apathy tends to first appear in the prodromal stage of AD,<sup>6</sup> and increases as the illness progresses from MCI to dementia along the spectrum of neurocognitive disorders (NCD). For example, one study showed a prevalence of 42% for mild, 80% for moderate, and 92% for advanced stages of AD.<sup>2</sup> In another cohort study of patients with probable AD, apathy was associated with an increased risk of death.<sup>7</sup> Despite its high prevalence, treatment of symptomatic apathy in AD has not been well studied.

## ASSESSMENT/DIAGNOSIS OF APATHY IN AD

Proposed as an independent syndrome separate from depression, apathy symptoms are put into a set of diagnostic criteria that are now validated for use in AD and stroke.<sup>8-11</sup> Robert and colleagues proposed that for diagnosing apathy in AD, (1) the core feature of apathy (diminished motivation) must be present for at least four weeks; (2) two of the three dimensions of apathy (reduced goal-directed behavior, goal-directed cognitive activity, and emotions) must also be present; (3) there should be identifiable functional impairments attributable to apathy; and (4) criteria are specified to exclude symptoms and states that mimic apathy.<sup>12</sup>

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A limitation of current data with the available diagnostic criteria is that most studies were performed prior to the development and validation of these criteria, which makes the evaluation of the evidence challenging. Nonetheless, most assessments of apathy in clinical samples use scales to measure the severity or to differentiate apathy from depression by excluding symptoms such as sadness and negative thoughts that are typically observed in depressive syndromes.

The Apathy Evaluation Scale (AES), a Likert-Like scale measure, was developed by Marin and colleagues.<sup>13</sup> This measure consists of three sections (with 18 items each) and allows collection of information on the symptoms from an informant, the clinician, and the patient. A shorter version is adapted for nursing home patients.<sup>14</sup> The Apathy Scale (AS), developed by Starkstein and co-workers, is an examiner-rated scale with 14 items based on the Marin's instrument.<sup>15</sup> Robert and colleagues developed the Likert-style Apathy Inventory (AI) built on Marin and colleagues' diagnostic criteria for apathy.<sup>16</sup> This 12-item scale collects information from both the patient and the caregiver by "yes/no" responses, and deals with behavioral changes that have occurred since the beginning of the disease. The caregiver section is structured similarly to the Neuropsychiatric Inventory (NPI)<sup>17</sup> such that when the caregiver response is negative, a score of zero is attributed and the rater proceeds to the next item. If the response is positive, frequency and severity of the items are explored. Strauss and Sperry developed the informant-based 16-item uni-dimensional Dementia Apathy Interview and Rating (DAIR) scale to assess apathy among individuals with cognitive decline.<sup>18</sup> This instrument collects information from the patient and an appropriate informant, and takes into consideration other sources such as patients' medical records or information from other medical providers. These scales are developed to capture apathy in patients with cognitive impairment, and are not specific to AD. They employ different approaches and constructs, and assess and capture the apathy severity-spectrum, which can affect the prevalence rate. This variation in the assessment method affects treatment evaluation and patient enrollment for clinical trials.

## NEUROBIOLOGY OF APATHY IN AD

Currently there is no guideline for treating apathy in AD, even though the many neurobiological hypotheses linking apathy to neuronal correlates has led to the development of a multitude of psychotropic medications.<sup>5</sup> The neurobiological hypotheses are based on the observation of patient groups with neurological or psychiatric impairment, suggesting that apathy arises from dysfunction of frontal-subcortical networks (namely amygdala, nucleus accumbens, and prefrontal cortex [PFC]).<sup>19-21</sup> The three sub-domains of apathy, including dysfunctional emotion processing, dysfunctional cognitive activity, and reduced self-activation, arise from impairment of the orbital, dorsolateral, and medial PFC, respectively. Neuroimaging studies of AD patients have supported this hypothesis, correlating apathy with dysfunction in key regions of the PFC-basal ganglia circuitry, including orbitofrontal cortex, anterior cingulate cortex (ACC), inferior frontal cortex, caudate nucleus, and putamen nucleus.<sup>22-24</sup> Dysfunction of these regions may have a neurochemical aetiology; that is, the putative mechanisms of AD pathogenesis (i.e. amyloid plaque formation, and hyper-phosphorylated tau aggregation) compromise neurotransmitter systems in the PFC-basal ganglia circuitry, giving rise to apathy symptoms.<sup>25</sup> There are

several important neurotransmitter-based hypotheses regarding the factors that exert an influence on the neuronal circuitry, including dopamine depletion, dysfunction of serotonin (5-HT), cholinergic and glutamate deficiency, and reduction of central GABA concentration. While a detailed review of the neurobiology of apathy is beyond the scope of the current work, we will highlight the main hypotheses.

The dopamine depletion hypothesis is supported by studies demonstrating reduced D<sub>2</sub>-like receptor density and lower levels of dopamine transporter in the striatum of AD patients with apathy.<sup>26-28</sup> In one study, a lower level of dopamine transporters in the caudate and putamen correlated with a lack of interest and initiative.<sup>28</sup> In light of the aforementioned neuroanatomical correlates these data seem to suggest that dopaminergic tone in the basal ganglia-ACC-frontal cortex circuitry, which is involved in motivated and goal-directed behaviour, is diminished in patients with AD and potentially mediates the apathetic behaviour. The link between disorders of central dopaminergic hypo-function (e.g. restless leg syndrome<sup>30</sup> and extrapyramidal symptoms<sup>31</sup>) and apathy symptoms in AD provides additional evidence for diminished dopaminergic tone. Importantly, impairment of this system is associated with decline in cognitive functioning, mainly in attention and working memory. The dopamine hypotheses points to the use of dopaminergic agents or stimulants such as methylphenidate in treating apathy.

Serotonin, although controversial, tends to inhibit dopamine transmission.<sup>32</sup> Dysfunction of the 5-HT system is widespread and varied in AD: 5-HT denervation of serotonin-releasing neurons is observed in the medial and dorsal raphe nuclei; levels of 5-HT and its primary metabolite are 40-80% lower compared to non-AD controls; synaptic densities of 5-HT<sub>1,2,4,6</sub> receptors are altered; and 5-HT transporter density is reduced by 20-40% in AD patients with apathy.<sup>33</sup> These changes are present in the aforementioned neuroanatomical correlates of apathy. Additionally, correlation between 5-HT dysfunction with depressive symptoms in AD has been reported.<sup>33</sup> For instance, one study linked 5HT dysfunction and depression severity with hypo-metabolism in the dorsolateral PFC. Given the considerable overlap between depression and apathy symptoms, the results of this study indirectly supports a role for 5-HT in apathetic behaviour. Based on considerable overlap of symptoms between depression and apathy, serotonergic and dopaminergic medications are reasonable treatment options for apathy in AD. However, this seems counterintuitive when apathy assessment scales attempt to exclude patients with depression. Selective serotonin reuptake inhibitors (SSRIs) antidepressants are theoretically the treatment of choice under this hypothesis.

Evidence for the acetylcholine hypothesis suggests that primary concentrations of cholinergic neurons in the brain originate from the nucleus basalis (positioned between the frontal cortex and cingulate gyrus,<sup>34</sup> two regions consistently correlated with apathy) that is significantly diminished in AD. The Glutamate hypothesis, on the other hand, emerges from therapeutic studies suggests a link between the glutamatergic system and apathy symptoms. Drug trials have demonstrated a role for glutamate receptor agonists in improving the negative symptoms of schizophrenia.<sup>35,36</sup> In AD, a double-blind RCT of mibampator, a glutamate receptor potentiator, significantly improved apathy in the treated group.<sup>37</sup> In addition, recent trials on cholinesterase inhibitors suggest some efficacy on apathy symptoms in AD patients.<sup>38</sup> The acetylcholine and glutamate hypotheses are the underlying reasons for using cholinesterase inhibitors or NMDA receptor agonists (e.g., memantine), respectively, for the management of apathy in AD.

Regarding the GABA system impairment in AD, studies report reduction of central GABA concentration (predominantly in late-stage AD) and up-regulation of GABA<sub>a</sub> receptors.<sup>39</sup> Although one study did correlate GABA reduction and GABA<sub>a</sub> receptor up-regulation with depressive symptoms, direct evidence correlating GABA dysfunction to apathy is lacking.<sup>40</sup> Although direct evidence correlating norepinephrine (NE) with apathy is also lacking, the link between apathy and inattention, which is effectively treated by adrenergic agents in ADHD patients, lends support to NE as a basis for apathy in AD.<sup>41</sup> Mood stabilizers or other multi-action compounds are presumed to be the suitable agents under these hypotheses.

The putative neurochemical underpinnings of apathy and the considerable clinical overlap between depression and apathy have prompted the use of various psychotropic medications in apathetic AD patients. However, individual drug trials have yielded mixed results, probably because most studies have not considered the temporal relationship between neurochemical dysfunction and AD pathogenesis. For example, 5-HT<sub>1a</sub> receptors are up-regulated in mild cognitive impairment,<sup>42</sup> but are significantly decreased in later stages of AD.<sup>33</sup> The drug's effects may therefore be stage-specific. In addition, many scales for apathy are based on older definitions, which largely focus on lack of motivation. Due to the established role of dopamine in the brain reward system,<sup>29</sup> these scales may detect changes resulting from dopaminergic therapy, but may less reliably detect non-dopaminergic drugs' effects on the emotional and cognitive domains of apathy. Similarly, variable diagnostic criteria may have skewed the treatment effects. Furthermore, most studies targeted a single neurotransmitter system. Given the multiple neurochemical alterations in apathetic AD patients and the interconnectedness of neurotransmitter systems,<sup>30,43,44</sup> drug therapy that has multiple mechanisms of action with tailored affinity may produce larger treatment effects.

#### EVIDENCE FROM OPEN-LABEL TRIALS

Twelve open-label trials were examined based on our search criteria for this meta-analysis. Five studies examined donepezil;<sup>45-49</sup> three, rivastigmine;<sup>46,50,51</sup> two, galantamine;<sup>46,52</sup> one, memantine;<sup>46</sup> one, gabapentin;<sup>53</sup> one, citalopram;<sup>54</sup> one, methylphenidate;<sup>55</sup> and one, atypical antipsychotic.<sup>56</sup> For these studies, average age ranged from 66 to 83 years. Average follow-up time was 31 weeks. Only one study examined apathy as a primary outcome (all others used the NPI-Apathy subscale).<sup>55</sup> Most studies did not report a statistically significant change from baseline. A small, statistically significant improvement from baseline was observed in two of three rivastigmine trials, and one of three donepezil trials. A relatively large statistically significant improvement in AES was reported in the methylphenidate study ( $n=23$ ; baseline: 52.70 [6.7]; endpoint: 32.43 [5.7];  $p < 0.00010$ .) Both galantamine trials reported a trend towards worsening apathy as examined by the NPI subscale, and one trial was statistically significant [ $n=33$ ; baseline: 0.38 (0.2); endpoint: 1.44 (0.54);  $p=0.045$ ]. Basically, from open label studies we see mixed results, with heterogeneity in drugs used, sample, and assessment approaches, which renders generalizability difficult.

Recent systematic reviews highlighted the challenge in using any compound for management of apathy in AD<sup>57</sup> and indirectly suggest that the treatment effect may be scale-dependent.<sup>58</sup> Additionally, current systematic reviews of neuropsychiatric pharmacotherapy are lacking specificity for apathy outcome and are confounded by poor reporting methods.<sup>59-63</sup> Taking into

account of these limitations, experts have recently recommended that studies investigating apathy in neurodegenerative disease should A) look for the correlation between depression and apathy, B) look for treatment duration of 3 months or more, C) control for concomitant medications, D) control for history of stroke, E) and diagnostic assessment methods.<sup>64</sup> Thus, we examined the available RCTs by taking into account these moderating variables.

#### MATERIAL AND METHODS

##### Eligibility criteria, Information sources & Search

On March 3, 2014, we conducted a search of the following databases for placebo-controlled RCTs (either parallel-group or cross-over): MEDLINE (1946-2014), EMBASE (1974-2014), PsycINFO (1597-2014), and the Cochrane Register of Controlled Trials (March 2014 issue). Additionally, we scanned <http://www.clinicaltrials.gov> and the reference lists of relevant systematic reviews.<sup>58,64</sup> The search was subsequently updated on June 25, 2015.

To be included, studies had to report on adult patients ( $\geq 40$  years old) with Alzheimer's disease; trial an on-market, single-entity psychotropic medication; and used a validated instrument to measure apathy severity or presence. Studies merging data in the absence of duplicates were included.

##### Study selections

Two authors (AAS and MS) independently screened titles and abstracts with *a priori* set selection criteria. Subsequently, they independently screened the full-text of the possible studies to verify for the availability of data. In cases of disagreements, discussion followed until they were resolved by consensus with the senior author (GYRH).

##### Data abstraction

One author abstracted data including characteristics of study participants, type of intervention, and apathy outcome data. A second author checked the data extraction for accuracy.

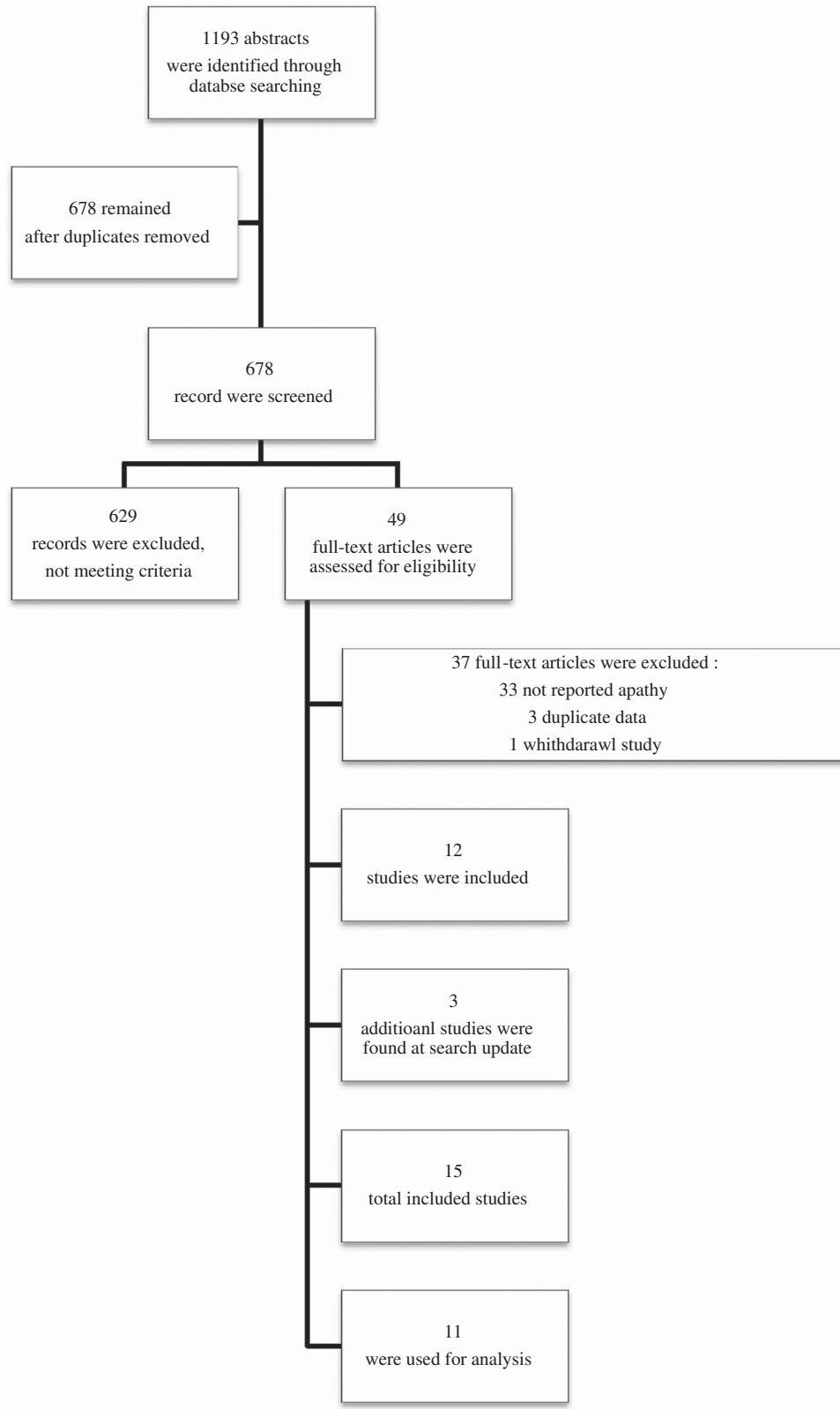
##### Bias, heterogeneity and effect size

Both visual and qualitative methods were used to examine for publication bias. Heterogeneity's presence and magnitude was examined using the  $q$ -statistics and I-square. An aggregate random effect Hedge's  $g$  effect size estimate was calculated using the comprehensive meta-analysis to examine the global magnitude in group differences (treatment vs. control).<sup>65</sup> In the absence of descriptive statistics (mean and standard deviation), when appropriate,  $p$ -values and sample size as reported by studies were used to generate the effect size. In the absence of reported exact non-significant  $p$ -values, alpha 0.06 (a liberal assumption) was used for analysis.

#### RESULTS

##### Study selection

The literature search for RCTs yielded 1193 citations from the search engines. Of the 678 unique abstracts, 49 were eligible for full-text review. Two authors (AAS and MS) independently reviewed and excluded articles, leaving 15 articles that met our entry criteria, which were included in our systematic review and meta-analysis (see Figure 1, flow diagram).



**Figure 1:** Flowchart showing study selection.

## Study characteristics

The amalgam of studies examined cholinesterase inhibitors, including three donepezil trials and one galantamine trial;<sup>66</sup> four memantine trials;<sup>67-70</sup> three psycho-stimulant trials;<sup>41,71,72</sup> two atypical antipsychotic trials;<sup>73,74</sup> and two trials in which the active treatment was classified as “other.”<sup>75,76</sup> These fifteen RCTs included 2819 active compound treated and 2045 placebo-treated patients (total = 4864). The average follow-up for each drug class varied. For the NMDA category, 24 and 28 weeks were the minimum and maximum duration of trials, respectively. For cholinesterase inhibitors, 12 and 24 weeks were the minimum and maximum median duration of treatment. For stimulant, 2 to 8 weeks was the treatment duration. For category “others,” duration was 6 and 24 weeks.

Both severity of dementia and class of drug varied across trials. For studies reporting demographic values, the average age, MMSE score, and NPI total score of the treated patients ranged from 73.3 to 86, 7.8 to 24.1, and 6.8 to 36.7, respectively. Furthermore, global samples ranged from 22 to 2033, and overall included more female participants (percent male ranged from 17 to 50). The minimum sample size for treatment was 11 and the maximum was 1347; for placebo arms the minimum sample size was 13 and the maximum was 686 patients (Please see Table 1 for details).

## Data synthesis

For cognitive enhancers (donepezil and galantamine), no significant apathy treatment effect was observed (Hedges'  $g = -0.055$ ; 95% CI: -0.322 to 0.213;  $P$ -value = 0.687;  $Q$ -value = 17.378;  $P$ -value = 0.001;  $I^2 = 82.737$ ;  $N = 4$ .) The average donepezil dosage was 10mg/day (three studies) while galantamine dosage ranged between 16 and 32 mg/day (an aggregate of data from trials). With the exception of one study, all studies used the NPI-apathy subscale as an outcome measure. These trials included mild to severe AD.

For NMDA category (memantine), a small and non-significant effect size estimate yielded in favour of treatment (Hedges'  $g = 0.092$ ; 95% CI: -0.134 to 0.318;  $P$ -value = 0.423;  $Q$ -value = 11.425;  $P$ -value = 0.010;  $I^2 = 73.742$ ;  $N = 4$ .) All memantine trials reported the same average dosage (20 mg/day), included moderate to severe AD, and used the NPI-apathy subscale.

For psycho-stimulant, compared to placebo, a small and non-significant treatment effect yielded (Hedges'  $g = -0.063$ ; 95% CI: -1.067 to 0.941;  $P$ -value = 0.903;  $Q$ -value = 12.486;  $P$ -value = 0.002;  $I^2 = 83.982$ ;  $N = 3$ .) All stimulant trials included mild to moderate AD and used multiple scales, including NPI-apathy and FrSBe apathy subscale. This analysis included mixed drugs with non-comparable dosage.

For antipsychotics and “other” classes of drugs with anti-depressant properties, not enough studies ( $N < 3$ ) were reported to allow analysis and support their use. Individual atypical antipsychotic studies did not support their use for apathy in AD.<sup>73,74</sup>

The analysis for psycho-stimulants was underpowered due to limited patient enrolment in each arm of the trials, but not so for ChEI and NMDA. Given the limited number of studies included under each drug class, examination of heterogeneity or publication bias was not possible. However, under each drug class, informants provided a majority of the collateral information, and little, but not quantifiable discrepancy was observed in terms of the type of studies (RCT, or

retrospective data from RCT's), or whether the study was primarily or secondarily investigating apathy (Please see Figure 2 for details).

## DISCUSSION AND CONCLUSION

To our knowledge this is the first meta-analysis examining the effect of multiple compounds for management of apathy in AD. This meta-analysis examined fifteen studies and found limited evidence to support the use of any of the medications we examined for management of apathy in AD. However, significant heterogeneity was observed under each drug class that we could not explain given the limited number of studies.

We speculate that the lack of an effect could be due to the clinical heterogeneity in the sample included. For example, AD severity ranged from early stage to severe. Thus, future studies should focus on one stage for more homogeneous effect. Additionally, the lack of an effect could be due to methodological issues. For example, sample size, attrition, using the last observation carried forward,<sup>77</sup> or use of a modified intention-to-treat approaches,<sup>78</sup> could have masked treatment effect. Unfortunately, because of limited number of studies under each drug class, further analysis and controlling for these factors were not possible. Moreover, we excluded many controlled trials because they did not report the NPI breakdown on apathy sub-score (we did not contact authors for pertinent information). The results may also be confounded by publication bias, and we have not examined the effect of compounds' affinity for specific neurotransmitter(s) in order to provide the neurobiological underpinning for specific treatment approaches. Also, our means aggregate did not examine the proportion of patients showing benefit versus no change or deterioration. Further assessment of clinical response and tolerance with respect to this difference is warranted, since this can vary within the same class of drugs.<sup>79</sup>

## CONCLUSION

### Direction for future research

The inability of current pharmacotherapy to provide a clinically meaningful effect on apathy may be a result of the drugs' ineffectiveness. However, owing to methodological limitations, the drugs' apparent ineffectiveness may be an artifact of poor trial designs that we have not systematically examined.<sup>80</sup> In support of a poor trial design hypothesis, we postulate methodological issues that might account for the lack of observable treatment effect on apathy. First, all trials used either NPI-apathy sub-score or AES to assess apathy; none use the newly proposed diagnostic criteria for apathy in AD. While NPI-apathy and AES are the most widely used and psychometrically robust apathy scales,<sup>81</sup> they largely define apathy as a lack of motivation; therefore, they may not fully capture the pleomorphic nature of apathy in AD. Other scales that are based on clearly defined and validated diagnostic criteria<sup>12</sup> that also differentiate depression from apathy, such as the apathy inventory (AI)<sup>16</sup> or the expanded NPI (NPI-C),<sup>82</sup> may better distinguish the apathetic AD patients' emotional, cognitive, and behavioral deficits.

### Direction for practice

Given the limited efficacy of the available drug options, we don't see supporting evidence for pharmacotherapy as a first-line treatment for apathy in AD. Several types of non-drug interventions have demonstrated a positive effect in at least a few trials,<sup>83</sup> which could represent potentially safer alternatives.

**Table 1: Descriptive of the included RCTs—Baseline characteristics (N = 15)**

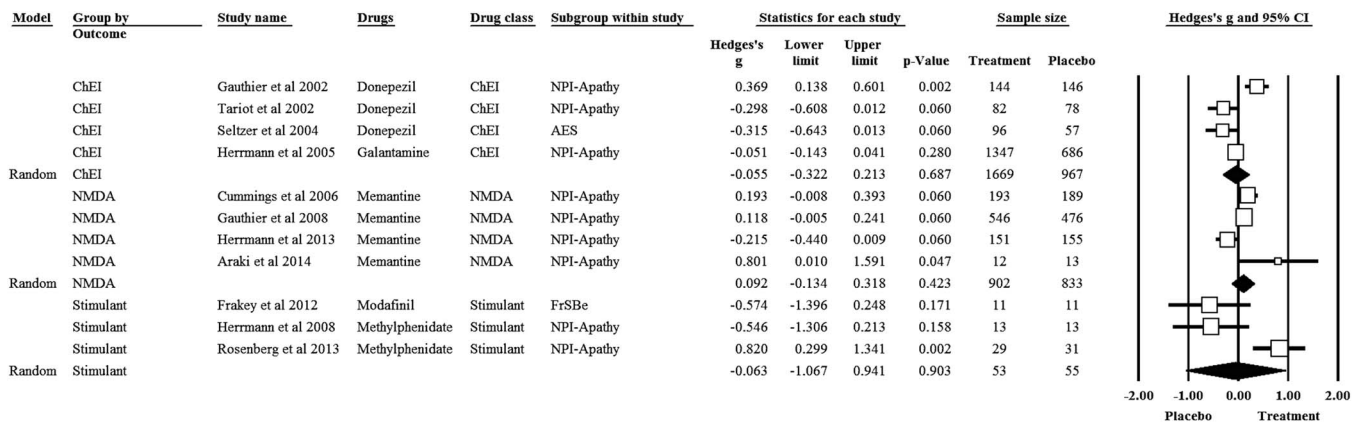
Study ID	Treatment	n	Baseline Characteristics (Treated group)				Follow-up (weeks)	Attrition (%)		Depression assessment (Yes/NR)	Patient Type (Environment)	AD Severity	Apathy Measure
	Dosage		Male	Age	MMSE	NPI		Plc	Txt				
<i>Araki 2014</i>	Memantine (20 mg/day)	37	30%	77.9 (9.8)	NR	NR	24	28	37	Yes	Outpatient	Mod-Sev	NPI-apathy
<i>Cummings 2006</i>	Memantine (20 mg/day)	403	37%	75.5 (8.45)	9.9(3.13)	13.7 (14.7)	24	25	15	Yes	Multicentre	Mod-Sev	NPI-apathy
<i>Frakey 2012</i>	Modafinil (200 mg/day)	22	NR	75.27 (8.34)	NR	NR	8	0	10	NR	Memory and Aging program	Mil-Mod	FrSBe-apathy
<i>Gauthier 2002**</i>	Donepezil (10 mg/day)	290	39%	73.3 (NR)	11.72 (5.96)	19.55 (24.86)	24	14	16	Yes	Multicentre	Mod-Sev	NPI-apathy
<i>Gauthier 2008</i>	Memantine (20 mg/day)	1826	32.8%	76.2 (8.1)	12.3 (4.2)	15.9 (14.7)	24-28	-	-	Yes	Multicentre	Mod-Sev	NPI-apathy
<i>Herrmann 2005</i>	Galantamine (16-32mg/day)	2033	38%	76.5 (7.7)	18.2 (3.9)	11.46 (12.91)	12-24	-	-	Yes	Multicentre	Mil-Mod	NPI-apathy
<i>Herrmann 2008</i>	Methylphenidate (20 mg/day)	13	46%	77.9 (7.8)	19.9 (4.7)	15.5 (11.30)	2	8	15	NR	Outpatient	Mil-Mod	NPI-apathy
<i>Herrmann 2013</i>	Memantine (20 mg/day)	369	42.3	74.7 (7.9)	11.9 (3.1)	30.9 (14.8)	24	17	17	NR	Multicentre	Mod-Sev	NPI-apathy
<i>Mohs 2009</i>	Atomoxetine (63.9 mg/day)	92	NR	NR	20.3 (4.5)	6.8 (14.1)	24	19	22	Yes	Multicentre	Mld-Mod	NPI-apathy
<i>Paleacu 2008*</i>	Quetiapine (200 mg/day)	40	35%	82.2 (6.4)	14.5 (6.3)	NR	6	40	25	Yes	NS	NS	NPI-apathy
<i>Peskind 2005***</i>	Propranolol (106 mg/day)	31	18%	86 (8)	7.8 (7.5)	25.5 (15.6)	6	73	35	Yes	Outpatient	NS	NPI-apathy
<i>Rosenberg 2013</i>	Methylphenidate (20 mg/day)	60	41%	78 (8)	19 (5)	15 (6)	6	7	3	Yes	Multicenter	Mil-Mod	AES, NPI-apathy
<i>Seltzer 2004</i>	Donepezil (10 mg/day)	153	50%	73.3 (9.6)	24.1 (1.7)	NR	24	19	27	Yes	Multicentre	Mild	AS
<i>Streim 2008</i>	Aripiprazole (2-15 mg/day)	256	22%	83 (NR)	13.94 (8.63)	36.74 (30.49)	10	49	34	Yes	Inpatients	NS	NPI-apathy
<i>Tariot 2002</i>	Donepezil (10 mg/day)	208	17%	85.4 (NR)	14.4 (5.4)	21.0 (14.5)	24	26	18	Yes	Multicentre	NS	NPI-apathy

NPI-NH: Neuropsychiatric Inventory-Nursing Home version; AES: Apathy Examination Scale; SIB: Severe Impairment Battery; ADCS-ADL: Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory; FrSBe: Frontal Systems Behavior Scale; ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive; CGIC: Clinical Global Impression of Change; NR: Not reported. Scores for age, MMSE, and NPI are in mean and (SD).

\*mean age and %male is based on the full sample;

\*\*Included patient data from Feldman et al 2001<sup>85</sup>;

\*\*\*MMSE Score is for trial completers only. NR: not reported; NS: Not specified. Depression assessment was defined by using any scale that report on depressive symptoms



**Figure 2:** Forest plot showing RCTs examining the effect of pharmacological compounds on apathy in AD. AE: Apathy evaluation scale; ChEI: Cholinesterase inhibitor; FrSBe: Frontal Systems Behavior Scale; NMDA: N-Methyl D-Aspartate agonist; NPI: Neuropsychiatry Inventory. Gauthier et al. 2002 used data from Feldman et al 2001.<sup>85</sup>

Where a patient with severe apathy fails adequate trials of multiple non-pharmacological treatments, a cautiously monitored trial of add-on methylphenidate or a switch to rivastigmine is reasonable. The methylphenidate RCT reported by Rosenberg et al. demonstrated the largest effect size. While no rivastigmine RCT fit our eligibility criteria in our current analysis, this compound demonstrated the largest effect on apathy in open label studies.<sup>84</sup> Consistent with a current view of the literature,<sup>58</sup> we recognize that the results of the methylphenidate RCT must be replicated in a larger RCT using validated diagnostic and assessment tools before the drug can be more widely recommended.

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#### DISCLOSURES

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#### STATEMENT OF AUTHORSHIP

Study concept and design: MS, AS; acquisition, analysis, and interpretation of data: all authors; drafting of the manuscript: MS, AS; critical revision of the manuscript for intellectual content: AS, GYRH; statistical analyses: AS; supervision: GYRH.

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