

Efficacy and Safety of Psychostimulants for Alzheimer's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction Several reports of the effectiveness of the use of psychostimulants for the treatment of Alzheimer's disease (AD) are available.

Methods A systematic review and meta-analysis was conducted including double-blind, randomized, placebo-controlled trials. Outcomes were the improvement of apathy scales score (primary), mini-mental state examination (MMSE) score, activities of daily living scale score, Zarit burden interview score, all-cause discontinuation, discontinuation due to adverse events, and incidence of at least 1 adverse event.

Results Three methylphenidate studies and 1 modafinil study were identified (n = 156). Results from combined psychostimulants were superior to placebo in the improvement of apathy scales score (standardized mean differences [SMD] = -0.63 (-1.22, -0.04), p = 0.04, all studies) and the MMSE score (SMD = -0.58 (-1.14, -0.02), p = 0.04, 3 methylphenidate studies). The modafinil study was excluded from the meta-analysis for the improvement of apathy scales score; therefore, the effect size increased (SMD = -0.82 (-1.43, -0.20), p = 0.009). However, no significant differences were observed in terms of other outcomes, including safety outcomes between the treatment groups.

Discussion Methylphenidate would be effective in treating apathy and cognitive impairment in AD patients.

Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder. Recently, Chicago health and aging population study showed that the 2010 census standardized prevalence of dementia caused by AD was 14.5% (95% confidence interval [CI] = 13.7–15.3), and the annual incidence rate was 2.3% (1.7–2.9) [1]. The symptoms of AD are classified into cognitive impairment and behavioral disturbances [2]. Behavioral disturbances include various psychiatric symptoms, such as depression, apathy, psychosis, anxiety, agitation, and sleep disturbances [2]. A recent systematic review and meta-analysis showed that memantine treatment is beneficial for psychosis, agitation, and sleep disturbances in patients with AD [3]. However, apathy is the most common neurobehavioral symptom associated

with AD, but currently approved anti-dementia drugs do not improve this symptom [4].

The pathophysiology of apathy includes impairment of dopaminergic neurotransmission in the brain areas, such as the ventral tegmental area [5, 6]. Prolonged exposure to amyloid oligomers decreases the release of glutamate and gamma-aminobutylic acid, reducing the possibility of dopamine release in the prefrontal cortex and hippocampus [5]. The progressive decrease of glutamate release from the prefrontal cortex reduces the stimulus for dopamine release in the nucleus accumbens, resulting in apathy [5]. Patients with AD and apathy show a blunted subjective response to dextroamphetamine challenge [7], suggesting that the use of psychostimulants increasing dopamine levels in the brain may improve

apathy. A recent double-blind, randomized, placebo-controlled trial (DBRPCT) of methylphenidate ($n = 60$), a psychostimulant, showed that this drug improved the apathy evaluation scale-clinician version (AES-C) [8] score in patients with AD as compared with a placebo [9]. However, another DBRPCT of methylphenidate ($n = 60$), which used the apathy evaluation scale-informant (AES-I) [10], did not show this effect in patients with AD [11]. Thus, the efficacy of methylphenidate remains inconclusive (► **Table 1**). The low statistical power (insufficient sample size) of these studies might make them difficult to accurately estimate the efficacy of methylphenidate. A meta-analysis can increase the statistical power of group comparisons and overcome the limitations of sample size in underpowered studies [12]. A recent meta-analysis reported that methylphenidate was superior to placebo in the improvement of apathy scales score [4]. When different studies use different scales, the Cochrane handbook recommends using random-effects models and standardized mean difference (SMD) analysis [12]. Our meta-analysis aimed to fill the gap in the literature in terms of the efficacy and safety of psychostimulants for the treatment of patients with AD. Therefore, we conducted a comprehensive systematic review and random-effect model meta-analysis (using SMD for continuous outcomes and risk ratios (RRs) for dichotomous outcomes as the response measures). This study aimed to produce conclusive evidence for the efficacy (improvement of apathy, cognitive impairment, activity of daily living, and burden of caregiving) and safety (discontinuation rate and incidence of individual adverse events) of a pooled psychostimulant group in patients with AD. We conducted this systematic review and meta-analysis by combining 2 psychostimulants (methylphenidate and modafinil) to overcome the limitations of sample size in underpowered studies.

Methods

This meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analyses guidelines [13]. The DBRPCTs using psychostimulants for AD were selected. Double-blind, randomized, placebo-controlled, crossover trials (DBRPCCOT) were included to increase the sample size for the meta-analysis. A systematic literature search was conducted according to the following aspects: patient (AD), intervention (psychostimulants), comparator (placebo), and outcomes (efficacy and safety outcomes). The review has been registered with PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>. CRD42018085983).

Search strategy

To identify relevant studies, 2 authors (T.K. and K.S.) independently searched databases, such as MEDLINE, Cochrane library, and Scopus, without language restrictions from the date of inception of these databases to January 6, 2019 using the following keywords: (random *) AND (stimulant OR psychostimulant OR methylphenidate OR cathinone OR methcathinone OR cocaine OR dexamethylphenidate OR amphetamine OR methamphetamine OR 3,4-methylenedioxymethamphetamine OR dextroamphetamine OR lisdexamfetamine OR atomoxetine OR modafinil OR armodafinil OR dexamphetamine OR bupropion OR mazindol OR selegiline) AND (Alzheimer *). The authors also searched the following to ensure the comprehensive inclusion of randomized controlled trials and

to minimize the possibility of publication bias: clinicaltrials.gov (<http://clinicaltrials.gov/>), ISRCTN registry (<https://www.isrctn.com/>), and international clinical trials registry platform (<http://www.who.int/ictrp/en/>). The authors independently evaluated the inclusion/exclusion criteria and selected the relevant studies. The references of the included articles and reviews were also searched for the citations of additional relevant published and unpublished studies, including conference abstracts.

Data sources, studies sections, and data extraction

The outcomes of our study were apathy (primary) scale score (i. e., frontal systems behavior scale apathy [14] from 1 study [15], AES-I from 2 studies [11, 16], and AES-C from 1 study [9]), mini-mental state examination (MMSE) score [17], instrumental activities of daily living scale (IADL) score [18], Zarit burden interview [19] score, all-cause discontinuation rate, discontinuation due to adverse events, and incidence of individual adverse event. For evaluating apathy, 1 study [15] used frontal systems behavior scale apathy, 2 studies [11, 16] used both AES-I and neuropsychiatric inventory (NPI) apathy score [20], and another study [9] used AES-C. There were 2 studies using the NPI apathy score. However, because the results of these 2 studies were consistent (► **Table 1**), we did not perform a meta-analysis using only the data of NPI apathy score. Where possible, an intention-to-treat or a full analysis set population was used. Although period 1 data was not available (before crossover) for crossover studies, we used those data for meta-analysis. If the data required for meta-analysis were missing, the investigators or the industries of the relevant study were contacted and asked to provide the unpublished data. Moreover, we extracted data from previous systematic reviews and meta-analyses [4].

Data analysis

The meta-analysis was conducted using the review manager software (version 5.3 for Windows; <http://tech.cochrane.org/revman>), and a random-effects model was selected because of the potential heterogeneity across several studies. Continuous outcomes were analyzed using SMD with 95 % CIs. Lower MMSE and IADL scale scores indicated a higher level of impairment or more severe symptoms; hence, the algebraic sign of the numerical scores was reversed for these scales. Dichotomous outcomes were presented as RRs. The methodological quality of the selected trials was assessed according to the risk of bias criteria in the Cochrane handbook for systematic reviews of interventions [12]. Study heterogeneity was evaluated using the heterogeneity statistic (I^2), considering $I^2 \geq 50\%$ to reflect considerable heterogeneity [21]. A sensitivity analysis was conducted for primary outcomes with considerable heterogeneity, methylphenidate studies vs. modafinil study, [1] and DBRPCTs vs. DBRPCCOT [2]. Because a funnel plot is generally used only if 10 or more studies are included in the meta-analysis, we did not utilize this plot for exploring potential publication bias [12].

Results

Of the 617 studies initially identified by searching the literature, 407 were excluded after reviewing the titles and abstracts. Reviewing the full text resulted in the exclusion of 1 systematic review and

► **Table 1** Characteristics of included double-blind, randomized, placebo-controlled trials.

(1) Study, (2) Country, (3) Sponsorship	Total n	Methods (1) Study design (2) Duration	Patients (1) Diagnosis (2) Inclusion criteria (3) Study defined disease severity	Intervention	N	Age (mean±SD), years	Male (%)	Race (%)	Apathy scales at baseline (mean±SD)	Efficacy outcomes ^a
Frakey 2012, USA, industry	23	(1) DBRPCT (2) 8w	(1) AD, NINCDS-ADRD (2) clinically elevated symptoms of apathy based on FrSBe scale, stable dose of ChEI for 30 days (3) mild to moderate	MOD 200mg/d	11	75.3±8.34	NR	NR	FrSBe apathy: 95.6±10.8	MOD = PLA: FrSBe apathy, IADL, DAFS, Zarit
				PLA	11	79.4±7.62	NR	NR	FrSBe apathy: 88.9±12.0	
Herrmann 2008, Canada, non industry	13	(1) DBRPCT (2) 5w (2w treatment phases with a 1w placebo washout between phases)	(1) AD, NINCDS-ADRD (2) age ≥55 y, MMSE≥10, NPI apathy≥1, stable dose of ChEI for at least 3 m (3) mild to moderate	MET 20mg/d	13	77.9±7.8	46.2	NR	AES: 48.3±11.0	MET > PLA: AES-I, NPI apathy MET = PLA: NPI total, MMSE
				PLA	12					
Padala 2017, USA, non industry	60	(1) DBRPCT (2) 12w	(1) AD, DSM-IV (2) MMSE≥18, AES-C≥40, stable dose of ChEI for at least 4 m or antidepressants for at least 2 m (3) mild	MET 20mg/d	30	77.0±7.5	100	Non-Hispanic Caucasian 93.3	AES-C: 51.8±7.1	MET > PLA: AES-C, IADL MET = PLA: MMSE, Zarit
					30	76.2±8.5	100	Non-Hispanic Caucasian 100	AES-C: 47.9±5.7	
Rosenberg 2013, USA and Canada, non industry	60	(1) DBRPCT (2) 6w	(1) AD, NINCDS-ADRD (2) MMSE≥10, clinical stability as judged by the local investigator, clinically significant apathy for at least 4 w (NPI apathy frequency of “often” or greater and an apathy severity of “moderate” or “marked”), stable dose for the prior 3 m, if treated with a SSRI (3) mild to moderate	MET 20mg/d	29	78.0±8	41	Non-Hispanic Caucasian 97	AES: 50±13	MET > PLA: NPI apathy MET = PLA: AES-I
				PLA	31	75.0±9	35	Non-Hispanic Caucasian 87	AES: 51±11	

a, primary outcomes in each study are underlined. AD: Alzheimer disease, IADL: instrumental activities of daily living, AES-C(Or -I): Apathy Evaluation Scale–Clinician (–Informant), d: day, DAFS: Direct Assessment of Functional Status, DBRPCT(CO)T: double-blind randomized, placebo-controlled (crossover) trial, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, FrSBe: Frontal Systems Behaviour Scale, m: month, MET: methylphenidate, MMSE: Mini-Mental State Examination, MOD: modafinil, n: number of patients, NINCDS-ADRD: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association, NPI, Neuropsychiatric Inventory: NR, not reported, PLA: placebo, SD: standard deviation, USA: United States of America, w:week, Zarit: Zarit Burden Interview.

meta-analysis study [4] (Supplementary ► Fig. 1S). No additional studies were retrieved further from the clinical trial registries.

Risk of bias

Three of 4 studies were DBRPCTs, and one was DBRPCCOT [16] (Supplementary ► Fig. 2S). Although this DBRPCCOT did not report the data obtained before crossover, we used crossover data for the meta-analysis. The primary outcome of all the studies was improvement in the apathy scale score. One of 4 studies was sponsored by the industry [15]. Two of 4 studies did not have any high risk of bias [9, 11].

Study selection and characteristics

We identified 4 randomized trials that compared psychostimulants and placebo in 156 patients with AD (► Table 1). All the studies were published in English and were conducted in the USA and/or Canada. The study duration ranged 2–12 weeks. Sample sizes ranged from 13–60. All the studies used standardized diagnostic criteria, including the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (3 studies) or the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (1 study). The mean age of the patients was 76.8 years.

Results of the efficacy outcomes in individual studies included in the current systematic review and meta-analysis

A study by Frakey (2012) has reported that modafinil was not superior to placebo in the improvement of the frontal systems behavior scale apathy score, IADL score, and Zarit burden interview score [15].

A study by Herrmann (2008) has shown that although methylphenidate was superior to placebo in the improvement of the AES-I and NPI apathy scores, no significant differences were observed in the MMSE score between the groups [16].

Padala (2017) has reported that although methylphenidate was superior to placebo in the improvement of the AES-C and IADL scores, no significant differences were observed in the MMSE and Zarit burden interview score between the groups [9].

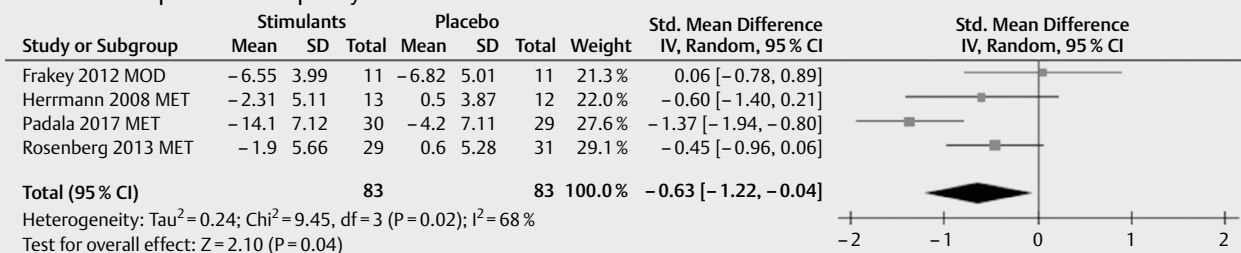
In 2013, Rosenberg has shown that methylphenidate was superior to placebo in the improvement of the NPI apathy score, but no significant differences were observed in the AES-I score between the groups [11].

Synthesized findings

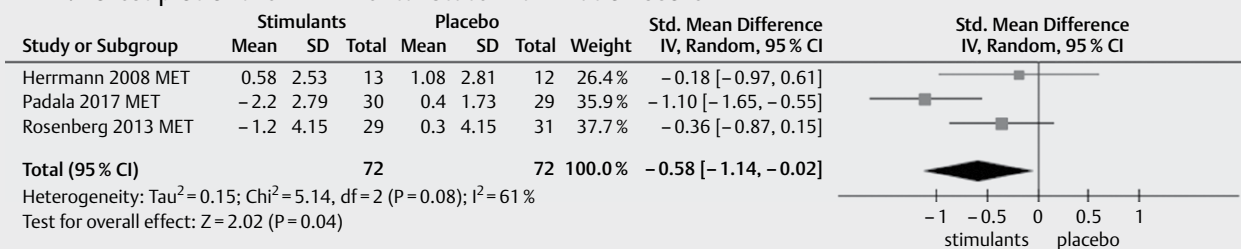
Combined psychostimulants were superior to placebos in the improvement of the apathy scale score (SMD = -0.63 (-1.22 , -0.04), $p = 0.04$, $I^2 = 68\%$, based on all included studies; (► Fig. 1-1) and MMSE score (SMD = -0.58 (-1.14 , -0.02), $I^2 = 61\%$, $p = 0.04$, based on the 3 methylphenidate studies; (► Fig. 1-2). However, no significant differences were observed with respect to other outcomes between the treatment groups (Supplementary ► Figs. 3S–8S).

Because we detected a considerable heterogeneity for the primary outcome, we conducted 2 sensitivity analyses. When the data of 1 modafinil study were excluded from the meta-analysis for the improvement of the apathy scales score, methylphenidate was found to be superior to placebo (SMD = -0.82 (-1.43 , -0.20), $p = 0.009$, $I^2 = 66\%$). When the data of 1 DBRPCCOT were excluded from the meta-analysis for the improvement of the apathy scale score, combined psychostimulants were not superior to placebo (SMD = -0.63 (-1.41 , 0.16), $p = 0.12$, $I^2 = 79\%$).

1 – 1. Forest plot of the apathy scale score



1 – 2. Forest plot of the Mini-Mental State Examination score



► Fig. 1 1 Forest plot of the apathy scale score. 2 Forest plot of the Mini-Mental State Examination score. (period) 95% CIs: 95% confidence intervals, IV: inverse variance, M-H: Mantel-Haenszel, MET: methylphenidate, MOD: modafinil, SD: standard deviation, Std mean difference: standardized mean difference

Discussion

We performed a comprehensive systematic review and meta-analysis to obtain robust evidence of the efficacy and safety of the combined psychostimulants in patients with AD. Methylphenidate was found to improve apathy and cognitive impairment in patients with AD. It is a drug approved by the U.S. Food and Drug Administration [22] for the treatment of attention deficit hyperactivity disorder and narcolepsy. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increases the release of these monoamines into the extraneuronal space [22]. The pathophysiology of apathy and cognitive impairment includes hypofunction of dopamine neurons in the brain [5, 6]. Methylphenidate can improve these symptoms by restoring the normal function of dopamine neurons. Although the study duration included in the current meta-analysis was short, no significant differences were observed in discontinuation rate as well as incidence of at least 1 adverse event between psychostimulants and placebo. However, the meta-analysis did not include other safety outcomes, as insufficient data was available on these outcomes.

Because we detected considerable heterogeneity in the primary outcome, we conducted 2 sensitivity analyses; however, these did not reveal any confounding factors. The considerable heterogeneity might have been observed because of small sample sizes. Because we did not utilize funnel plot for exploring potential publication bias, our study results might include a publication bias. Moreover, because the number of RCTs and patients included in our meta-analysis was small, we cannot rule out a “small study effect,” in which smaller studies tend to show larger treatment effects than larger studies [23].

Limitations

First, the number of studies and patients included in this meta-analysis are limited. Second, because all the included studies had short trial durations, we could not determine whether psychostimulants would have long-term effects on apathy and cognitive impairment. Although the use of psychostimulants poses a risk of drug dependence, cardiovascular disease, psychiatric symptoms, such as psychosis and mania, as well as seizures [22], the current systematic review and meta-analysis did not evaluate the association between psychostimulants and these risks in patients with AD. Moreover, we did not perform a meta-analysis in terms of safety outcomes other than discontinuation rate and incidence of at least 1 adverse event. Third, because a funnel plot is generally used only if 10 or more studies are included in the meta-analysis, we did not utilize such method for exploring potential publication bias [12].

Conclusions

Our results suggest that methylphenidate is effective in treating apathy and cognitive impairment in patients with AD. However, the number of patients and studies included in the current systematic review and meta-analysis was limited. Moreover, the duration of the included studies was short. Therefore, we considered that a long-term study with larger sample size must be conducted to obtain robust results.

Contributors

All authors had full access to all study data and are responsible for the integrity of the data and the accuracy of any data analysis. All authors drafted the final manuscript.

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Competing Interests

The authors have declared that there are no conflicts of interest in relation to the subject of this study. We have had the following interests within the past 3 years. Dr. Kishi has received speaker's honoraria from Daiichi Sankyo, Dainippon Sumitomo, Eisai, Janssen, Kyowa, Meiji, MSD, Otsuka, Tanabe-Mitsubishi and Yoshitomi, and has received a Health Labor Sciences Research Grant, Grant-in-Aid for Scientific Research (C), and a Fujita Health University School of Medicine research grant. Dr. Sakuma has received speaker's honoraria from Otsuka and Torii and has received a Grant-in-Aid for Young Scientists. Dr. Iwata has received speaker's honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, Glaxo-SmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer and has had research grants from Daiichi Sankyo, Dainippon Sumitomo, Meiji, and Otsuka.

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