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A Systematic Review on the Pharmacologic Treatment of Apathy in Dementia

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ABSTRACT

Introduction: Dementia is a neurocognitive disorder that causes functional impairment usually accompanied by neuropsychiatric symptoms. Majority of individuals with dementia suffer from behavioral dysfunction. Apathy, defined as presence of diminished initiative, interest and emotional expression, is a common neuropsychiatric symptom of dementia which currently has no established pharmacologic treatment.

Methodology: This systematic review was performed according to the PRISMA using the databases, PubMed, Cochrane, Embase, CINAHL, Web of Science, and Google Scholar. The study evaluated six randomized controlled trials (RCT) that addressed the pharmacologic treatment of apathy in dementia.

Results: A total of 484 subjects with dementia were assigned randomly to both the pharmacologic treatment and control groups. Those under pharmacologic treatment were given methylphenidate, sertraline, escitalopram, nicergoline, modafinil, and bupropion. Outcomes such as apathy evaluation scale (AES), digit span (DS), neuropsychiatric inventory (NPI), frontal systems behavior scale (FrSBe), and Alzheimer's Disease cooperative study clinical global impression of change (ADCS-CGIC) were assessed. Among the six RCTs, significant outcomes with methylphenidate were noted with improvement in AES at 55+11 ($p=0.06$) at 6 weeks and AES (-9.9, 95% CI=-13.6 to -6.2, $p<0.001$) at 12 weeks. There was also noted improvement in apathy score (AS) from baseline for those taking sertraline from 20.8+5.2 to 16.8+6.1 with $p=0.05$.

Conclusion: This study revealed that methylphenidate 10mg tab twice daily and sertraline with an average dose of 31.8mg per day were efficacious and well-tolerated treatments in the management of apathy in dementia.

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Introduction

Dementia is defined as a state of significant cognitive decline from a previous level of performance in one or more cognitive domains that interferes with everyday activity [1]. Its global incidence has doubled and between 2015-2050, the increase is predicted to be 223% in lower to middle-income countries, such as the Philippines. Dementia is the 5th leading cause of death globally accounting for 2.4million deaths per year [2]. Several reports indicate that, aside from the decline in performance of cognitive domains, approximately 90% of patients with dementia suffer from behavioral and psychological symptoms of dementia (BPSD). Apathy is a highly prevalent form of BPSD across different forms of dementia, present in 62-65% of cases [3-5]. A consensus diagnostic criteria for apathy was introduced by Miller D, et al, which states that an individual diagnosed with neurocognitive disorder manifests with diminished initiative, interest, emotional expression/responsiveness that persists for more than 4 weeks causing significant functional impairment [6,7]. The neuropathology of apathy in dementia is linked to increased neurofibrillary tangle8, neuronal loss and increased tau levels in the CSF [8,9]. Implicated in the lack of self-initiated behavior involves the mesolimbic-mesocortical pathway and the nigrostriatal dopamine pathway [10]. Further, serotonergic, cholinergic, and noradrenergic systems are also crucial for the functionality of the circuits interconnecting the amygdala, ventral striatum, and prefrontal cortex [10]. The loss of cognitive goal-directed behavior also involves the dorsal prefrontal cortex while the affective dysfunction involves the orbito-mesial frontal cortex and basal ganglia particularly the ventral striatum [7,11]. Hence, dysfunction in the dopaminergic system which has a role in the reward circuit as well as the cholinergic, serotonergic, and noradrenergic systems which regulate the function of the limbic system and prefrontal cortex will contribute to the occurrence of apathy [12,13].

Currently, there is no established intervention for the management of apathy in patients with dementia. Several nonpharmacological interventions were studied, however, their efficacy remain limited [3]. Hence, this study aims to review pharmacologic treatment in the management of apathy in dementia patients based on the most current evidence.

Methodology

The review process was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram to identify and appraise all relevant studies. Identification of relevant studies with the help of the following databases, PubMed, Cochrane, Embase, CINAHL, Web of Science and, Google Scholar was done using search terms such as dementia, apathy, and medications with inclusion of Boolean search operators such as "and", "or" and "not" (Figure 1). Further search includes inclusion criteria such as patients with dementia, >60 years old, with apathy and are on pharmacologic treatment or medications on apathy. Studies included were on randomized controlled trials (RCT), published in English and peer-reviewed. Further, only studies from January 2010 to June 2024 were included. Studies whose populations with other comorbid conditions causing memory loss (e.g. traumatic brain injuries, neoplasm, central nervous system infection, and other structural causes) as well as articles that discussed nonpharmacologic treatment were excluded. The search terms such as apathy, dementia, and medications and their keyword combinations were used (Figure 1). Data were independently extracted using a standardized data collection form by the Cochrane Effective Practice and Organization of Care group.

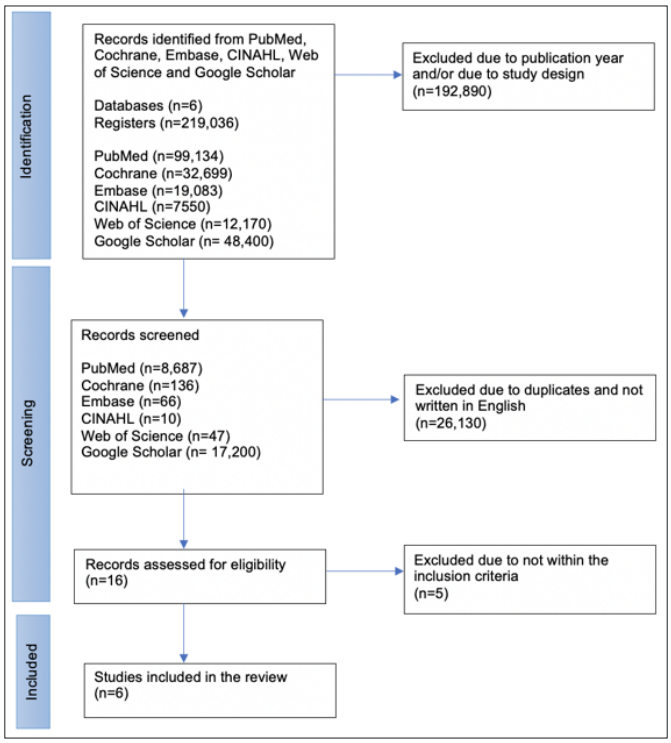

Figure 1: Prisma Flow Diagram

The reviewer compiled recorded findings into a table detailing category: author & year published, sample size, median age, diagnosis, treatment and dosage, duration, and measurement tools (Table 1).

Results

The online searches performed in January 2010 to June 2024 retrieved 219,036 records. In addition, after the exclusion and removal of duplicates, 11 studies were screened and lastly 6 studies were read and reviewed in full text (Table 1).

Table 1: Summary of Findings

Author & Year Published	Sample size (N) and median age (A)	Diagnosis	Treatment & Dosage	Duration	Primary Outcomes Assessed	Results
Lanctôt, K., et al. (2013)	N = 60 (M:23; F:37) A = 76	Mild to moderate Alzheimer's Disease	Methylphenidate (10 mg) PO BID	6 weeks	AES DS	17 subjects with improved AES at 55±11(p=0.06) DS total (δ=1.01 (95% CI: 0.09–1.93), p=0.03) favored MPH
Mintzer, J., et al. (2021)	N = 200 (M:131; F:68) A = 76	Mild to moderate Alzheimer's Disease	Methylphenidate (10 mg) PO BID	6 months	NPI ADCS-CGIC	NPI mean diff=-1.25; 95% CI-2.03 to -0.47; P=0.002 ADCS odds ratio 1.90 (95% CI, 0.95-3.84; p=0.07)
Padala, P., et al. (2018)	N = 60 A = 76	Mild Alzheimer's Disease	Methylphenidate (10mg) PO BID	12 weeks	AES; AES domains	AES (-9.9, 95% CI=-13.6 to -6.2, p<0.001) Behavioral domain (-2.6, 95% CI=-4.0 to -1.2, p<0.001) Cognitive domain (-3.6, 95% CI=-5.5 to -1.6, p<0.001) Emotional domain (-1.1, 95% CI=-1.8 to -0.4, p=0.003) Motivation domain (-1.6, 95% CI=-2.5 to -0.6, p=0.001)
Takemoto, M., et al. (2020)	N = 33 (M:10; F:23) A = 77	Alzheimer's Disease	Sertraline (31.8 mg) Escitalopram (7.3 mg) Nicergoline (14.5 mg)	3 months	AS	Sertraline: baseline 20.8±5.2 to 3 mos 16.8±6.1; P=0.05 Escitalopram: baseline 20.3±8.2 to 3 mos 17.5±6.3; P=0.42 Nicergoline: baseline 16.9±7.7 to 3 mos 18.2±5.7; P=0.36
Frakey, L., et al (2012)	N=23 A=75	Mild to moderate Alzheimer's Disease	Modafinil 200mg OD	8 weeks	FrSBe	FrSBe experimental: 95.64 to 89.09 FrSBe control: 88.91 to 82.09 P=0.157
Maier, F, et al (2020)	N=108 (M: 67; F: 41) A=75	Mild to moderate Alzheimer's Disease	Bupropion 150mg OD x 4 wks then 300mg OD x 8wks	12 weeks	AES-C	AES-C mean change, 2.22; 95% CI, -0.47 to 4.91; p=0.11

N: sample size; **A:** age; **M:** male; **F:** female; **AES:** Apathy Evaluation Scale; **DS**: Digit span; **AS:** Apathy Scale; **AES-C:** Apathy Evaluation Scale-Clinician Version; **NPI:** Neuropsychiatric Inventory; **ADCS-CGIC:** Alzheimer's Disease Cooperative Study Clinical Global Impression of Change; **FrSBe:** Frontal Systems Behavior Scale

The size of the studies reviewed was between 23 and 200 subjects, with a total of 484 subjects with dementia, assigned randomly to both the pharmacologic treatment and control groups. Most of the subjects in the trials stayed in hospitals while some were assessed in the community.

Lanctot K, et al, and Minzter J, et al, evaluated the effect of methylphenidate on patients with dementia under the Apathy in Dementia Methylphenidate Trial (ADMET) and ADMET 2 trial [14,15]. Subjects were randomized to methylphenidate or placebo. The methylphenidate group was started initially on 5mg tab twice daily for 3 days and the dose was titrated to 10mg tab twice daily for 6 weeks and 6 months period respectively [14,15]. Lanctot K, et al, included subjects with mild to moderate AD using the MMSE as a tool for their diagnosis combined with significant apathy using the AES tool [14]. Sixty AD patients were enrolled in the study and assessments were performed at baseline, 2nd week, 4th week, and 6th weeks. Of the 60 randomized subjects, 57 completed the study with 17 subjects showed improved apathy scores from AES 51+12 to 55+11. Those who responded to methylphenidate had a significant change in attention score as well at p=0.03 using the digit span [14].

Due to the limited study period by the ADMET trial, results and a number of subjects were lacking. Hence, the ADMET 2 trial extended the administration of methylphenidate to 6 months. The study included patients diagnosed with possible and probable AD using the National Institute of Neurological and Communicative Disorders and Stroke/ Alzheimer's Disease and Related Disorders (NINDS-ARD) and MMSE with significant apathy using the NPI apathy subscale [15]. Subjects were randomized to methylphenidate or placebo in 1: 1 ratio using the SAS statistical software and of the 307 subjects screened, 52 did not pass the screening process and 55 were not eligible following the baseline eligibility criteria [15]. The 200 remaining subjects were randomized, 99 were assigned to methylphenidate and 101 to placebo. The study observed that a significant difference between methylphenidate groups in the NPI apathy score from baseline was noted compared with the placebo group (mean difference = −1.25; 95% CI, −2.03 to −0.47; P = .002) [15]. The largest change in NPI apathy occurred during the first 2 months of treatment. ADCS-CGIC at 6 months showed improvement at 43.8% (39 of 89) of subjects in the

methylphenidate group compared with 35.2% (32 of 91) in the placebo group. The odds ratio of having an improved rating on the ADCS-CGIC for methylphenidate compared with placebo was 1.90 (95% CI, 0.95-3.84; P = .07), favoring methylphenidate over placebo [15]. The adverse events noted in the reviewed trials were the weight loss of 7% from baseline body weight among subjects in the methylphenidate group [15]. There was only one serious adverse event noted which was the presence of seizure in the methylphenidate arm leading to hospitalization [15].

Furthermore, Padala P, et al, studied methylphenidate for apathy in community-based setting for 12 weeks from which patients were given initially with methylphenidate 5mg tab twice daily and titrated to 10mg tab twice daily after 2 weeks for 12 weeks duration [16]. Sixty eligible subjects were included and randomized. The assessments were done on 4th week, 8th week and, 12th week visit using the Apathy Evaluation Scale- Clinician Version (AES-C) with domains. One primary outcome of the study was a significant difference over time for apathy in the methylphenidate group with a mean difference of -9.9 compared to the placebo group [16]. The improvement was driven by improvements in multiple apathy domains. The behavioral domain had greater improvement in the methylphenidate group compared with the placebo group at 12 weeks (-2.6, 95% CI=-4.0 to -1.2, p<0.001). The cognitive domain showed greater improvement (-3.6, 95% CI=-5.5 to -1.6, p<0.001). The emotional domain favoring the methylphenidate group reached statistical significance only at 12 weeks (-1.1, 95% CI=-1.8 to -0.4, p=0.003). Lastly, the motivation domain improved (-1.6, 95% CI=-2.5 to -0.6, p=0.001).19 As for the adverse events, there was a report of dizziness and insomnia however these did not prompt hospitalization among the study participants and were managed symptomatically [16].

In the study by Takemoto M, et al, dementia subjects were determined using the NINDS-ADRD criteria and used the MMSE [17]. It determined the Apathy Scale (AS), from which all of the subjects have high AS with a score of >16. The study enrolled 33 subjects who were randomly assigned to escitalopram group=13; sertraline group=11; and nicergoline group=9. Doses given were escitalopram at an average of 7.3mg per day, sertraline at 31.8mg per day average dose, and nicergoline at 14.5mg per day average dose for a duration of 3 months. The result of the study revealed that the sertraline group showed significant improvement in AS score from baseline (20.8 ± 5.2) to 3 months (16.8 ± 6.1, p = 0.05) compared to the escitalopram group and nicergoline group. Further, adverse effect of the different medications was not recorded in the study [17].

Furthermore, a study by Frakey L, et al, included 23 subjects with mild to moderate AD using the NINDS criteria who were randomized into the modafinil group (n=11) and given 100mg tab in the morning for 1 week then titrated to 200mg tab in the morning for 7 weeks versus the placebo group [18]. Both the experimental and control groups showed reductions in apathy on the Frontal Systems Behavior Scale (FrSBe) from 95.6 to 89.09 and 88.91 to 82.09 respectively. However, these reductions showed no significant difference in the apathy score in both modafinil and placebo group p=0.157 [18].

Lastly the study by Maier F, et al, initially had 140 subjects but only 110 were included due to a decline in participation and screening failure with the diagnosis of dementia using the NINDS and MMSE [19]. The 110 subjects were randomized to the bupropion group who were given 150mg once a day then titrated to 150mg tab twice daily after 4 weeks versus the placebo for a study duration of 12 weeks. Outcome measure which is the AES-C was assessed at baseline, 4 weeks, 8 weeks, and 12 weeks. The study showed no significant change in the AES-C score between the bupropion group and placebo groups (mean change, 2.22; 95% CI, -0.47 to 4.91; p=0.11) [19]. The adverse effects were noted in 39 subjects under bupropion, 5 required hospitalization but were unrelated to the study medication and no death occurred. The most frequent adverse effects noted were gastrointestinal symptoms among 6 patients under the bupropion group [19].

Risk of Bias Analysis

The risk of bias for the six studies included in the review was marked low across all five domains as calculated using the Revised Cochrane risk-of-bias tool for randomized trials (Table 2).

Table 2: Summary of Risk of Bias Analysis using the RoB 2 Method

	Domain 1 Randomization	Domain 2.2 Effect of Adherence	Domain 3 Attrition	Domain 4 Detection	Domain 5 Reporting
Lanctôt K, et al.	low	low	low	low	low
Padala P, et al.	low	low	low	low	low
Mintzer J, et al.	low	low	low	low	low
Takemoto M, et al.	low	low	low	low	low
Frakey L, et al.	low	low	low	low	low
Maier F, et al.	low	low	low	low	low

Discussion

This systematic review evaluated the pharmacologic treatments of apathy in dementia. Six randomized controlled trial articles were reviewed, and this study determined that methylphenidate and sertraline were efficacious and safe medications that can be used in the treatment of apathy in dementia. Other psychostimulant drugs such as modafinil and bupropion did not show any significant improvement in apathy among dementia patients.

Methylphenidate

Methylphenidate acts by blocking the reuptake of two neurotransmitters, dopamine, and norepinephrine (NE) in presynaptic neurons. More specifically, it inhibits the transporters of these neurotransmitters, increasing the concentration of dopamine and NE in the synaptic cleft creating its classic stimulant effect within the central nervous system (CNS), mainly in the prefrontal cortex [20]. As a psychostimulant drug used in Attention Deficit Hyperactive Disorder (ADHD) and Narcolepsy, methylphenidate was also noted to improve apathy since dopaminergic neurons have projections to attention areas of the brain and these attention-associated areas show reduced activity in apathetic patients [20]. Motivation as one of the key deficits in apathy was also noted to be closely related to attentional components in reward processing [14]. These concepts were adopted and then studied by Lanctot K, et al, through the ADMET trial in 2013 and Minzter J, et al, through the ADMET 2 trial in 2021, from which both studies yielded significant results with regards to improvement in apathy in patients taking methylphenidate after the trial duration [14,15]. In addition, a community-based study by Padala P, et al, in 2018, showed the improvement on the AES-C in the methylphenidate

group which was driven by improvements in multiple apathy domains namely the cognitive, behavioral, emotional and motivational domains [16].

Sertraline

Sertraline is a selective serotonin reuptake inhibitor (SSRI) particularly acts by inhibiting presynaptic reuptake of serotonin from the synaptic cleft which increases extracellular serotonin, with the least effect on dopamine and NE levels in the amygdala and nucleus accumbens. It is commonly used in the treatment of depression. Hence, the study of Takemoto M, et al, revealed that only the sertraline group with 11 subjects showed significant improvement in AS score from baseline to 3 months compared to escitalopram and nicergoline [17].

Modafinil

Modafinil is an atypical, selective dopamine reuptake inhibitor, that indirectly activates the release of orexin neuropeptides and histamine as well as NE agonist in the hypothalamus making it a medication for narcolepsy and obstructive sleep apnea. As a psychostimulant, its mechanism of action is almost the same as that of methylphenidate and significant results were noted however most of these studies were done on animal studies [21]. Hence, the study of Frakey L, et al, showed that after 8 weeks of intake of modafinil among subjects compared to placebo, there was noted no significant difference in apathy score using the FrSBe [18].

Bupropion

Bupropion is a dopamine and NE reuptake inhibitor usually used as an antidepressant. As a dopamine reuptake inhibitor, it has been shown to increase psychomotor activity. Maier F, et al, studied the effect of bupropion on dementia patients and showed no significant change in the apathy score (AES-C) between the bupropion group and placebo groups. Further, gastrointestinal side effects were noted as the most common [19].

Through this review, methylphenidate and sertraline were two pharmacologic treatments noted to be effective and safe as medications for apathy in dementia. But among the two pharmacologic treatments, methylphenidate trials had a larger sample size of 17 and 99 based on the ADMET and ADMET2 trials respectively. The dose of methylphenidate is 10 mg tablet twice a day with its effect as early as 6 weeks and marked improvement of apathy symptoms at 2 months until 6 months. On the other hand, sertraline, although effective at 31.8mg per day for 3 months, the sample size was small at 11 subjects hence further study with larger sample size is needed in future studies.

Conclusion

Apathy is defined as an individual diagnosed with neurocognitive disorder that manifests with diminished initiative, interest, and emotional expression/responsiveness that persists for more than 4 weeks causing significant functional impairment [7]. In this systematic review, six randomized controlled trials regarding the pharmacologic treatment of apathy in dementia from January 2010 to June 2024 were evaluated. Methylphenidate and sertraline were found to be efficacious and safe in treatment of apathy in dementia. Both pharmacologic agents have mild adverse effects such as weight loss, dizziness, and insomnia. However, further studies are necessary to establish other treatment options for apathy as noted by the limited research evaluated in this study [22-25].

Limitations of the Study

The study focuses on the systematic review of the pharmacologic treatment of apathy in dementia and did not utilize meta-analysis due to varied and others having small sample sizes. The study only included RCTs published from January 2010 to June 2024.

Disclosure

The authors report no disclosures relevant to the manuscript.

Contributions

All the authors participated in the conceptualization of work. The main author (LGD), was the one who acquired and analyzed of data. All the authors participated in the drafting and revising. All the authors read and approved the final manuscript.

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