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Review Article

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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 utilized PRISMA in the evaluation of six randomized controlled trials that addressed the pharmacologic management of apathy in dementia.

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

Keywords

Apathy, Dementia, Pharmacologic treatment, Methylphenidate, Sertraline

Introduction

Dementia is defined as a state of significant cognitive decline from a previous level of performance in one or more cognitive domains which interferes in everyday activity [1]. This disorder has doubled its global incidence 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 2.4 million deaths per year [2]. Several reports indicate that aside from symptoms of cognitive decline and decline in performance of cognitive domains, approximately 90% of patients with dementia suffer from behavioral and psychological symptoms of dementia (BPSD). Apathy is highly prevalent form of BPSD across different forms of dementia [3,4]. 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 [5,6]. The neuropathology of apathy in dementia is linked to increased neurofibrillary tangle [7], neuronal loss [8], and increased tau levels in the CSF [8]. Implicated in the lack of self-initiated behavior are associated with dysfunction in neural circuits innervated by the mesolimbic-mesocortical pathway with its dopaminergic afferents from the substantia nigra pars compacta and ventral tegmental area, and by the nigrostriatal dopamine system that provides dopamine to the striatum [9]. Further, serotonergic, cholinergic and noradrenergic systems are also crucial for the functionality of the circuits interconnecting the amygdala, ventral striatum and prefrontal cortex [9]. 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 [6,10]. Hence, dysfunction in the dopaminergic system which has a role in the reward circuit as well as the cholinergic, serotonergic and noradrenergic system which regulates the function of the limbic system and prefrontal cortex will contribute to the occurrence of apathy [11,12].

Despite the high prevalence if apathy, there is no established intervention for its management in patients with dementia. Several pharmacological interventions were studied; however, their efficacies were limited [13]. Hence, this study aims to review pharmacologic treatment in the

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management of apathy in dementia patients based on 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 (Figure 1). The inclusion criteria included patients diagnosed with dementia, ≥ 60-years-old, with apathy and had pharmacologic treatment. Studies included were on randomized controlled trials (RCT), published in English and peer-reviewed. Further, only studies from year 2010 to 2022 were included. Studies whose population with other comorbid conditions causing memory loss (e.g. traumatic brain injuries, neoplasm, central nervous system infection and other structural cause) as well as articles that discussed nonpharmacologic treatment were excluded. The search terms such as apathy, dementia, medications and its 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.

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

Results

The online searches performed in 2010 and 2022 retrieved 19, 352 records. In addition, after exclusion and removal of duplicates, 11 studies were screened and lastly 6 studies were read and reviewed in full text (Table 1).

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 from community particularly the

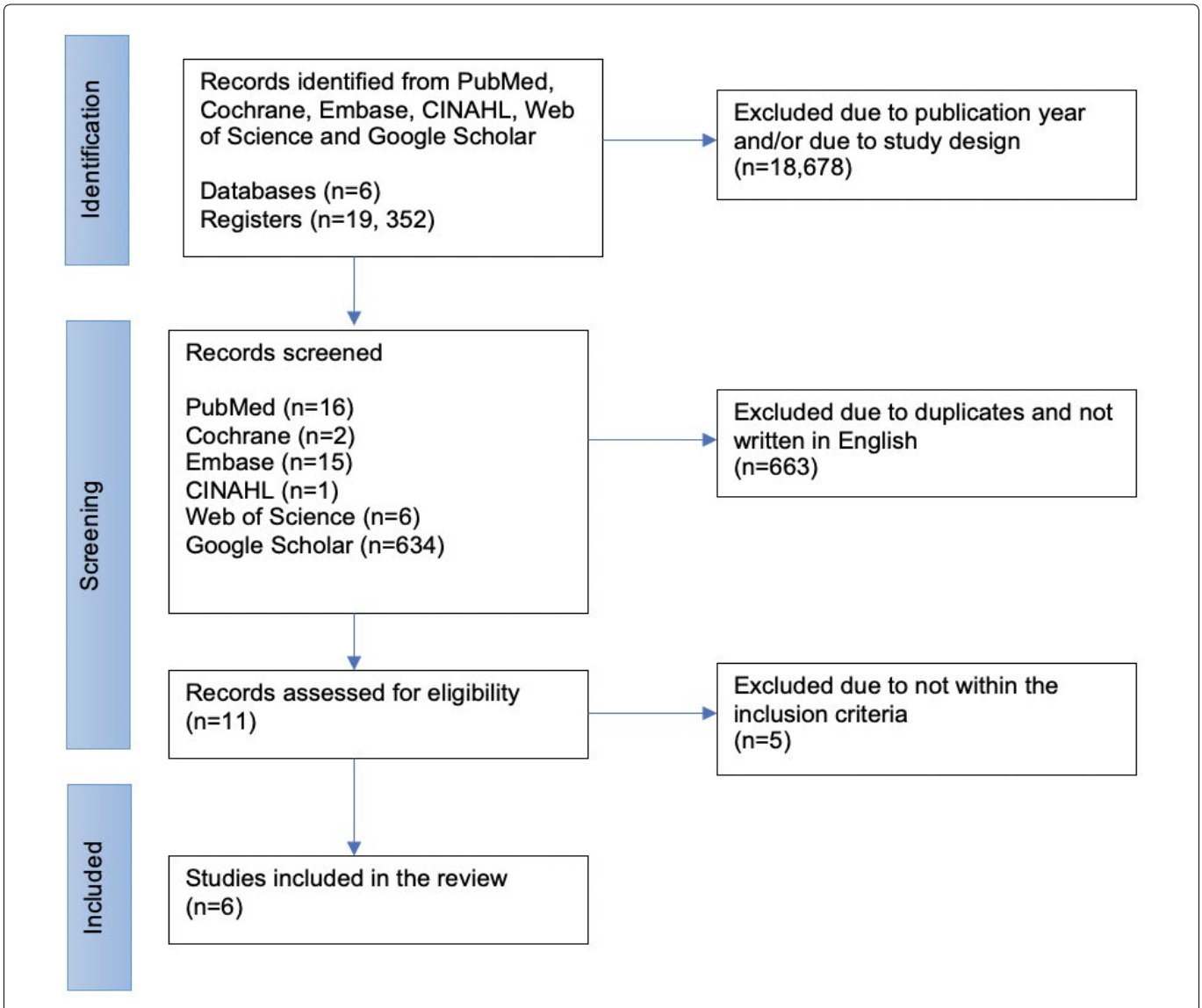

Figure 1: PRISMA flow diagram.

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) [17]	N = 60 (M:23; F:37) A = 76	Mild to moderate Alzheimer's Disease	Methylphenidate (10 mg) PO BID	6 weeks	DS AES	DS (p = 0.03) AES from baseline (p = 0.06)
Padala P, et al. (2018) [14]	N = 60 A = 76	Mild Alzheimer's Disease	Methylphenidate (10 mg) PO BID	12 weeks	AES; MMSE NPI; CGI; ZBS	AES (p = 0.001) MMSE (2.6, 95% CI = 1.1-4.0, p = 0.001) NPI (2.3, 95% CI = 0.7-3.9, p = 0.005) CGI (-1.3, 95% CI = -1.9 to -0.6, p ≤ 0.001) ZBS (-5.8, 95% CI = -10.1 to -1.4, p = 0.011)
Mintzer J, et al. (2021) [18]	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 difference = -1.25; 95% CI, -2.03 to -0.47; *P* = 0.002 ADCS-CGIC Odds ratio 1.90 (95% CI, 0.95-3.84; *P* = 0.07)
Takemoto M, et al. (2020) [15]	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; MMSE; HDS-R; GDS	AS baseline (20.8 ± 5.2) to 3 months (16.8 ± 6.1) p = 0.05 with Sertraline GDS (8.2 + 3.5) to 3 months (5.7 + 2.6) p = 0.04 with Escitalopram
Frakey L, et al. (2012) [19]	N = 23 A = 75	Mild to moderate Alzheimer's Disease	Modafinil 200 mg OD	8 weeks	FrSBe ADLQ DAFS ZBS	FrSBe (p = 0.932) ADLQ (p = 0.611) DAFS (p = 0.465) ZBS (p = 0.053)
Maier F, et al. (2020) [20]	N = 108 (M:67; F:41) A = 75	Mild to moderate Alzheimer's Disease	Bupoprion 150 mg OD × 4 wks then 300 mg OD × 8 wks	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; DS: Digit span; AES: Apathy Evaluation Scale; GDS: Geriatric Depression Scale; AS: Apathy Scale; MMSE: Mini-Mental State Examination; HDS-R: Hasegawa Dementia Rating Scale-Revised; AES-C: Apathy Evaluation Scale-Clinician Version; CGI: Clinical Global Impairment; ZBS: Zarit Burden Scale; NPI: Neuropsychiatric Inventory; ADCS-CGIC: Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change; FrSBe: Frontal Systems Behavior Scale; ADLQ: Lawton and Brody ADLQ; DAFS: Direct Assessment of Functional Status Scale

study of Padala P, et al. [14]. In the study by Takemoto M, et al., they initially determined the dementia subjects using the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders (NINDS-ADRD) criteria and used the Mini-Mental Status Examination (MMSE) as well as the Hasegawa Dementia Rating Scale (HDS-R) as assessment tools hence 33 subjects were enrolled [15]. It also determined the Apathy Scale (AS) and Geriatric Depression Scale (GDS), from which all of the subjects have high AS with a score of > 16 and GDS > 5. The subjects were divided randomly into three groups, one group was given with escitalopram at an average dose of 7.3 mg per day, one group was given with sertraline at 31.8 mg per day average dose, and one group was given with nicergoline at 14.5 mg per day average dose for a duration of 3 months. The study enrolled 33 subjects who were randomly assigned to escitalopram group = 13; sertraline group = 11; and nicergoline group = 9. The dosage of each drug was decided according to each patient's physical condition (i.e., body weight, drug sensitivity) within the optimal dose range. The result of the study revealed that 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 escitalopram group with small improvement in AS score. However, the nicergoline group showed a decline in the AS score. The other function tests such as MMSE, HDS-R, and GDS yielded no significant effect as well. Further, adverse effect on the different medications was not recorded in the study [15,16].

On the other hand, Lanctot K, et al., and Minzter J, et al. evaluated methylphenidate on patients with dementia using the design Apathy in Dementia Methylphenidate Trial (ADMET) and ADMET 2 trial [17,18]. Subjects were randomized to methylphenidate or placebo and were started initially on methylphenidate 5 mg tab twice daily for 3 days and the dose was titrated to 10 mg tab twice daily for 6 weeks (Lanctot, K et al.) and 6 months (Minzter J, et al.) period respectively [17,18]. 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 [17]. Sixty AD patients were enrolled in the study wherein one group was given methylphenidate 10 mg tab twice daily for 6 weeks while the other group was given with the placebo. Assessments were performed at baseline, 2nd week, 4th week and 6th weeks. Of the 60 randomized subjects, 57 completed the study with 17 subjects showing improved apathy score and 40 did not improved. Those who respond to methylphenidate had a significant change in attention score at p = 0.03 using the digit span with a trend towards higher baseline AES scores however was not significant at p = 0.06. Also, the study noted that baseline attention scores did not predict apathy outcome [17]. Due to the limited time brought about by the ADMET trial, another trial, the ADMET 2 extended the administration of methylphenidate among subjects for 6 months. This was studied by Mintzer J, et al. in 2021 where they included patients diagnosed with possible and probable AD using the NINDS and MMSE with significant apathy using the NPI apathy subscale [18]. 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 [18]. The 200 remaining subjects were randomized, 99 were assigned to methylphenidate and 101 to placebo. Ten study subjects in the methylphenidate group and 7 in the placebo group withdrew from the study due to missed visits occurred throughout the study, with some delayed or missed owing to COVID-19. Baseline data were missing also for 1 subject. Hence, at 6 months, using an adjusted longitudinal model, it was 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* = 0.002) [18]. The largest change in NPI apathy occurred during the first 2 months of treatment. Further, 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* = 0.07), favoring methylphenidate over placebo [18]. In addition, Padala P, et al., also studied the methylphenidate for apathy in community based setting for 12 weeks from which patients were given initially with methylphenidate 5 mg tab twice daily and titrated to 10 mg tab twice daily after 2 weeks for 12 weeks duration [14]. Sixty eligible subjects were included and randomized given with methylphenidate 10 mg twice daily or placebo for 12 weeks. One subject withdrew from each arm due to caregiver unavailability. The assessments were done on 4th week, 8th week and 12th weeks visit using the Apathy Evaluation Scale-Clinician Version (AES-C), MMSE, Zarit Burden Scale (ZBS), Clinical Global Impairment (CGI) and Cornell Scale for Depression (CSD). One primary outcome of the study was a significant difference over time for apathy in the methylphenidate group (p = 0.001) but not in the placebo group (p = 0.983) [14]. The improvement was seen in scores on the AES-C in the methylphenidate group and was driven by improvements in multiple apathy domains. The behavioral domain had greater improvement in the methylphenidate group compared with the placebo group at 8 weeks (22.4, 95% CI = 23.8 to 21.0, p = 0.001) and at 12 weeks (22.6, 95% CI = 24.0 to 21.2, p = 0.001). Similarly, the cognitive domain showed greater improvement in the methylphenidate group compared with the placebo group at 8 weeks (21.9, 95% CI = 23.9 to 0.0, p = 0.050) and at 12 weeks (23.6, 95% CI = 25.5 to 21.6, p = 0.001). Improvement in the emotional domain favoring the methylphenidate group reached statistical significance only at 12 weeks (21.1, 95% CI = 21.8 to 20.4, p = 0.003) [14]. The motivation domain improved significantly in the methylphenidate group compared with the placebo group at 8 weeks (21.3, 95% CI = 22.2 to 20.4, p = 0.009) and at 12 weeks (21.6, 95% CI = 22.5 to 20.6, p = 0.001) [14].

Furthermore, a study by Frakey L, et al., included 23 subjects with mild to moderate AD using the NINDS criteria were randomized into modafinil group (n = 11) given 100 mg tab in the morning for 1 week then titrated to 200 mg tab in the morning for 7 weeks versus the placebo group (n = 11) [19]. One subject withdrew from the study. All participants underwent a baseline assessment and re-assessment after 8

weeks using the ADLQ, Direct Assessment of Functional Status (DAFS), ZBS and apathy was assessed using the Frontal Systems Behavior Scale (FrSBe) which showed no significant difference in the apathy score in both modafinil and placebo group (p = 0.157). Also, both groups did not show significant changes in ADLQ (p = 0.611), DAFS (p = 0.465) and ZBS (p = 0.611) [19].

Lastly, a study by Maier F, et al., initially included 140 subjects but only 110 were included due to decline in participation and screening failure with the diagnosis of dementia using the NINDS and MMSE [20]. The 110 subjects were randomized to bupropion group who were given 150 mg once a day then titrated to 150 mg tab twice daily after 4 weeks versus the placebo for a study duration of 12 weeks. Outcome measures which is the AES-C was assessed at baseline, 4 weeks, 8 weeks and 12 weeks. A total of 17 subjects were excluded to bupropion group and 10 from placebo group due to protocol violation, withdrawal of consent, nonadherence and lost to follow up. 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) [20]. 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 bupropion group. The limitation of this study was the study failed to reach the estimated sample size (n = 216) [20].

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).

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. Furthermore, 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 which creates its classic stimulant effect within the central nervous system (CNS), mainly in the prefrontal cortex [21]. As a psychostimulant drug use 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 [21]. Motivation as one of the key deficits in apathy was also noted to be closely related to attentional components in reward processing [22]. 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 wherein subjects were started initially on methylphenidate 5 mg tab twice daily for 3 days and the dose was titrated to 10 mg tab twice daily for 6 weeks and 6 months period respectively [17,18]. Both studies yielded significant results with regards to improvement in attention and apathy in patients taking methylphenidate after the trial duration. It was also noted that the largest change in NPI apathy occurred during the first 2 months of treatment [18]. In addition, a study regarding the effect of methylphenidate on apathy in dementia patients was done by Padala P, et al. in 2018. Unlike the two studies of methylphenidate mentioned, this study was a community-based study focusing on veterans with mild AD. In this study, the improvement was seen in scores on the AES-C in the methylphenidate group and was driven by improvements in multiple apathy domains namely the cognitive, behavioral, emotional and motivational domains [14].

Lastly, the adverse events noted in the reviewed trials were the weight loss of 7% from baseline body weight among subjects in the methylphenidate group [18]. There was also report of dizziness and insomnia however these did not prompt hospitalization among the study participants and were managed symptomatically [14]. There was only one serious adverse event noted which was the presence of seizure in methylphenidate arm leading to hospitalization [14].

Sertraline

Sertraline is a selective serotonin reuptake inhibitor (SSRIs) particularly acts by inhibiting presynaptic reuptake of serotonin from the synaptic cleft which increases extracellular

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. (2013) [17]	low	low	low	low	low
Padala P, et al. (2018) [14]	low	low	low	low	low
Mintzer J, et al. (2021) [18]	low	low	low	low	low
Takemoto M, et al. (2020) [15]	low	low	low	low	low
Frakey L, et al. (2012) [19]	low	low	low	low	low
Maier F, et al. (2020) [20]	low	low	low	low	low

serotonin, with 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. in 2020 reviewed the efficacy of some medications namely sertraline, escitalopram, and nicergoline in the treatment of apathy in AD. The study revealed that only the sertraline group showed significant improvement in AS score from baseline to 3 months. The other function tests such as MMSE, HDS-R, and GDS yielded no significant effect and adverse reactions were not reported as well [15].

Modafinil

Modafinil is an atypical, selective dopamine reuptake inhibitor, 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 [23]. Hence, the study of Frakey L, et al., which investigates the effect of modafinil on apathy symptoms of patients with dementia. However, after 8 weeks intake of modafinil among subjects compared to placebo, there was noted no significant difference in apathy score (FrSBe), DAFS, ZBS and ADLQ scores [19].

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. Case reports of its treatment on apathy to an FTD patient as well as poststroke apathy, studies have shown significant improvement [24,25]. Maier F, et al., studied these effect among dementia particularly those with AD. The study showed no significant change in the apathy score (AES-C) between the bupropion group and placebo groups. Further, gastrointestinal side effects were noted as most common [20].

Through this review, methylphenidate and sertraline were two pharmacologic treatments noted to be effective and safe as medications for apathy in dementia. 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 at 31.8 mg per day was noted to be effective at 3 months.

Conclusion

Apathy is defined as 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]. In this systematic review, six randomized controlled trials regarding the pharmacologic treatment of apathy in dementia from 2010 until 2022 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.

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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