REVIEW

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The Role of Dopamine in Symptoms and Treatment of Apathy in Alzheimer's Disease

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SUMMARY

Background: Alzheimer's disease (AD) is characterized by a number of serious and debilitating behavioral and psychological symptoms of dementia (BPSD). The most common of these BPSD is apathy, which represents a major source of morbidity and premature institutionalization in the AD population. Many studies have identified discrete changes to the dopaminergic (DAergic) system in patients with AD. The DAergic system is closely related to the brain reward system (BRS) and some studies have suggested that dysfunction in the DAergic system may account for symptoms of apathy in the AD population. **Method:** Changes to the dopamine (DA) system in AD will be reviewed, and evidence supporting the involvement of the DAergic system in the development of apathy will be examined. Additionally, some pharmacological interventions with DA activity have been identified. The utility of these treatments in the AD population will be reviewed, with a focus on apathy as an outcome. **Results:** Evidence presented in this review suggests that DA dysfunction in discrete brain areas is an important correlate of apathy in AD and that the DAergic system may be a rational target for pharmacological treatment of apathy.

Introduction

Alzheimer's disease (AD) is a progressive and incurable neurodegenerative disease that affects a rapidly increasing number of individuals over the age of 65 [1]. It is the most common cause of dementia [2], representing a major source of morbidity and mortality in the elderly [3]. Behavioral and psychological symptoms of dementia (BPSD) are important manifestations of AD, and contribute to decreased patient and caregiver quality of life [4–6]. Apathy is a BPSD defined by Marin as a diminished level of motivation, not resulting from emotional distress, an intellectual deficit, or a decreased level of consciousness [7,8]. Apathy is the most common BPSD, affecting up to 47% of those with mild AD and up to 80% of those with moderate AD [9]. Apathetic AD patients are often unable to attend to basic activities of daily living [10], and apathy is the only BPSD that has a more marked effect on activities of daily living than impairments caused by deficits in cognition [11]. Additionally, AD patients with apathy are at a higher risk of premature institutionalization [12]; and BPSD, including apathy, substantially increase health care costs [13].

Treatment of AD since the early 1990s has focused on the cholinergic system, using cholinesterase inhibitors (ChEIs) in an effort to limit the progressive cognitive decline seen in most AD patients [14]. Recent studies suggest, however, that between 38% [15] and 60% [16] of AD patients with baseline BPSD fail to improve after ChEI treatment. There have been no randomized controlled trials (RCTs) of ChEIs that focus on apathy as a primary outcome, though some studies have noted benefits in apathy as a secondary measure or a *post hoc* analysis [17–20]. Other studies have shown that ChEIs are not necessarily effective in the treatment of behavioral symptoms, such as apathy, in the moderate-to-severely

impaired AD population [21]. In addition to ChEIs, a noncompetitive NMDA-receptor agonist, memantine, has been studied and approved for the treatment of moderate-to-severe AD. A number of RCTs have demonstrated the use of memantine in the treatment of BPSD and cognitive decline associated with AD [22–24]. Unfortunately, there have been no published RCTs that focus on apathy as a primary outcome, with only one study reporting improvements in apathy in a *post hoc* analysis [25].

In lieu of inconsistent data supporting ChEIs and memantine in the treatment of apathy and other BPSD, case reports and small open label studies [26] in the late 1990s proposed the use of psychostimulants—acting primarily on the dopaminergic (DAergic) brain reward system (BRS)—for the treatment of apathy in AD. The BRS is a widely studied neural network that is known to play a role in mediating reward behavior and guiding an individual toward ends that are considered to be rewarding [27,28]. Rewards are cognitive or biological stimuli that generate and increase the frequency of behavior that contributes to a positive emotional state [28,29]. Rewards are inherently linked to motivation [27] and are therefore—according to Marin's definition [7,8]—closely related to apathy. The neural pathways of the BRS are extensive and dysfunction of activity in the BRS is strongly related to feelings of apathy in both healthy and impaired individuals [30,31]. Hence, treatment for apathy and other behavioral symptoms in AD may theoretically be achieved by pharmacotherapies focused on the DAergic system.

This review will summarize evidence supporting the role of impaired DA activity in AD, specifically focusing on the role of DA in apathy associated with AD. Pharmacotherapies that may have a beneficial effect on the treatment of these symptoms will be summarized—focusing discussion on the function and clinical relevance of central nervous system (CNS) psychostimulants including: methylphenidate, dextroamphetamine, modafinil, bromocriptine, and amantadine. Articles were retrieved using electronic databases (MEDLINE, EMBASE) and cross-references from relevant articles. The following keywords were used: Alzheimer's disease, dementia, apathy, dopamine, dopamine metabolism, dopamine receptor, dopamine transporter, SPECT, PET, MRI, methylphenidate, dextroamphetamine, modafinil, amantadine, bromocriptine

The Dopaminergic System in AD

DA is a complex neuromodulator, which is neither strictly excitatory nor strictly inhibitory—but rather depends on the functional state of target neurons [32]. DA binds to five distinct DA receptors, divided into two general categories by downstream signaling cascade: D_1-like receptors (D_1 and D_5) and D_2-like receptors (D_2, D_3, D_4) [32]. DA levels in the synapse are regulated by the dopamine transporter (DAT), which is located on the presynaptic membrane of DAergic neurons and is responsible for the reuptake of DA, thus terminating its activity in the synapse [33,34]. The neural pathways of the BRS are extensive, originating in the substantia nigra and ventral tegmental area and projecting extensively throughout the brain, reaching the nucleus accumbens, striatum, amygdala, hippocampus, medial prefrontal cortex, cerebral cortex, thalamus, and olafactory cortex [28,35]. DAergic activity is separated into four major anatomical pathways—the nigrostriatal, the mesolimbic, the mesocortical, and the tuberoinfundibular [36]. This discussion will focus on the nigrostriatal, mesolimbic, and mesocortical pathways. The nigrostriatal pathway connects the substantia nigra with the striatum, and is strongly implicated in movement disorders and Parkinson's Disease [36]. The mesolimbic pathway begins in the ventral tegmental area and projects to the nucleus accumbens in the striatum, the amygdala, the hippocampus, and the medial prefrontal cortex [35]. The mesocortical pathway connects the ventral tegmental area to the cerebral cortex, and is closely associated with the mesolimbic pathway [35]. Both the mesocortical and mesolimbic pathways are involved in the BRS, and are implicated in feelings of motivation and apathy [37]—making both pathways and their associated brain structures important to our discussion. There is substantial and convincing evidence demonstrating DAergic dysfunction in the various structures of these neural pathways in subjects with AD, reviewed below.

Findings from Postmortem Studies

Postmortem studies on the brains of AD patients have revealed varying levels and locations of damage sustained within the DAergic system in AD. Storga et al. [38] found lower DA levels in the striatum, amygdala, substantia nigra, cingulate gyrus, and raphe nucleus of postmortem AD brains compared to those of controls. Other postmortem studies of AD brains have demonstrated that DA levels are decreased in the striatum [39–41] and the temporal cortex [42], but remain unchanged in the frontal cortex [43]. Additionally, levels of homovanillic acid (HVA)—a major metabolite of DA—have been demonstrated to be decreased in the amygdala [39], the hippocampus [42], and the striatum [44]. Storga et al. [38] found that decreased DA levels in affected areas of the brain correspond to increases in tyrosine—the

primary precursor of DA—in the same regions. It has been suggested that decreased DA in these regions may be a result of impaired tyrosine hydroxylase, the rate-limiting enzyme in DA biosynthesis [45]. In terms of broader DAergic pathways, these findings point to changes within the mesocorticolimbic (striatum, amygdala, hippocampus, cingulate gyrus, temporal cortex) and nigrostriatal (striatum) pathways.

Other postmortem studies have demonstrated changes in DA receptor density and distribution in AD. Receptor binding studies have found that the density of D_2-like receptors is significantly reduced in the striatum of AD patients compared to age-matched healthy controls [46–48]. Studies examining D_1-like receptors (D_1 and D_5) have found that there are no significant differences in the densities of these receptors between AD patients and age-matched controls in the frontal cortex or striatum [48–51]. A recent binding study of postmortem AD brains found that, in the frontal cortex, D_2, D_3, and D_4 receptor expression is markedly reduced, while D_5 expression is increased compared to age-matched healthy controls [52]. Interestingly, this study also found an increase in D_1 receptors in the frontal cortex of AD brains compared to healthy controls. A study on healthy brains from Goldsmith et al. [53] showed that there is a modular organization of bands throughout the rostral and midlevels of the temporal cortex that are rich in D_2 receptor density. Joyce et al. [54] demonstrated that these D_2 receptors bands are largely absent from postmortem AD brains. These studies suggest that a change to DA receptor density and distribution occurs in the AD brain. Changes seem to be most marked in the D_2-like receptor family within the striatum of patients with AD and possibly extending to the temporal or frontal cortex. Changes to these brain structures suggest dysfunction in the DAergic mesocorticolimbic pathway that connects the ventral tegmental area to the cortex and the striatum.

DA dysfunction may also be attributed to lower levels of DAT in AD patients. Mice with a lower density of DAT exhibit decreased DA release [55]. A number of studies in the AD population have reported various results with regard to DAT changes. Two studies [56,57] reported that AD patients exhibited significantly lower DAT synthesis than controls, while another [58] found no difference in DAT levels between AD patients and normal controls. Another recent study found that polymorphisms in the DAT gene of AD patients are associated with various behavioral symptoms [59]. These discrepant DAT findings are difficult to reconcile. In humans, DAT levels have been shown to decrease by age 50, suggesting an age-related reduction in the quantity of DAT, which may complicate findings [60]. It is also possible that DAT changes only occur in a subpopulation of AD patients that experience extrapyramidal, or movement, symptoms [56,57] as will be discussed below.

Findings from *In Vivo* Studies

Postmortem studies are limited by the delay between death, freezing and tissue analysis, and the fact that findings cannot always be accurately attributed to the antemortem state. Fortunately, neuroimaging studies have verified, *in vivo*, many findings from postmortem studies regarding changes to the DA system in AD patients. A positron emission tomography (PET) study by Pizzolato et al. [61] used [^{123}I]-IBZM (a radiolabeled D_2-specific antagonist) and demonstrated a significant decrease in D_2 receptors levels in the striatum of AD patients. It should be noted that IBZM is an antagonist and may bind to DA receptors in both high-affinity (G-protein coupled form) and low-affinity (G-protein uncoupled form) states [62]. Decreased levels of D_2 receptors found in this study, therefore, may not simply be attributed to a change in receptor affinity state. Another PET study, using [^{11}C]raclopride (another D_2 antagonist) observed a marked decrease in D_2 receptors in the striatum of AD patients who manifested BPSD compared to controls [63]. Interestingly, and in stark contrast to postmortem studies and other *in vivo* studies, Piggott et al. found no differences in D_2 binding between AD and control brains, but did find a 20% increase in D_3 receptor binding in the nucleus accumbens of AD brains [64]. In a more recent study, Piggott and colleagues once again found that D_2 receptor density was unchanged in AD brains compared to age-matched control brains [65].

Other neuroimaging studies have measured the uptake of various radiolabeled DA analogues as a marker of DA neuron levels. One PET study using [^{18}F] 6-fluoro-L-dopa (FDOPA)—a radioligand which is taken up by DA neurons—demonstrated decreased FDOPA uptake in the striatum of AD patients, which correlated with decreased cognitive scores in this population [66]. Another study used a different uptake ligand—[^{3}H]GBR-12935—to assay DA uptake and found a 50% reduced uptake in the putamen (a structure within the striatum) of AD patients [67]. Yet another uptake study used a radiolabeled dopamine analogue ([^{11}C]β-CFT) and demonstrated a 21% decrease in DA uptake in the putamen and a 23% decrease in the caudate nucleus compared to healthy controls [68]. In contrast to these studies, a study by Murray et al. showed no decrease in DA uptake in the putamen, but rather a 48% reduction in uptake in the nucleus accumbens of AD patients compared to normal controls [56]. Although variable, these findings largely corroborate findings from postmortem studies,

and strongly suggest dysfunction of the DAergic system within the striatum of AD patients.

The specific effects of DA disruption within the striatum are uncertain. Damage to the nigrostriatal tract of the DA system is implicated in motor disorders [36], and it follows that AD patients with extensive DA dysfunction in the striatum may also exhibit symptoms of parkinsonism (discussed in more detail below). With respect to BPSD and apathy, the effects of damage to the striatum are less clear. Many of the above PET studies are limited by the radioligands that have been used, which tend to be striatum-specific and do not measure other brain areas involved in the BRS. Newer DA radioligands, such as [^{18}F]Fallypride, have been shown to bind with equal specificity to extrastriatal brain areas [69,70]. Future PET studies on AD patients may be done using [^{18}F]Fallypride to measure possible DA dysfunction in cortical brain areas involved in the mesocorticolimbic BRS.

Postmortem and *in vivo* evidence linking DA disruption to AD consists of significant decreases in the metabolism of tyrosine to DA, decreased DA receptor availability, decreased presynaptic DAT levels, and an overall decrease in the uptake of labeled DA analogues within the striatum. Since the time of these changes to the DA system is unknown, it is unclear how these changes progress and how they relate to the underlying neurodegenerative process of AD. Substantial evidence suggests, however, that changes to the DA system are associated with specific functional and behavioral outcomes in AD patients, which will be reviewed below.

Dopaminergic System and Apathy (Table 1)

DA neurons in the mesocorticolimbic and nigrostriatal pathways innervate a number structures in the striatum and frontal cortex which are believed to mediate feelings of motivation and reward-seeking behavior [27,28,32,37]. A large body of evidence suggests that DA mediates reward pursuit behavior by attributing incentive salience ("wanting") to reward stimuli. Indeed, it is suggested that DA contributes causally to incentive salience and is, in fact, necessary for normal "wanting" [71]. Additional research has suggested that DA agonists tend to promote reward-seeking behavior, while DA antagonists tend to attenuate reward-seeking behavior [72–77]. Using Marin's definition of apathy as "the absence or lack of emotion, interest, concern or motivation" [7,8] and bearing in mind the relationship between DA and reward-seeking, or "wanting" behavior, many studies have proposed a DAergic basis of apathy in AD. Imaging studies have identified correlates between pathophysiological changes to DAergic neuron-containing BRS structures and feelings of apathy in AD patients.

SPECT Studies

Several studies have used single-photon emission computerized tomography (SPECT) to estimate regional cerebral blood perfusion in AD patients who exhibit symptoms of apathy. Most of these studies have demonstrated dysfunction within the anterior cingulate [78–83] and orbitofrontal regions [79,81–83]. Some studies have also found perfusion to be decreased in temporal regions [79,81,84] and other areas [85]—these findings are inconsistent however, and have not been replicated in other perfusion studies investigating the same regions [31,83,86]. Many of the above studies [79–85] did not differentiate between apathetic AD patients with depressive symptoms and apathetic AD patients without depressive symptoms. Apathy is frequently comorbid with depression, but can also be a separate diagnosis [87–91], and it is important to exclude patients with depressive symptoms from these studies. A recently published SPECT study examined findings from a large group of AD patients ($n = 51$) without symptoms of depression [31]. Results corroborated those of previous studies, showing significantly decreased blood perfusion to the anterior cingulate and orbitofrontal cortex regions of AD patients with apathy.

Apathy has been previously noted as the hallmark behavior in patients with lesions to the anterior cingulate [92]; however, the importance of lesion laterality is disputed. Some studies have associated apathy with bilateral hypoperfusion in the anterior cingulate [79,80], while others have found predominantly left-sided [31,81,83] or predominately right-sided [78,82] hypoperfusion. Similarly, significance of lesion laterality in the orbitofrontal cortex is not known, with studies reporting different findings with regard to the side of hypoperfusion related to apathy in the orbitofrontal cortex. The anterior cingulate and orbitofrontal regions are both crucial areas of the BRS and are involved in DAergic-mediated reward and pleasure behavior in healthy individuals [93–95]. The findings from these perfusion studies, therefore, suggest a link between the DAergic system and symptoms of apathy in dementia. Further evidence of this link is provided in a recent study on patients with Parkinson's Disease [96]. This study demonstrated that, following subthalamic nucleus deep brain stimulation (STN-DBS), patients demonstrated decreased glucose metabolism within the anterior cingulate region. It was found that this decreased metabolism in the anterior cingulate correlated strongly

Table 1 Neuroimaging studies of AD patients with apathy

Study	Finding	Comments
SPECT Perfusion Studies		
Benoit 1999 [78]	Apathy (NPI apathy) correlated with hypoperfusion in right cingulate.	63 total patients with AD; apathy in 37 patients; SPECT only done on 20 patients
Benoit 2002 [83]	Apathy (NPI apathy) correlated with hypoperfusion in left anterior cingulate, left orbitofrontal gyrus, right inferior frontal gyrus, and the right gyrus lingualis.	30 total AD patients; 15 with apathy
Benoit 2004 [82]	Apathy (IA—lack of initiative and interest score) correlated with hypoperfusion in bilateral superior orbitofrontal gyrus (controlling for NPI depression), and right anterior cingulate cortex.	30 total patients with AD; 14 with apathy
Craig 1996 [79]	Moderate-to-severe apathy (NPI apathy) correlated with hypoperfusion in the anterior cingulate, orbiofrontal, dorsolateral, and anterior temporal regions.	31 patients with AD; 21 with more than mild apathy
Lanctôt 2007 [31]	Apathy (NPI apathy) correlated with hypoperfusion in right orbitofrontal corex and left anterior cingulate	51 total nondepressed AD patients; 23 with apathy
Lopez 2001 [85]	Apathy correlated with hypoperfusion in bilateral dorsolateral prefrontal cortex and bilateral basal ganglia.	8 total AD patients; 1 with apathy; 1 with major depression; 1 with emotional lability; 5 controls
Migneco 2001 [80]	Apathy (NPI apathy) correlated with hypoperfusion in bilateral anterior cingulate.	41 total patients; 28 patients with AD and 13 patients with mild cognitive impairments; 21 patients with apathy
Ott 1996 [84]	Apathy severity (AES) correlated with hypoperfusion in right posterior temporal and right parietal regions.	40 total patients with AD;
Robert 2006 [81]	Apathy (IA—lack of initiative and interest score) correlated with hypoperfusion in right frontal lobe, right anterior cingulate, and right inferior temporal lobe (in each case controlling for IA emotional blunting, NPI depression).	31 total patients with AD; 19 with apathy
MRI studies		
Jonsson 2009 [97]	Apathy (STEP) significantly correlated with increased volume of white matter hyperintensities.	167 total patients with dementia; 84 with AD; 127 with apathy
Starkstein 2009 [98]	Apathy (AES) significantly correlated with increased volume of white matter hyperintensities in the frontal lobe.	79 total AD patients; 14 with apathy; 10 with both apathy and depression

Abbreviations: AD, Alzheimer's Disease; AES, Apathy Evaluation Scale; IA, Apathy Inventory; NPI, Neuropsychiatric Inventory; STEP, Stepwise Comparative Status Analysis.

with increased apathy—further suggesting a structural link between dysfunction in BRS structures and apathy. Another recent SPECT study investigated glucose metabolism in the brains of AD patients with apathy, and also found decreased metabolic activity in the anterior cingulate and orbitofrontal cortex, reinforcing findings from hypoperfusion studies [99]. A study from David et al. built upon blood perfusion and metabolic SPECT findings by examining the association between *in vivo* DAT binding (using DA analogue, ^{123}I-FP-CIT) and apathy in AD patients [100]. That study demonstrated that AD patients with apathy had significantly decreased DAT binding in the putamen—strongly implicating a link between apathy and DAergic dysfunction in BRS structures of the AD population.

MRI Studies

White matter changes are frequently found in radiological images of patients with AD. In MRI images of AD patients, these changes typically appear as white matter hyperintensities [101]. Hyperintensities on MRI are often the result of an insult to microvascular networks within the brain [102–104]. These hyperintensities occur regularly in older adults with small vessel disease and the development of these lesions has been linked to a decline in cognitive function [105]. Two recent studies [97,98] in the AD population have found that these hyperintensities occur in greater volume in the brains of apathetic AD patients than in nonapathetic AD patients. Starkstein et al. found that patients with apathy had a

significantly greater volume of white matter hyperintensities in their frontal lobes than patients without apathy [98]. Unfortunately, that study did not distinguish brain regions beyond the principal lobes of the brain (frontal, parietal, temporal, occipital) and it is unknown whether those white matter changes occurred specifically in the orbitofrontal area, as suggested by SPECT perfusion studies previously mentioned. Jonsson et al. [97] also found that white matter changes occur in significantly greater volume in AD patients with apathy than AD patients without apathy, but also did not specify where in the brain these white matter hyperintensities occurred. Bearing in mind the relationship between these hyperintensities, microvascular injury, and small vessel disease [102–105], it is possible that the increased volume of hyperintensities in the brains of AD patients with apathy is associated with decreased blood perfusion, and neuronal death, in the orbitofrontal and anterior cingulate regions of these patients (as suggested previously by SPECT studies). More MRI surveys are needed to elucidate specific areas of increased white matter hyperintensity in patients with apathy in AD.

Extrapyramidal Symptoms and Apathy

A number of patients experience extrapyramidal symptoms, or parkinsonism, in addition to the typical cognitive symptoms of AD. The prevalence of parkinsonism in AD is largely disputed, with rates ranging from 11% to 53% [106–110]. Extrapyramidal symptoms include movement disorders, such as akinesia and akathisia, which are typically seen in patients with Parkinson's disease [110]. A number of investigators have demonstrated that symptoms of apathy are significantly associated with the presentation of extrapyramidal symptoms in AD patients [111,112], suggesting a possible link in pathophysiological mechanisms between the two symptoms. Several studies in this population have found interesting, yet conflicting findings with regard to the association between DA dysfunction and extrapyramidal symptoms. One study demonstrated that AD patients with extrapyramidal symptoms had lower DAT synthesis than non-parkinsonism AD counterparts [56]. In contrast to this, a more recent study found no changes to DAT levels in AD patients exhibiting extrapyramidal symptoms [58]. Other studies investigating changes to D_2 receptors found a marked decrease in D_2 receptor levels in the striatum of AD patients with extrapyramidal symptoms compared to AD patients without extrapyramidal symptoms [61,113]. A study by Rinne et al. [68] demonstrated that a decrease in the reuptake of a dopamine ligand correlated with the severity of extrapyramidal symptoms in an AD population. Despite some conflicting results, the majority of these studies provide strong evidence linking dysfunction in the DA system with the presence or severity of extrapyramidal symptoms. A study from Starkstein et al. [112] demonstrated in a large AD population ($n = 169$) that patients with apathy at baseline exhibited a significant increase in extrapyramidal symptoms at follow-up. This finding suggests that apathy and extrapyramidal symptoms in AD may be the result of a common mechanism. Considering extensive changes to the DA system in both apathy and extrapyramidal symptoms, the common mechanism may be a dysfunction within the DA system.

Taken together, findings from SPECT studies, MRI studies, and extrapyramidal symptom studies point to dysfunction in the DAergic system and BRS structures as an important pathophysiological correlate of apathy in AD patients. Based on this evidence, it is reasonable and clinically relevant to target the DAergic system for the treatment of apathy in AD patients.

Pharmacotherapy (Table 2)

Treatment for cognitive decline in AD has typically focused on the use of ChEIs. Some recent evidence suggests that ChEIs may also be effective in treating various BPSDs [16,18]. These results are inconsistent however, and other studies have found that only 40% [16] to 62% [15] of AD patients improve in BPSDs with ChEI treatment. Some studies of ChEIs have examined apathy as a secondary outcome, and have found varying results. A meta-analysis of galantamine found a reduction in NPI score, but no significant reduction in the NPI apathy item [114]. A number of studies have examined donepezil in the treatment of AD, with improvement in apathy as a secondary measure—those studies have produced widely conflicting results with regard to apathy [18,20,115–119]. Rivastigmine has been studied in RCTs on the AD population, with improvements of apathy reported as a secondary outcome. Findings in those studies are conflicting, with one RCT finding an improvement in NPI apathy score [120], and another finding no change [121]. At therapeutic concentrations, ChEIs may interact with the DAergic system and stimulate DA release through the nicotinic acetylcholine receptors (nAChR) [122]. This is particularly true of the ChEI galantamine, which is a known nicotinic modulator. Therefore, the striatal nicotinic cholinergic system may influence DA levels, and ChEIs may have a potential secondary effect on apathy.

Memantine, a novel NMDA-receptor agonist has shown promise as a treatment for severe AD, but has not been used in an RCT where apathy has been a primary outcome measure. While one case report has noted its potential utility in the treatment of apathy [25], apathy is not considered a memantine-responsive symptom [123].

Table 2 Characteristics and findings of CNS stimulant trials on apathy

Study	Type of trial	Population and sample size	Intervention	Finding
Drayton 2004 [124]	Chart review	30 patients with executive dysfunction and dementia	Amantadine (50–400 mg/day)	17 of 30 patients were "much improved" or better on CGI.
Kraus 1997 [125]	Case report	7 patients; 6 with TBI; 1 with meningitis	Amantadine (25–400 mg/day)	Four patients "responded" and three patients "partially responded" to amantadine.
Van Reekum 1995 [126]	N of 1, double-blind placebo-controlled trial	1 TBI patient	Amantadine (300 mg/day)	Improvement in symptoms of apathy (based on clinical observation).
Debette 2002 [127]	Case report	1 postanoxic encephalopathy patient with apathy	Bromocriptine (15 mg/day), levodopa (200 mg/day), and bensarizine (50 mg/day)	Improved symptoms of apathy in one case, but was not helpful in two other cases (based on clinical observation).
Marin 1995 [128]	Case report	1 patient with postsurgical occipital lobe infarction	Bromocriptine (90 mg/day) and methylphenidate (50 mg/day)	Improvement in symptoms of apathy (based on clinical observation).
Huey 2008 [129]	Double-blind case crossover trial	8 FTD patients	Dextroamphetamine (20 mg/day) or quentiapine (150 mg/day)	Improvement in symptoms of apathy (based on NPI apathy item) in patients taking dextroamphetamine.
Lanctôt 2008 [130]	Open-label *d*-AMPH probe study	20 AD patients	Dextroamphetamine (10 mg single dose)	Patients with apathy (NPI apathy subscore >3) had a diminished subjective response to *d*-AMPH (based on ARCI).
Chatterjee 2002 [131]	Case report	1 PD patient with apathy	Methylphenidate (10 mg/day)	Improvement on apathy item of UPDRS.
Galynker 1997 [26]	Open-label study	27 AD and vascular dementia patients	Methylphenidate (10–20 mg/day)	Improvement of negative symptoms (including apathy) on SANS.
Herrmann 2008 [132]	Double-blind randomized controlled trial	13 AD patients	Methylphenidate (20 mg/day) or placebo	Greater improvement in symptoms of apathy (based on AES) in patients taking MTP than patients taking placebo ($P = 0.045$).
Keenan 2005 [133]	N of 1, double-blind ABBA design (placebo, drug, drug, placebo)	1 patient with idiopathic normal pressure hydrocephalus	Methylphenidate (20–40 mg/day)	Improvement in symptoms of apathy (based on AES self-rated scale).
Maletta 1993 [134]	Case report	3 AD patients with anorexia secondary to apathy	Methylphenidate (10–20 mg/day)	Improvement in symptoms of apathy in each case (based on clinical observation).
Padala 2005 [135]	Case report	1 patient with major depression	Methylphenidate (40 mg/day)	Improvement in symptoms of apathy (based on AES).
Padala 2007 [136]	Case report	4 patients; 2 with major depression, 1 with vascular dementia; 1 with PTSD	Methylphenidate (20 mg/day)	Improvement in symptoms of apathy (based on AES).
Padala 2010 [137]	Open-label study	23 AD patients	Methylphenidate (20 mg/day)	Improvement in symptoms of apathy (based on AES).
Ravindran 2008 [138]	Double-blind randomized controlled trial	145 patients with major depression taking an SSRI or Dual action agent antidepressant	Methylphenidate OROS (18–54 mg/day) or placebo	Improvement in symptoms of apathy (based on AES) in treatment group compared to placebo ($P = 0.01$).
Spiegel 2009 [139]	Case report	3 patients with cerebrovascular accidents	Methylphenidate (5–12.5 mg/day)	Improved in symptoms of apathy (based on NPI apathy item).
Padala 2007 [140]	Case report	1 patient with dementia and depression	Modafinil (200 mg/day)	Improved in symptoms of apathy (based on AES).

Abbreviations: AD, Alzheimer's disease; AES, Apathy Evaluation Scale; ARCI, Addiction Research Centre Inventory; CGI, Clinical Global Impression; FTD, frontotemporal dementia; MTP, methylphenidate; OROS, osmotic-release oral system; PD, Parkinson's disease; PTSD, posttraumatic stress disorder; SANS, Scale for the Assessment of Negative Symptoms; SSRI, Selective Serotonin Reuptake Inhibitor; TBI, traumatic brain injury; UPDRS, Unified Parkinson's Disease Rating Scale.

Given that apathy is prevalent in up to 80% of moderate AD patients [9], it is vital that an effective and targeted pharmacotherapy is explicated for the treatment of this BPSD. Based on evidence for the involvement of the DA system in apathy as outlined previously, the use of targeted DA agents for the treatment of apathy in AD patients has been proposed.

Methylphenidate

Methylphenidate (MTP) is a CNS psychostimulant that exerts a therapeutic effect by increasing the synaptic concentration DA. This increase in synaptic DA is accomplished by MTP blocking presynaptic DAT and decreasing the reuptake of DA into presynaptic terminals [141,142]. The blockage of DAT by MTP has been shown to increase synaptic DA levels at a rate proportional to DAT blockage [142]. MTP is not specific to the DAergic system, however, and also has prominent effects in the norepinephrine system—it is not entirely known whether MTP's beneficial effects are due to actions in the DAergic system or other neurotransmitter systems [143]. MTP binds with the highest specificity in the caudate-putamen, nucleus accumbens, bed nucleus of the stria terminalis, and the median eminence [144]—areas that are associated with the BRS [27,28]. This CNS stimulant has been most widely used in the treatment of attention deficit hyperactivity disorder (ADHD) [145], but more recently has had expanded therapeutic utility in other areas, including the treatment of dementia.

Maletta and Winegarden reported using MTP on nursing home patients with dementia in a series of case reports published in 1993 [134]. Those case reports suggest that MTP is effective in reversing anorexia secondary to apathy in these patients. Galynker et al. [26] measured the effect of MTP on "negative symptoms of dementia"—which included apathy—in a sample of 27 patients with AD or vascular dementia. Results from that study demonstrate that negative symptoms of dementia—including apathy—seem to be responsive to MTP treatment. Jansen et al. [146] used MTP in a case crossover, double-blinded, randomized trial with one patient. That study showed efficacy in treating apathy in the single patient, using a low dose of MTP (5 mg bid). In a RCT investigating the treatment of apathy in AD with MTP [132], 13 AD patients using 20 mg/day of MTP (10 mg bid) were assessed in a placebo-controlled crossover design. That trial measured apathy as a primary outcome—using the Apathy Evaluation Scale (AES) [8]—and demonstrated that MTP significantly improved scores of apathy. A recent open-label trial investigated the use of 20 mg/day of MTP in 23 patients with AD and baseline apathy (>40 on the AES scale) [137]. That study found a significant improvement in AES scores after 12 weeks of treatment. Other case reports have described using MTP to effectively treat apathy in the depressed population [135,136], the Parkinson's population [131], cerebrovascular accident patients [139], and patients with idiopathic normal pressure hydrocephalus [133]. Another recent RCT reported that apathy scores improved significantly in depressed patients who were treated with MTP in combination with an antidepressant, compared to patients using the antidepressant alone [138].

These studies point to the positive effect of MTP on a number of behavioral symptoms, most notably apathy. A small sample size limits the interpretation of results from the only RCT looking specifically at the treatment of apathy by MTP [132]. Results from that RCT also suggest that MTP tolerability may be a concern in this population as a significantly greater number of patients dropped out from the treatment arm of the study than the placebo arm, due to adverse effects of MTP. In the open-label MTP trial [137], no patients dropped out due to adverse events, but two patients required dose reductions because of a decreased appetite attributed to MTP treatment. Safety studies, and eventually more large-scale, double-blinded RCTs are needed to further demonstrate the effectiveness of MTP in the treatment of apathy in AD.

Dextroamphetamine

Dextroamphetamine (*d*-AMPH) increases the concentration of DA in the synapse by preventing the re-uptake of DA by presynaptic DAT [147,148] and by releasing DA from newly synthesized central stores into the synaptic cleft [149]. *In vivo* SPECT and PET studies with animal models [150,151] and with humans [152,153] have demonstrated that *d*-AMPH stimulates D_2 and D_3 receptor binding in a dose-dependant manner. The effect of *d*-AMPH on the DA system seems to be most pronounced in BRS structures within the striatum [152,154,155] and as result, *d*-AMPH tends to produce feelings of subjective euphoria and pleasure in patients [156]. *d*-AMPH has been demonstrated to reliably increase synaptic concentrations of DA within the BRS in several studies [152,153,157–159] but has not been widely used in the dementia population, due to uncertain tolerability in an older cohort. One small study (n = 8) in patients with frontotemporal dementia found that scores of apathy improved in patients taking *d*-AMPH over a period of 4 weeks [129]. That study did not look at apathy as a primary measure however, and found apathy improvement in a *post hoc* analysis of NPI subscales.

d-AMPH was used as a probe for DA function in a sample (n = 20) of AD patients with and without

apathy [130]. Apathetic AD patients had significantly lower scores on the Addiction Research Center Inventory (ACRI) drug reward composite score [160] than patients without apathy. This reward score is a measurement of perceived positive effects from amphetamine treatment. PET studies have linked positive feelings following *d*-AMPH administration specifically to D_2 receptor binding [152,161,162]. The decreased ACRI score found in apathetic patients following *d*-AMPH probe suggests an association between DA dysfunction and apathy in the AD population. This method has been validated by other studies using *d*-AMPH as a probe in the major depression disorder population [163,164] and an alcohol-dependent population [165]. Findings from this *d*-AMPH probe study may have treatment implications, and provide further evidence that apathetic AD patients stand to benefit from a drug that specifically targets the DA system.

The safety of both *d*-AMPH and MTP in an older dementia population remains unclear. As mentioned previously, tolerability in the only RCT of MTP was a concern, with dropouts in the study occurring exclusively in the treatment arm, due to adverse effects of MTP treatment [132]. None of the above MTP or *d*-AMPH studies reported abuse or dependency problems. Since *d*-AMPH use has not yet been examined in any large-scale trials of an elderly dementia population, its safety is somewhat unclear. In the study by Huey et al. using *d*-AMPH in eight frontotemporal dementia patients, all patients were able to tolerate a 20 mg/day dose of *d*-AMPH for 4 weeks without reporting adverse effects due to medication [129]. Regardless of this report, both *d*-AMPH and MTP must be used with caution in an elderly population considering the potential adverse effects of treatment, which include: hypertension, tachycardia, anorexia, abuse liability, exacerbation of anxiety and/or psychosis, and problems in a coronary artery disease population (positive ionotropic effects). Safety studies of both drugs in elderly dementia patients are clearly required.

Modafinil

Modafinil is a stimulant that is pharmacologically distinct from *d*-AMPH and does not seem to have the same associations with dependency [166,167]. The mechanism of action of modafinil is not entirely known, but evidence points to increased activity within the DA system [168–170] and decreased GABAergic activity [171]. Modafinil promotes vigilance and has been widely used as a long-term treatment for narcolepsy [172–174]. Recent studies have also demonstrated its effectiveness in improving cognitive performance [175,176]. One case report [140] investigated modafinil treatment for symptoms of apathy in a 78-year-old man without a formal diagnosis of AD and a history of depression. After 4 weeks of treatment, improvements in motivation were noted and after 10 weeks, a significant improvement in the patient's apathy was measured on the AES. Modafinil has a low risk of dependency, relatively good tolerance and a lack of drug interactions [166,167,140–178]. These characteristics, in concert with modafinil's DAergic activity, make it an attractive potential therapy for the treatment apathy in AD—and warrant larger studies investigating its utility in this population.

Other Dopaminergic Therapies

Amantadine is another drug with DA effects that has been investigated in the treatment of apathy. The exact mechanism of action of amantadine is not fully understood, but it has been demonstrated to stimulate the release of DA and delay DA reuptake [179]. It is also a potent NMDA receptor antagonist. One study investigated the use of 300 mg/day of amantadine in a patient with apathy following traumatic brain injury [126]. Four treatment-blind therapists each noted improvements in this patient's apathy, with no side effects reported by the patient. Another series of case reports describe the treatment of apathy in six traumatic brain injury patients and one meningitis patient with 25–400 mg/day of amantadine [125]. That study found that four patients with apathy were "responders" to amantadine, while three were "partial responders" based on caregiver reports and clinical observation. In a chart review of 30 dementia patients treated with 50–400 mg/day of amantadine, 17 patients (56.7%) were rated as "much improved" or better on the clinical global impression (CGI) scale [124]. In that study, only 3 patients (10%) reported side effects, with none being severe enough to a warrant discontinuation of amantadine. The findings from these studies, and the activity of amantadine on the DAergic system, point to its possible use in the apathetic AD population.

Bromocriptine is a DA agonist [180] that has been used in combination with other therapies to reduce apathy in non-AD patients. Bromocriptine (90 mg/day) and methylphenidate (50 mg/day) reduced symptoms of apathy in a 49-year-old postinfarct patient [128]. Another series of case reports described using bromocriptine in combination with levodopa (50 mg/day) or benserazide (12.5 mg/day) to improve apathy in patients with postanoxic encephalopathy [127]. That report demonstrated marked improvements in apathy in one patient, but no changes to symptoms of apathy in two other patients.

Both amantadine and bromocriptine have activity in the DA system and have potential utility in the treatment of apathy. Unfortunately, they are associated with a

number of serious side effects including anxiety, agitation, seizures, and exacerbation of psychiatric symptoms of schizophrenia. As a result, both pharmacotherapies warrant safety trials before being considered for treatment of apathy in AD.

It should be noted that amantadine and MTP have been previously considered for the treatment of behavioral symptoms of dementia. Roccaforte and Burke [181] review a number of older studies that report the beneficial effects of amantadine and MTP on "amotivational states," "senility," and recovery from "poor motivation syndrome." As that review demonstrates, psychostimulants have been studied for use in the treatment of apathy for some time, and the findings from these early studies remain somewhat relevant to our current discussion.

Conclusions

The majority of studies investigating the DAergic system in AD have demonstrated a decreased density of DA receptors, decreased levels of extracellular DA, decreased levels of DA metabolites, decreased density of DAT, and decreased DA reuptake by DAT. Cumulatively, these findings suggest DAergic neuronal destruction in the brains of AD patients. Many of these findings are from postmortem studies and it is important to note that conclusions are somewhat restricted due to limitations inherent with this methodology. Postmortem findings represent the physiological state at the time of death that cannot necessarily be applied to the antemortem AD state. Fortunately, findings from many *in vivo* imaging studies support the results from postmortem studies. *In vivo* studies provide evidence of a significant decrease in D_2 family receptor density and decreased DA reuptake in the brains of AD patients. These findings seem to be most pronounced in structures associated with the nigrostriatal and mesocorticolimbic tracts of AD patients—most notably the striatum. The time course of these changes is largely unknown and it is not clear how DAergic dysfunction is related to the underlying neurodegenerative processes of AD.

DA is known to mediate feelings of motivation and pleasure, and it is likely that dysfunction in the DAergic system of AD patients is responsible, at least in part, for this population's high prevalence of apathy. SPECT studies have shown that AD patients who experience apathy have decreased blood perfusion to their anterior cingulate and orbitofrontal cortex—areas that are innervated by DAergic neurons and are associated with feelings of pleasure and motivation. Recent MRI studies have shown that AD patients with apathy have an inordinately high volume of white matter hyperintensities in their frontal lobes. These hyperintensities are typically associated with microvascular insult and decreased blood flow. Taken in concert with SPECT perfusion findings, these results suggest that decreased blood flow or vascular insult to orbitofrontal and cingulate regions may be partially responsible for DAergic neuron destruction and resultant symptoms of apathy in these AD patients. Evidence linking DAergic dysfunction to apathy is provided by a d-AMPH challenge study [130]. Additional evidence linking DAergic dysfunction to apathy is provided in studies investigating AD patients with parkinsonism. Many AD patients with extrapyramidal symptoms have irregularities in DA uptake or DA receptor density. As reported by Starkstein et al. [112], a significant number of these patients also develop apathy—suggesting a mechanistic similarity of DAergic dysfunction between apathy and extrapyramidal symptoms in these patients.

CNS stimulants that target DA have been successful in the treatment of apathy. Some of these pharmacotherapies, most notably MTP, have been found to safely ameliorate symptoms of apathy in the AD population. Unfortunately, there have been few large-scale RCTs investigating the use of other CNS stimulants to treat apathy in an elderly AD population. Paucity of data concerning the use of these drugs is likely a result of concerns about their tolerability in the elderly population and risks associated with dependency. Findings from preliminary studies, however, suggest the utility of many of these therapies in the treatment of apathy, and warrant larger RCTs. Modafinil may be particularly useful in this population, given its demonstrated cognitive benefits, its low risk of dependency, and its high tolerability.

DA dysfunction in discrete brain areas is an important correlate of apathy in AD, but it is still unclear at what time during the course of AD changes to the DAergic system occur, or whether the extent of DAergic disruptions preclude it as a target for pharmacotherapy. Evidence presented in this review suggests that the DAergic system may be a useful and rational target for pharmacotherapies in the treatment of this BPSD. Given the morbidity associated with apathy, it is vital that the application of currently available treatments are further investigated, and that novel interventions are proposed and explored.

Conflict of Interest

The authors have no commercial or financial involvements that may present a conflict of interest in connection with this article.

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