

Current Treatment Options for Alzheimer's Disease and Parkinson's Disease Dementia

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Abstract: Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders encountered in clinical practice. Whilst dementia has long been synonymous with AD, it is becoming more widely accepted as part of the clinical spectrum in PD (PDD). Neuropsychiatric complications, including psychosis, mood and anxiety disorders, and sleep disorders also frequently co-exist with cognitive dysfunctions in AD and PDD patients. The incidence of such symptoms is often a significant source of disability, and may aggravate pre-existing cognitive deficits. Management of AD and PDD involves both pharmacological and non-pharmacological

measures. Although research on pharmacological therapies for AD and PDD has so far had some success in terms of developing symptomatic treatments, the benefits are often marginal and non-sustained. These shortcomings have led to the investigation of non-pharmacological and novel treatments for both AD and PD. Furthermore, in light of the diverse constellation of other neuropsychiatric, physical, and behavioural symptoms that often occur in AD and PD, consideration needs to be given to the potential side effects of pharmacological treatments where improving one symptom may lead to the worsening of another, rendering the clinical management of these patients challenging. Therefore, the present article will critically review the evidence for both pharmacological and non-pharmacological treatments for cognitive impairment in AD and PD patients. Treatment options for other concomitant neuropsychiatric and behavioural symptoms, as well as novel treatment strategies will also be discussed.

Keywords: Alzheimer's disease, cognition, dementia, mild cognitive impairment, non-pharmacological treatment, Parkinson's disease, pharmacological treatment.

1. INTRODUCTION

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders encountered in clinical practice. Whilst dementia has long been synonymous with AD, it can be separated into different clinical stages ranging from prodromal Mild Cognitive Impairment (MCI) through to mild, moderate, and severe dementia [1]. The annual rate of transition from MCI to AD is estimated as 19% [2] and as such the early identification of this prodromal stage might afford critical opportunities for intervention. Cognitive decline is also becoming more widely accepted as part of the clinical spectrum in PD. At presentation, 25% of individuals with PD exhibit mild cognitive impairment (PD-MCI) [3] and longitudinal studies have documented that up to 80% of these patients will progress to dementia (PDD) over 20 years [4]. In addition to cognitive impairment, a range of other symptoms, including psychosis, hallucinations, agitation, aggression, sleep disturbances and depression also frequently occur during the

course of both AD and PD [5-8]. The incidence of these neuropsychiatric and behavioural symptoms will often aggravate cognitive deficits, and thereby worsen the severity of dementia.

Both AD and PD are associated with substantial impairment in their wellbeing, caregiver strain, increased mortality, as well as increased healthcare and institutionalization costs [9-13]. In response to these demands, several pharmacological options have been developed for the treatment of cognitive impairment in both conditions. Current Food and Drug Administration (FDA) -approved drugs for AD include Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, and the cholinesterase inhibitors (ChEIs) Donepezil, Galantamine, and Rivastigmine. Current treatments for PDD are mostly derived from those utilized in AD, with ChEIs and Memantine being two of the main approaches. However, Rivastigmine is the only FDA-approved therapy that is currently licensed for PDD.

Although pharmacotherapies appear to slow aspects of cognitive impairment in both AD and PD, the benefits are often marginal and non-sustained. These shortcomings have led to the evaluation of non-pharmacological and novel treatments for both AD and PD. Furthermore, in light of the diverse constellation of other neuropsychiatric, physical, and

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behavioural symptoms that often occur in AD and PD, consideration needs to be given to the potential side effects of pharmacological treatments where improving one symptom may lead to the worsening of another, rendering the clinical management of these patients challenging.

Therefore, the present article will critically review the evidence for both pharmacological and non-pharmacological treatments in AD and PDD/PD-MCI patients. Furthermore, treatment options for other concomitant neuropsychiatric and behavioural symptoms, as well as novel treatment strategies will also be discussed.

2. PHARMACOLOGICAL TREATMENTS

2.1. Cholinesterase Inhibitors

Significant cholinergic deficits have been observed in both neuropathological and imaging studies of AD and PDD patients [14, 15]. Indeed, these deficits may be even more pronounced in PDD than in AD patients with similar levels of cognitive impairment [16, 17]. Cholinergic deficits are primarily seen in the hippocampus of AD patients, in contrast to PDD patients, where such cholinergic deficits are more localized to the cholinergic system of the basal forebrain and brainstem [18]. There is also ample evidence indicating that there is a substantial reduction in cortical cholinergic activity in both conditions [19-22]. Such deficits in the cholinergic system have been reported to correlate with cognitive deficits in both AD and PD patients [19, 22], leading to the suggested administration of ChEIs to treat memory impairments.

A substantial amount of research has been carried out to investigate the efficacy of ChEIs in AD [23-27]. The primary indicators of response to treatment have often involved the Clinician Interview-Based Impression of Change-plus [CIBIC-plus] [28-30] which evaluates global function, and the Alzheimer's Disease Assessment Scale-Cognitive section (ADAS-Cog) [28, 29, 31] which assesses the severity of dementia. Obviously, along with the Mini Mental State Examination (MMSE) [30-32], which is also frequently employed as secondary outcome measures, these assessments do not require rigorous cognitive testing of the patient and may miss how any clinical improvements translate into real world activity.

The ChEIs Rivastigmine, Donepezil, and Galantamine have been found to be efficacious in improving cognitive functioning for patients with mild to moderate AD, which is usually defined as a MMSE score between 24 or 26 and 10 or 11, respectively [24]. Although adverse effects such as vomiting, diarrhea, and nausea were documented in some cases, ChEIs are considered safe and well-tolerated in the AD population. However, with regard to non-demented patients with MCI, there is very little evidence to suggest that these drugs can actually slow progression and it is clear that they do not prevent the development of dementia over three years [33, 34].

Rivastigmine has been approved for the symptomatic treatment of mild-to-moderate AD. Rivastigmine selectively inhibits cortical acetylcholinesterase (AChE) in the central

nervous system, and also inhibits butyrylcholinesterase (BuChE) which is documented to be the predominant cholinesterase in many key regions affected in both AD and PDD, including the hippocampus, thalamic nuclei, and amygdala [26, 35, 36]. The treatment of mild to moderate AD with Rivastigmine has been the subject of several systematic reviews and meta-analyses [24-26, 37, 38]. The results from these studies (ranging from 9-52 weeks) revealed statistically significant improvement in cognitive performance, with the most significant effect observed in individuals on the highest dose of the medication (6 to 12mg daily). Modest clinical benefit in cognition was also reported with the treatment of high-dose Rivastigmine, which was associated with a two-point improvement on the ADAS-Cog over a period of 26 weeks, as compared to placebo. However, statistically significantly higher numbers of adverse events, such as nausea, diarrhea, vomiting, and dizziness were also reported among patients taking high-dose Rivastigmine, as compared to those taking placebo [37].

Adverse events commonly associated with orally administered Rivastigmine, such as gastrointestinal adverse events, are believed to be at least partly caused by the rapid increase in acetylcholine in the central nervous system [39]. With the aim of reducing such adverse events, a transdermal Rivastigmine patch formulation was developed. By providing continuous delivery of Rivastigmine through the skin into the bloodstream, thereby reducing fluctuations in plasma concentration associated with oral administration, the patch formulation may potentially help improve patient tolerability [39]. The efficacy of the Rivastigmine transdermal patch has been investigated previously [40]. In a 24-week, large clinical trial that involved 1195 participants with AD, the Rivastigmine (9.5mg/24hour) patch was associated with significant improvement in ADAS-Cog and MMSE scores. These improvements were of comparable efficacy to that of the Rivastigmine capsules (6mg, twice daily), but with two-thirds fewer reports of vomiting (6.2% versus 17.0%) and nausea (7.2% versus 23.1%). Therefore, Rivastigmine transdermal patch may also be an effective treatment option for AD patients.

Donepezil is a reversible and highly centrally selective inhibitor of AChE that delays the breakdown of acetylcholine released into synaptic clefts, thereby enhancing cholinergic transmission [26]. Donepezil has also been found to be efficacious in treating cognitive impairment in patients with mild to moderate AD. Compared with placebo, studies evaluating Donepezil have revealed significant benefits on both the ADAS-Cog and MMSE [24, 41, 42]. Donepezil was fairly well-tolerated among AD patients, with common adverse events reported (*e.g.* nausea, vomiting, diarrhea, muscle cramps) being consistent with the cholinergic actions of the drug in this population. In addition, tolerability of a lower dose of Donepezil (5mg/day) was documented to be better than that of a higher dose (10mg/day). Whilst most of the AD studies have focused on mild to moderate severity patients, several studies with Donepezil have suggested that its benefits can be extended into the more advanced stages of disease [23, 43, 44]. For example, in one randomized, double-blind, placebo-controlled study 290 individuals with moderate to severe AD were randomized to receive either

Donepezil or placebo for 24 weeks. Results showed beneficial effects for participants receiving Donepezil as compared to those receiving placebo, including improvements on CIBIC-plus and MMSE scores. Very good tolerability was also reported, with the majority of individuals experiencing adverse effects (*e.g.* diarrhea, headache, and dizziness) rating the experience as mild, and only 8% of Donepezil treated patients discontinued because of the side effects [23]. Similarly, beneficial effects on cognitive measures with a 12-month Donepezil treatment were also reported in another study that involved 295 patients with moderate to severe AD [43].

Previous research (one RCT and one open-label) has also been carried out to compare the efficacy of Donepezil and Rivastigmine on cognitive functioning in AD [45, 46]. One 104-week double-blinded randomized trial compared Donepezil (5mg/day for the first 8 weeks and 10mg/day thereafter) and Rivastigmine (3mg/day for week 1-4, 6mg/day for week 5-8, and 12mg/day thereafter) in 994 patients with moderate to severe AD. Nevertheless, no evidence of significant difference between the two ChEIs was reported [45]. Similarly, a 12-week open-label study compared Donepezil (5mg/day for week 1-4, and 10mg/day thereafter) and Rivastigmine (3mg/day for week 1-4, 9mg/day for week 5-6, and 12mg/day thereafter) reported comparable improvements in cognition [46].

Galantamine is another ChEI commonly administered in the AD population. Galantamine has very little activity in inhibiting butyrylcholinesterase, and is characterized by two pharmacological mechanisms which involves inhibiting acetylcholinesterase, as well as binding to nicotinic acetylcholine receptors in order to allosterically modulate ligand actions [26, 47]. The significant benefit of Galantamine on cognitive functioning (*e.g.* significant improvement on ADAS-Cog scores) in individuals with mild to moderate AD has been documented in previous reviews, with greater effect observed over six months compared to three months. Most adverse effects reported were mild, with gastrointestinal symptoms being the most commonly reported adverse events [24, 25, 33, 48, 49].

The efficacy of Galantamine has also been compared to Donepezil in two open-label trials in AD patients. However, the results from these two trials are somewhat conflicting. Whilst one study found significant improvement in cognitive outcomes in favour of Donepezil over a 12-week trial [50], the other study reported no significant differences in performances on the ADAS-Cog between participants receiving the two drugs over a 52-week trial [51].

In contrast to AD, there have been relatively few clinical trials conducted on ChEI treatment of cognitive impairment in the PD population. Most studies carried out for this purpose have been open-label with small sample sizes, except for two large, randomized, controlled trials (RCTs). Recent systematic reviews and meta-analyses evaluating all available ChEIs studies in PDD suggested that ChEIs treatment for PDD is associated with positive effects, including improvements in global assessment and cognitive functioning [52, 53]. There is also growing research regarding the effects of ChEIs on the rate of falls in PD, as it is a major source of disability in the disease, whose risk can

be further increased with the presence of PDD [54, 55]. However, to date, no conclusive results have been obtained regarding the effect of ChEIs on reducing rate of falls in this population [55]. Research on ChEIs treatments for cognitive deficits in non-demented PD patients with cognitive impairment is also expanding, but has yielded mixed results so far [56-59]. While Galantamine has been reported to be ineffective in improving cognitive performance (*i.e.* attention, executive functioning, memory, and visuospatial performance) in non-demented PD patients [57], Donepezil and Rivastigmine have showed significant effect and a trend effect respectively for improvements on global measures of cognition in non-demented PD patients with MCI [54, 59].

Rivastigmine is the only FDA approved medication for the treatment of mild-to-moderate PDD. The efficacy of Rivastigmine in PDD was demonstrated in one of the two large RCTs in this population, the EXPRESS study [60]. In this study, 541 mild to moderate PDD participants were assigned to receive either Rivastigmine (up to 12mg/day) or placebo over 24 weeks. PDD patients treated with Rivastigmine showed improvements on both of the two primary outcome measures: the ADAS-Cog and the Clinical Global Impression of Change Scale (CGIC) cognition, which measures clinically meaningful improvements. Improvements on secondary outcomes, including tasks that assess attention and executive function were also observed. Subsequent reports from the same dataset showed that such response pattern was indistinguishable from that seen in AD [61]. Although not common, an increased frequency of vomiting, nausea, and tremor was documented in some cases of the treatment arm compared to placebo. In a longitudinal follow-up study of the original EXPRESS trial, the observed improvement derived from Rivastigmine was sustained for up to 48 weeks, although there was some decline in efficacy [62]. Nevertheless, no indication of worsening of motor function was observed over the course of 1 year treatment, which is clearly reassuring given the physical disability of these patients [63].

As with AD, the Rivastigmine transdermal patch has also been employed for the treatment of PDD. In a 76-week, open-label study, the long-term safety of the 9.5mg/24hour patch was explored in 583 patients with mild to moderate severe PDD [64]. The results showed that although the incidences of bradykinesia, muscle rigidity, and fall were similar between the two groups, the incidence of tremor was lower with the patch group, as compared to the 6mg, twice daily capsule group (9.7% versus 24.5%). There were also lower incidences of gastrointestinal events (vomiting, diarrhea, and nausea) with the patch group (2.8%, 5.6%, and 8.3% respectively) as compared to the capsule group (15.3%, 9.2%, and 40.5% respectively). In addition to safety outcomes, the efficacy outcomes of the Rivastigmine transdermal patch were investigated as secondary measures. Improvement in cognitive functioning, as measured by the Mattis Dementia Rating Scale (MDRS), was greater in the capsule group, as compared to the patch group at week 24 to 76. While improvements on the MDRS from baselines were observed in both groups at week 24 and 52, such improvement was maintained through week 76 for the capsule group only, but not for the patch group (where scores on the MDRS returned to just below baseline at week 76). Nevertheless, the authors

suggested that the potential long-term decline in efficacy associated with the patch group can be compensated by an increase in the patch dose.

Several small-scale RCTs with Donepezil in PDD have also showed some degree of improvement on at least one of the assessed cognitive outcome measures (for a review, see Seppi *et al.* (2011) [65]). Similarly, in the second large RCT that assessed 550 PDD patients on Donepezil, some benefits were observed in comparison with the placebo arm [66]. In this study, participants were randomized to receive 5mg Donepezil ($n = 195$), or 10mg Donepezil ($n = 182$), or placebo ($n = 173$) for 24 weeks. No significant difference was observed between the treatment groups and the placebo group on the primary outcome measures of ADAS-Cog and the CIBIC-plus, although results on the CIBIC-plus and the ADAS-Cog for the 10mg group (but not the 5mg group), showed statistically significant superiority compared to the placebo group in relation to primary outcome measures. Significant differences on some secondary measures including the MMSE, and some cognitive measures (e.g. D-KEFS and the Brief Test of Attention) were also observed. The incidence of adverse events (e.g. nausea, vomiting, and diarrhea) was higher in the treatment groups than the placebo group, but such events were mostly mild or moderate in severity.

Two small open-label studies have suggested that Galantamine may have beneficial effects in PDD patients [67, 68]. Of the two open-label studies on Galantamine, one 8-week study in 16 PDD patients found no significant change on the MMSE [68], although an improvement on the clock drawing test (a quick screen for visuo-spatial cognitive impairment) was observed. In contrast, a longer, 24-week study in 41 PDD patients found significant improvements on several cognitive outcome measures, including ADAS-Cog and MMSE [67]. However, this open-label data in small numbers has provided insufficient evidence for the recommended use of Galantamine in PDD patients [65]. Typical adverse events reported in the two studies involve gastrointestinal side effects.

2.2. N-Methyl D-Aspartate [NMDA] Receptor Antagonist

Memantine is an NMDA receptor antagonist that modulates the flow of glutamatergic neuronal transmission and blocks the toxic effects of overactive glutamatergic activity (e.g. impaired synaptic plasticity and neuronal damage) [69]. Glutamate dysfunction has been implicated in AD [69,70], and circumstantial evidence has also been observed in PDD [71, 72].

Memantine has been approved for the treatment of moderate to severe AD. Several systematic reviews have documented that Memantine has a small, beneficial, but clinically detectable effect on cognition in patients with moderate to severe AD [73-76]. However, the action of the drug remains unclear [77]. Memantine was well tolerated among patients with moderate to severe AD. Typical adverse events associated with the drug include dizziness, headache, and confusion. Such events were reported to be infrequent and comparable to that of placebo [73, 76]. Findings from *in vitro* and *in vivo* studies have suggested that Memantine may

also have neuroprotective potential. However, more data to confirm such activity is required [69].

The benefits of Memantine have been explored in a few RCTs evaluating patients with PDD. However, results regarding its efficacy have been conflicting [78, 79]. In one study in which Aarsland *et al.* (2009) [78] included 72 patients either with PDD or dementia with Lewy bodies (DLB) patients, a significant effect in favour of Memantine on the CGIC score and speed on attentional tasks was observed. This effect was believed to be driven mainly by improvement in the PDD group in the subsequent post-hoc analysis. However, in a larger RCT involving 199 PDD and DLB patients, no statistically significant differences were observed on global outcome scores between the Memantine and placebo groups [79]. This null finding was also reproduced in the sub-analysis of the PDD population included. Nevertheless, while there is insufficient evidence for the efficacy of Memantine in PDD patients, it is considered safe and well-tolerated in this population [65], with the incidence of adverse events (e.g. fall and tiredness) being low and similar to that of the placebo group [78, 79].

3. NON-PHARMACOLOGICAL TREATMENTS

There is growing interest in non-pharmacological treatments for cognitive impairment in AD and PD, with cognitive training and physical exercise/physical therapy being two of the most researched treatment options. The efficacy of non-pharmacological treatments in AD has been studied substantially. However, research into the efficacy of such treatments for PDD and PD-MCI patients is limited. Although a recent systematic review evaluated non-pharmacological therapies in PD, none of these studies focused on PDD patients [80]. In general, previous research regarding non-pharmacological treatments in both AD and PD applied diverse design methods, comparison conditions, and outcome measures, making direct cross-studies comparisons difficult, and restrained any conclusions that can be drawn [81, 82].

3.1. Cognitive Remediation

Building on the observation that cognitively-stimulating activities may help protect against cognitive decline in later life in healthy older adult [83], these techniques have been developed to help maintain or enhance cognitive functioning in individuals with early-stage AD. The term cognitive intervention can be used generally to refer to a number of non-pharmacological techniques including cognitive training, cognitive stimulation, and cognitive rehabilitation that aim at improving cognition in individuals experiencing a decline in cognitive functioning [84]. These interventions may be administered in individual or group formats, and tasks may be presented in paper and pencil or computerized form [81, 84]. Cognitive training (CT) methods typically involve repeated practice of a set of standardized task designed to reflect particular cognitive functions, such as memory, attention, or executive function [81, 85]. These methods rest on an underlying assumption that regular or routine practice may have the potential to improve or at least maintain functioning in a given cognitive domain. An additional assumption is that any effects of practice can be

generalized beyond the immediate training context [81, 86]. Cognitive stimulation (CS) refers to a more non-specific approach, where a range of group activities and discussions are employed to enhance general cognitive and social functioning. In comparison with CT and CS, cognitive rehabilitation involves a more individualized approach aimed at helping individuals with specific impairments arising from illness or injury achieve or maintain an optimal level of physical, psychological, and social functioning so as to perform desired function or task [86, 87].

To date, there is no strong evidence to support the premise that CT and cognitive rehabilitation reduces or slows the progression of cognitive impairment in the AD population. A recent Cochrane systematic review reported no indication of any significant positive or negative effects on cognitive outcome measures in patients with mild to moderate AD. However, the researchers noted that some gains resulting from the included intervention might not be captured adequately as the studies included were in general, of low to moderate quality. Well designed studies are needed to provide more definite evidence [86]. In contrast to results from studies that employed CT and cognitive rehabilitation techniques, findings from another recent Cochrane review and meta-analysis regarding the efficacy of CS in AD suggested such approach significantly improved scores on ADAS-Cog and MMSE [85, 88].

The benefits of cognitive interventions have also been reported in a recent review that included both individuals with MCI and healthy older adults [89]. The results showed that cognitive training can be effective in these populations in relation to improving various aspects of cognitive functioning, including executive functioning, memory, attention, and processing speed. However, the authors also noted that much work needed to be done in relation to methodological heterogeneity across studies.

There is a growing area of research into studies on the effectiveness of cognitive training in PD patients. However, these studies are typically in non-demented samples [e.g. 90-96]. These trials as a whole suggest that CT may have some potential benefits in improving cognitive function in PD, suggesting the need for more rigorous exploration. It remains to be investigated whether cognitive remediation represents a preventive technique for PD-MCI patients at risk of further cognitive decline, and whether such approach would benefit PDD patients.

3.2. Exercise and Physical Activities

In recent years, there has been an increasing interest in the potential cognitive benefits of exercise and physical activities in both AD and PD patients. The positive effects of exercise and physical activities on cognition have been well-established in healthy individuals [91], and it is suggested that exercise and physical activities improve brain function *via* a number of mechanisms, including: (1) enhancing the expression of nerve growth factors related to better cognitive functioning and plasticity, (2) promoting glucoregulation and cardiovascular health that, when compromised, increase the risk of developing cognitive impairment, and (3) increasing several neurotransmitters which are involved in cognitive functioning, such as dopamine and acetylcholine [97, 98].

Indeed, it is also known that low levels of exercise and physical activity are one of the greatest risk factors for age-related cognitive decline. In addition, several experimental studies using transgenic mouse models in AD and PD have documented that physical exercise can have a marked effect on cognitive functioning [99, 100]. Based on these findings, there is a theoretical rationale for beneficial effects from exercise and physical activities on cognitive performance in AD and PD.

A systematic review based on six RCTs that exclusively considered the effect of exercise in AD patients showed that exercise yielded a positive effect on slowing the rate of cognitive decline in AD in general. In addition, exercise intervention had a positive effect on global cognitive functioning in this population. The consistency of positive findings, albeit in small sample sizes and varying study design, highlighted the potential benefit of a range of exercise interventions for individuals with AD [99].

The positive effect of exercise on cognition has also been observed in individuals with MCI [98, 101, 102]. Findings from a systematic review that evaluated 8 RCTs, with a total of 1021 participants, showed that all except one study demonstrated some positive effects on one or several domains of cognition, executive function, or attention. However, the pooled effect sizes of exercise on global cognition, which was assessed through ADAS-Cog improvement in two of the included studies, appeared to be only mild [103].

Exercise and physical activities have merit for improving motor manifestations of PD [104, 105], and accumulating evidence has suggested that such approach may also have benefits for cognitive functioning in PD patients [106-110]. For instance, in a study that investigated the impact of Tango in non-demented PD patients, improved spatial cognition was observed and maintained 10-12 weeks post-intervention [110]. However, whether such benefits can be extended to PD patients with cognitive deficits remains to be investigated.

Although research on both cognitive training and exercise and physical activity have both demonstrated some positive results in both AD and PD, well designed studies of these non-pharmacological interventions are needed to obtain more definite evidence [86]. Issues such as the amount, duration, intensity and type of cognitive training/exercise deemed to be most effective for each of these populations should also be addressed. In addition, it is also theorized that additive effects can be achieved through combining cognitive training and physical activity therapies, but further research into this area is needed due to limited evidence available and the wide variations across methodology and study design.

4. NOVEL EXPERIMENTAL APPROACHES

Research on AD and PDD therapy has so far had some success in terms of symptomatic treatments. However, their neuroprotective effects are still debated. Therefore, it is critical to develop a broader and more fundamental therapeutic approach to both AD and PD, with much effort in this regard focused on identifying disease-modifying therapies.

The accumulation of neuritic plaques consisting of the β -amyloid (A β) peptide and neurofibrillary tangles (NFT) comprised of hyperphosphorylated tau (τ) protein [111] are recognized as the two key characteristics of AD. As such, strategies aimed at modulating these two characteristics have attracted increasing attention [111]. Currently, most disease-modifying therapies in AD are designed to target A β via a number of approaches, including (1) to reduce the formation of toxic A β species in the first place, (2) to prevent A β aggregation, and (3) to promote A β clearance through active immunotherapy, which consists of the administration of vaccines of the antigen itself combined with an immune boosting adjuvant to promote the production of anti-antigen antibodies, or passive immunotherapy, which consists of the administration of vaccines of monoclonal antibodies or polyclonal immunoglobulins directed against A β to promote its clearance (for a review, see Mangialasche *et al.* (2010) [112]). Although anti- τ therapies have not received as much attention as those targeting A β loads, therapies aimed at preventing τ - τ binding and subsequent tangle formations have been considered as a potential approach, and are currently under investigation [111, 112]. To date, only limited success has been reached with regards to disease-modifying therapies in AD [111-114], and many clinical and experimental studies are still ongoing.

No clinical trials to date have investigated the potential for disease-modification in PDD or evaluated compounds that may have disease-modifying components in preventing the progression to dementia in PD patients [111, 115]. Active and passive immunotherapies directed against alpha-synuclein, whose accumulation is associated with PD [116] and PDD [117], have shown promising results in animal models of PD [118]. These findings have important implications for the employment of immunotherapy for PD and PDD patients. The Monoamine Oxidase Type-B (MAO-B) inhibitor, Rasagiline has also been proposed to be disease-modifying in PD [119, 120] although longer follow-up data on these patients would seemingly challenge this view [119]. Rasagiline inhibits the breakdown of dopamine, which helps enhance central dopaminergic transmission. Therefore, treatment with Rasagiline may have potential benefits in the PD population, as severe dopaminergic depletion is well recognized as the predominant histological feature of PD. One study of Rasagiline in PD did not specifically address cognition [119], but a subsequent report documented improvements in activities of daily living, including global motor and non-motor aspects, such as cognition [120]. In another study, the efficacy of Rasagiline was investigated in 55 non-demented PD patients with cognitive impairment. Participants were randomly assigned to receive Rasagiline treatment or placebo for 12 weeks. Findings showed that Rasagiline had a statistically significant beneficial effect on composite attention score. However, no significant differences between the two groups were observed in the other cognitive domains [121].

5. CO-EXISTING NEUROPSYCHIATRIC SYMPTOMS IN AD AND PD

Neuropsychiatric complications, including psychosis, mood and anxiety disorders, and sleep disorders often co-

exist with cognitive dysfunctions in AD and PDD patients. The incidence of such symptoms is often a significant source of disability, and may aggravate pre-existing cognitive deficits. However, the treatment of such symptoms in AD and PDD patients may confer challenging clinical management decisions as the symptoms may be the result of progressive and widespread pathological changes of the diseases, or they may result from other factors, such as side effects related to treatment administered or emotional reactions to the disease. As such, the selection of intervention for such symptoms should be guided by investigation into the context within which they develop, mode of onset, and course of symptoms [72]. Currently, there are multiple classes of pharmacological agents in use for the treatment of such symptoms, including, but not limited to antipsychotics, cholinesterase inhibitors, NMDA receptor modulators, and antidepressants. There has also been increasing evidence on the benefits of non-pharmacological methods in treating these symptoms.

5.1. Behavioural and Psychiatric Symptoms

Over 80% of individuals with dementia develop at least one behavioural/psychological symptom in addition to their dementia over the course of their illness [122]. A substantial number of trials have focused on atypical antipsychotics, which have been widely prescribed for the treatment of psychotic symptoms in AD. In general, these trials have suggested that atypical antipsychotics, such as Aripiprazole, can confer significant improvements in agitation and aggression in this population over a 6-12 week period [123-125]. In addition to having beneficial effects on behavior symptoms, atypical antipsychotics can also lead to modest benefits for psychosis, as documented in a recent review [124]. Some commonly reported adverse effects of atypical antipsychotics include sedation, falls, gait disturbances, and extrapyramidal symptoms. Further, increasing concerns have been expressed regarding the potential for serious adverse outcomes including stroke and death in AD who are treated with long-term atypical antipsychotics [5, 124].

There is accumulating evidence to suggest that cholinergic dysfunction is also associated with neuropsychiatric deficits. As such, ChEIs have also been considered in the treatment of such symptoms in AD [126]. Findings from a recent systematic review demonstrated that ChEIs could improve neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) in AD patients, although specific breakdown of benefits in specific subscores was not reported [127]. However, scores for each sub-domain of the NPI were not reported. Findings from meta-analysis and pooled analysis also indicated that Memantine confers a beneficial effect in the prevention and treatment of agitation and aggression, as well as psychosis over 3-6 months in patients with AD [75, 77, 128, 129].

Given the potential adverse outcomes associated with the administration of pharmacological treatment for behavioural and neuropsychiatric symptoms, there is increasing support for the use of psychological interventions. For instance, Cohen-Mansfield and colleagues [130, 131] reported that the implementation of psychological intervention based on personalized activities and interaction (*e.g.* personalized

music and structured social interaction) within a care home setting can have significant benefits for agitation in AD patients. Nevertheless, the level of skill required of the care staff may constrain the implementation of these individualized interventions [5].

Previous research has reported that up to 89% of PDD patients have at least one neuropsychiatric symptom [9]. In contrast to that in AD, the use of atypical antipsychotics in PDD patients is a difficult clinical dilemma because atypical antipsychotics block dopamine (D2) receptors, which can lead to worsening of motor symptoms in PD [132] (for a review of atypical antipsychotics for the treatment of PD psychosis, see Goldman and Holden (2014) [133]). Another potential complication relates to severe neuroleptic sensitivity, which has a severe psychomotor adverse reaction (which can resemble neuroleptic malignant syndrome) to atypical antipsychotics [133, 134]. Based on the finding that cholinergic deficits in PD may predispose them to psychosis as well as many of the cognitive deficits seen in PD [135], ChEIs such as Rivastigmine and Donepezil have been explored in the context of treating PDD patients and PD patients with cognitive impairment [136-138]. Subgroup analyses of the EXPRESS study [21] described above revealed that as compared to non-hallucinators, Rivastigmine was more effective in improving cognitive outcome measures and hallucinations in hallucinators [136].

Recent research has suggested that Pimavanserin, a serotonin 5-HT_{2A} inverse agonist, may be another potential treatment option for psychosis in PD patients by targeting non-dopamine neurotransmitter [139, 140]. In PD, the presence of visual hallucinations are reported to be linked to increased numbers of 5-HT_{2A} receptors in visual processing areas [141]. Recent genetic research also suggested that psychotic symptoms in PDD patients are associated with polymorphisms of the 5HTTLPR serotonin transporter [142]. While atypical antipsychotics target the 5-HT_{2A} pathway, other receptor families are also affected at varying levels [139]. As such, with the receptor selectivity of Pimavanserin, this drug has been in development as a treatment for psychosis in PD [140]. Preliminary evidence of Pimavanserin's antipsychotic benefits and good tolerability has been reported in previous studies [139, 143-145]. However, the potential benefits of Pimavanserin treatment for psychosis are yet to be specifically determined in PDD patients.

5.2. Mood

Considering the high prevalence of depression in AD, with approximately 20-25% AD patients experiencing depressive features [6], research on interventions for depression in AD has received growing attention. In addition to improving cognition, previous work has also suggested that ChEIs can lead to improvements in mood (e.g. apathy, depression) in AD patients [23, 146]. In a study that investigated the efficacy of Donepezil on cognitive outcomes in AD, the drug's efficacy in relation to NPI scores was also explored [23]. Findings showed that participants who received Donepezil treatment exhibited significant benefits on apathy, depression, and anxiety as compared to the control group [23]. In addition to ChEIs, a few small studies

have also suggested that serotonergic reuptake blockers (e.g. Citalopram, Paroxetine) may offer some benefit in treating depression in AD patients [49].

In addition to pharmacological treatments, previous work has suggested that non-pharmacological interventions may have some positive effects on dysphoric mood in AD. For instance, several studies have investigated the effect of exercise intervention, but results have been mixed [147-150]. Teri *et al.* [147] reported that daily 30-minute physical training focusing on aerobic, flexibility and strength reduced depressive symptoms in 153 AD patients. However, Rolland *et al.* (2007) [148] observed no effect on depression in a 12-month collective exercise program (1 hour, twice weekly of walk, strength, balance, and flexibility) in a group of 134 AD patients.

Depression is common in PD patients, with approximately 40% of patients experiencing depressive symptoms [151]. A meta-analysis of studies of both antidepressant treatment and placebo for depression in PD demonstrated large effect sizes for both groups [152]. Previous research has also rated antidepressants Pramipexole, Nortriptyline, and Desipramine to be efficacious (Pramipexole) and likely efficacious (Nortriptyline and Desipramine) for the treatment of depression in PD [65]. Despite such high prevalence, there have been surprisingly few antidepressant studies in the PD and to date, no RCT on anti-depressants in PDD has been done so far.

5.3. Sleep

Sleep disturbance is a common occurrence in AD, affecting up to 56% of patients in clinic samples [7]. A recent systematic review evaluated both pharmacological (e.g. Melatonin, acetylcholinesterase inhibitors, second generation antipsychotics) and non-pharmacological treatment strategies to ameliorate sleep disturbance in AD patients. Findings showed that pharmacological treatments of sleep in AD demonstrated limited efficacy. In contrast, non-pharmacological interventions, involving behavioral modification (decreasing time spent in bed during daytime) and bright light therapy (increasing daily sunlight exposure) showed significant improvement in sleep symptoms. Further research will be necessary to improve the armamentarium of treatments available, which may help improve treatment outcomes [153].

In addition to poor sleep, PDD patients often have excessive daytime sleepiness, Rapid Eye Movement (REM) Sleep behaviour disorder (RBD), and sleep fragmentation/insomnia [115]. However, pre-existing data on treatment for sleep disturbances in PDD patients is sparse. As a follow-up to the Aarsland *et al.* (2009) [78] study on Memantine in PDD and DLB patients described above, Larsson *et al.* (2010) [154] carried out an analysis of secondary outcome measures of sleep disturbances to investigate whether Memantine brought improvement in the severity of excessive daytime sleepiness and RBD in participants included in that study ($n = 42$) more so than those treated with placebo. It was reported that probable RBD, as assessed by the Stavanger Sleep Questionnaire, was decreased by Memantine, and both diagnostic groups (PDD and DLB)

Table 1. Summary of pharmacological treatments for AD and PDD.

Drug Name	Drug Type	Standard Dosage in AD	Standard Dosage in PDD	Mechanism of Action	Efficacy in AD	Efficacy in PDD	Common Side Effects in AD	Common Side Effects in PDD
Rivastigmine	Cholinesterase inhibitor	Capsule: 3-12mg/day, Patch: 4.6-13.3mg/day	Capsule: 3-12mg /day, Patch: 4.6-9.5mg/day	Inhibits the action of acetylcholine and butyrylcholine in the brain	Efficacious for the treatment of mild to moderate AD	Efficacious for the treatment of mild to moderate PDD	Nausea, vomiting, diarrhea, dizziness, loss of appetite, weight loss, muscle weakness	Nausea, vomiting, diarrhea, loss of appetite, dizziness, tremor
Donepezil	Cholinesterase inhibitor	5-10mg/day	5-10mg/day	Delays the breakdown of acetylcholine released into synaptic clefts	Efficacious for patients with mild, moderate, and severe AD	Insufficient evidence	Nausea, vomiting, diarrhea, dizziness, headache, loss of appetite, weight loss, muscle cramps, fatigue	Nausea, vomiting, diarrhea, insomnia
Galantamine	Cholinesterase inhibitor	8-24mg/day	4-24mg/day	Inhibits acetylcholinesterase, and stimulates nicotinic acetylcholine receptors to release more acetylcholine in the brain	Efficacious for the treatment of mild to moderate AD	Insufficient evidence	Nausea, vomiting, diarrhea, dizziness, headache, loss of appetite, weight loss	Nausea, vomiting, diarrhea
Memantine	NMDA receptor antagonist	5-20mg/day	5-20mg/day	Regulates glutamate activation and blocks the toxic effects of overactive glutamatergic activity	Efficacious for the treatment of moderate to severe AD	Insufficient evidence	Dizziness, headache, confusion, constipation	Dizziness, tiredness, fall

contributed equally to the outcome. However, no significant improvement was observed in the severity of excessive daytime sleepiness. Memantine also appeared to be well tolerated in both diagnostic groups. At present, there are no approved treatments for sleep disturbances in PD. Nevertheless, several drug agents may hold some promise in treating sleep disturbances in PD. This includes Modafanil for the treatment of excessive daytime sleepiness, Eszopiclone for insomnia, as well as Clonazepam and Melatonin for RBD (for a review, see Trotti and Bliwise (2014) [155]). However, the potential side effects of Clonazepam, such as excessive daytime sleepiness, confusion, and cognitive impairment, may limit its usefulness in the PD population [155]. Such findings are encouraging and suggest the need for exploration in PDD patients.

6. CONCLUSION

In conclusion, research on pharmacological therapies for AD and PDD has so far had some success in terms of developing symptomatic treatments (See Table 1. for summary). However, research is needed to develop a broader and more fundamental therapeutic approach to both AD and PD, including an emphasis on disease-modifying therapies.

Until new preventive or disease-modifying treatments are approved, it is vital that clinicians optimize the use of available pharmacological and non-pharmacological interventions for AD and PDD. For patients with mild to moderate AD, ChEIs are the traditional first line of pharmacological treatment, whereas for patients with moderate to severe AD, treatment with Memantine and Donepezil are both indicated. With regard to patients with mild to moderate PDD, Rivastigmine is currently the only approved pharmacological treatment. In addition, non-pharmacological therapies, such as cognitive training and exercise may also play a role in improving cognitive functioning in these populations. However, well designed studies are needed to provide more definitive evidence. The treatment of any co-existing conditions in both AD and PDD patients is also vital as they may aggravate pre-existing cognitive deficits. Importantly, treatments for such symptoms require careful consideration as they may not be part of the disease process itself, and may result from other factors, such as side effects related to the treatment administered. Furthermore, the drug interactions between medications for PD (e.g. dopamine agonist) and PDD have not been systematically evaluated, and should be approached with caution.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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