Drugs & Aging (2019) 36:589–605
https://doi.org/10.1007/s40266-019-00668-7

REVIEW ARTICLE

Current Agents in Development for Treating Behavioral and Psychological Symptoms Associated with Dementia

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Published online: 8 April 2019

Abstract

Behavioral and psychological symptoms associated with dementia are highly prevalent and are associated with an increased risk of institutionalization and mortality. Current pharmacological treatments for these symptoms include cholinesterase inhibitors, antipsychotics, and selective serotonin reuptake inhibitors. When used for treating behavioral and psychological symptoms associated with dementia, they are associated with limited efficacy and/or serious adverse events. As such, there has been extensive research into novel agents with varying mechanisms of action targeting behavioral and psychological symptoms associated with dementia. In this article, we present the results of a comprehensive literature search and review that evaluates current agents that have completed or are currently in clinical trials for treating behavioral and psychological symptoms associated with dementia as a primary outcome. We highlight novel agents from miscellaneous drug classes, such as dextromethorphan/quinidine, bupropion/dextromethorphan, lumateperone, deudextromethorphan/quinidine, methylphenidate and scyllo-inositol, and drugs from various therapeutic classes (including atypical antipsychotics, selective serotonin reuptake inhibitors, and cannabinoids) that have demonstrated promising results and were generally well tolerated. Future research with large appropriately powered studies using validated outcome measures for behavioral and psychological symptoms associated with dementia should be conducted to further establish the clinical utility of these agents.

Key Points

Discovering new medications for treating behavioral and psychological symptoms associated with dementia is an active area of research.

We discuss results from recently completed clinical trials (e.g., methylphenidate, nabilone, dronabinol, and citalopram) and review medications that are still being investigated in clinical trials (such as dextromethorphan/quinidine, bupropion/dextromethorphan, lumateperone, deudextromethorphan, scyllo-inositol, brexpiprazole, and pimavanserin).

Results from recent advances can inform future research into this field and potentially improve treatment.

1 Introduction

There are close to 50 million people worldwide living with some form of dementia [1]. Major forms of dementia include Alzheimer's disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementias [1]. In its early stages, dementia consists of significant deterioration in cognitive functions and capabilities. These impairments include deficits in memory, such as working, episodic, and semantic memory, processing information, executive functioning, judgment, learning capacity, and language, all of which decline as the disease progresses [2, 3]. Alzheimer's disease is the most common form affecting roughly 60–70% of people with dementia and it is anticipated to affect 115 million people by 2050 [3].

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In addition to cognitive impairment, individuals affected with dementia often experience neuropsychiatric symptoms, also known as behavioral and psychological symptoms related to dementia (BPSD) [2, 3]. These symptoms include depression, irritability, hallucinations, delusions, sleep disturbances, eating problems, anxiety, apathy, agitation, and aggression [4]. Moreover, clusters of BPSD, such as hyperactivity (agitation and aggression), affective disorder (anxiety and depression), and psychosis (delusions and hallucinations) are common [5]. A study by Steinberg et al. estimated the 5-year point prevalence of BPSD in a sample of 408 patients with dementia, with symptoms assessed annually starting at baseline [6]. They found that the point prevalence for delusions was 18% at baseline compared to 34–38% at year 5 [6]. Additionally, the point prevalence of hallucinations went from 10 to 19–24%, agitation from 13 to 24%, depression from 29% at baseline compared to 41–47%, apathy from 20 to 51%, and anxiety from 14 to 24–32% [6]. The point prevalence for any symptom was 56% at baseline, and 76–87% at year 5. The 5-year point prevalence was greatest for depression at 77%, followed by apathy (71%) and anxiety (62%) [6].

Over the course of the disease, 98% of those with dementia experience at least one neuropsychiatric symptom [3, 6, 7]. This not only reduces the quality of life for the patients, but also places significant distress on the caregiver and the patients' family [8]. Economically, the impact of BPSD on healthcare costs is significant, with severity of symptoms being associated with increases in the cost of care [9, 10]. The presence of BPSD has been shown to be a significant predictor of a patient becoming institutionalized, requiring extensive care, and having an increased risk of mortality [4, 5].

The diagnostic criteria for dementia produced by the National Institute of Aging, American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association have been pivotal tools in improving treatments in clinical research settings based on significant improvements in understanding the etiology and neuropathological changes associated with dementia. Furthermore, advocacy for biomarker-based diagnostic criteria for AD has stimulated further research into novel and personalized treatment protocols.

The prevalence and impact of BPSD have led to recognition of the need for pharmacological interventions. The pharmacological management of BPSD requires an understanding of the medical, social, and psychological context in which the symptoms present, and usually occurs after the implementation of non-pharmacological treatments as first-line interventions [11]. Professional healthcare providers must first control for precipitating factors that may influence BPSD prevalence, such as environmental triggers, comorbidities, and pain [5]. When non-pharmacological interventions prove to be difficult to implement or ineffective in reducing symptoms, pharmacological treatments can be considered. Many current pharmacological agents have been repurposed in clinical trials for treating BPSD. The traditional agents aimed at treating cognitive symptoms of dementia are cholinesterase inhibitors and memantine. Cholinesterase inhibitors, which have modest benefits for cognition, can improve neuropsychiatric symptoms [12]. Atypical antipsychotics, such as risperidone, olanzapine, and aripiprazole, have demonstrated efficacy for improving agitation, aggression, and psychosis symptoms associated with dementia [13–15]. Symptoms of depression and anxiety are often treated with selective serotonin reuptake inhibitors (SSRIs) [16]. Similarly, benzodiazepines have been prescribed for the management of anxiety on an acute basis [16].

While BPSD can sometimes be managed with pharmacotherapies, these agents are associated with adverse events, requiring careful consideration of the risk/benefit ratio. The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease trial compared olanzapine, quetiapine, risperidone, and placebo, finding that those atypical antipsychotics had similar efficacy for improving BPSD but resulted in cognitive decline over time [15]. Numerous meta-analyses have concluded that atypical antipsychotics can increase the risk of cerebrovascular accidents and mortality in patients with dementia and these agents therefore have black–box warnings in this population [17]. Some SSRIs also carry a risk of experiencing cardiovascular events; the Citalopram for Agitation in Alzheimer Disease (CitAD) study found that a 30-mg/day dose of citalopram resulted in prolonged QT intervals [18–20]. The adverse events associated with benzodiazepines include sedation, ataxia, falls, and negative cognitive effects; hence there is wariness with prescribing these agents long term in elderly populations [16, 21].

The treatment of BPSD is dependent upon accurately and specifically measuring these symptoms. There are numerous BPSD measures that have been validated for symptoms like depression, agitation, and psychosis such as the Neurobehavioral Rating Scale (NBRS) and the Neuropsychiatric Inventory (NPI) [22]. The NPI is most notably used to measure the 12 BPSD associated with AD and dementia and has a version available to be used in nursing homes known as the Neuropsychiatric Inventory-Nursing Home (NPI-NH). The NPI furthermore includes caregiver distress as a measure to look at the secondary effects of behavior on caregivers. Scales for depression include the Geriatric Depression Scale, the Center for Epidemiologic Studies Depression Scale, the Hamilton Depression Rating Scale, and the Cornell Scale for Depression in Dementia [23, 24]. Behavioral disturbances such as agitation and aggression can be measured by the

Behavioral Pathology in Alzheimer's Disease [25], Cohen Mansfield Agitation Inventory (CMAI) [26], NPI-Agitation/Aggression Subscale [27], and Pittsburgh Agitation Scale [28]. Apathy is often measured by the Apathy Evaluation Scale (AES) as well as with the Apathy Subscale of the NPI [29].

The NPI is often used in clinical trials because of its comprehensiveness, lack of symptom overlap, ease of administration, and flexible approach to observing BPSD [22]. Studies utilizing the NPI have examined the rate of behavioral change annually, relationship to cognitive, global, and functional measures, standard deviations, and also requirements for determining sample size in clinical trials [22]. As a result, its use in clinical trials has good content validity with internal consistency, with positive test–retest and inter-rater reliability across various groups [4, 22].

Given that there are few options for treating BPSD, further research into understanding the etiology of these symptoms in association with AD and dementia, and the allocation of resources towards developing novel agents that uniquely target neuropsychiatric symptoms is warranted. Fortunately, a new era of pharmacological interventions targeting novel methods of treating BPSD may shed light on providing care for patients with dementia, while reducing the risk of adverse events. Therefore, this review intends to focus on current and novel agents being investigated for treating BPSD as the primary outcome in clinical trials.

Three reviewers individually searched ClinicalTrials.gov for investigational agents in completed and ongoing clinical trials explored for the treatment of neuropsychiatric symptoms associated with dementia (up to July 2018). We searched the terms "depression", "irritability", "hallucinations", "delusions", "anxiety", "apathy", "agitation", "aggression", "sleep disturbances", and "eating disorders" in conjunction with "neuropsychiatric symptoms" or "behavioral and psychological symptoms related to dementia" for the condition "dementia". We included studies where BPSD were evaluated as a primary outcome, using validated rating scales for the symptom in question. We included agents that were explored in randomized, double-blind, placebo-controlled trials. We excluded devices that were being explored for BPSD and phase IV studies. We then completed a comprehensive search of the literature using the OVID databases for published clinical trial results and associated studies of the included agents and inquired into findings reported by the pharmaceutical company websites when published results were unavailable.

The advantages of this approach include the assurance that all studies included in this review were randomized, double-blind, placebo-controlled studies and allowed us to discuss ongoing studies investigating agents for which results have not yet been published. A disadvantage of this approach is that we could not conduct this review as a systematic review or meta-analysis. Table 1 summarizes study characteristics of ongoing clinical trials included in this review.

2 Atypical Antipsychotics

Up to 60% of patients with dementia in hospitals and long-term care homes are prescribed antipsychotics to treat neuropsychiatric symptoms related to dementia and AD [5, 14, 30]. The majority of these antipsychotics are second-generation atypical antipsychotics; while having been studied extensively, further research into these agents is necessary given the effect sizes in previous studies performed, poor drug tolerability, and increased risk of mortality related to their use [5, 30]. Newer agents that have been explored in this class include brexpiprazole, lumateperone, and pimavanserin.

Brexpiprazole was originally approved by the US Food and Drug Administration in July 2015 to treat adults with schizophrenia and as an added treatment with antidepressants to treat adults with major depressive disorder. It is a quinolinone derivative of aripiprazole and its mechanism of action is not fully elucidated. Its efficacy is hypothesized to be mediated by a combination of partial agonism at dopamine D_2 receptors and at serotonin 5-HT_{1A} receptors, as well as antagonist activity at 5-HT_{2A} receptors with high affinity, with additional antagonistic affinity for α1B/2C adrenergic receptors [31, 32].

Two phase III, randomized, double-blind, placebo-controlled, multicenter studies with 700 individuals in total, examined the efficacy, safety, and tolerability of brexpiprazole. Both studies recruited outpatients and institutionalized patients aged 51–90 years diagnosed with probable AD and symptoms of agitation, who were required to have a total score of ≥ 4 on the agitation/aggression item of the NPI at screening and baseline to be included in the study. Participants were assigned fixed doses of 1 mg/day, 2 mg/day, or placebo in one trial, and 0.5 mg/day, 1 mg/day, or 2 mg/day or placebo in the other trial [33]. Primary outcome measures focused on changes from baseline in the CMAI total score after 12 weeks. In the first trial ($n = 430$), patients demonstrated significantly reduced CMAI scores compared with placebo [33]. However, while the second study ($n = 270$) showed an overall reduction in total CMAI in the brexpiprazole group, it was not significantly different compared to placebo [33]. Adverse events in both trials were reported with an incidence of 3% or greater in active vs. control groups, with insomnia (4.7% vs. 3.3%, respectively), agitation (3.5% vs. 2.9%), and somnolence (3.3% vs. 2.2%) being the most common adverse events [33]. There

Table 1 Agents currently being investigated in ongoing clinical trials for behavioral and psychological symptoms associated with dementia

Agent	Clinical trial identifier	Phase	Participant diagnosis	Number of participants	Study design	Dose	Study duration	Behavioural or psychiatric symptom targeted	Primary outcome	Tentative study completion date
Brexpiprazole	NCT03620981	III	Clinical diagnosis of AD	407	Randomized, double-blind, placebo-controlled, parallel-group	Low dose or high dose once daily	10 weeks	Agitation	Change in CMAI score from baseline to 10 weeks	December 2020
Lumateperone	NCT02817906	III	Clinical diagnosis of AD	360	Randomized, double-blind, placebo-controlled, parallel-group	9 mg/day	4 weeks	Agitation	Change in CMAI score over 4 weeks	August 2018
Escitalopram	NCT03108846	III	Clinical diagnosis of AD, based on NIA-AA criteria	392	Randomized, double-blind, placebo-controlled, parallel-group	5–15 mg/day	12 weeks	Agitation	Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change over 12 weeks	August 2022
Cannabis oil	NCT03328676	II	Diagnosis of dementia (NCD), based on DSM-V criteria for at least 6 mo prior	60	Randomized, double-blind, placebo-controlled, parallel-group	Each Avidekel oil drop is approximately 0.04 mL in volume containing about 12 mg of CBD and 0.6 mg of 9-THC	16 weeks	Agitation	Proportion of subjects achieving a CMAI $\geq$ 4-point decrease during the treatment period	May 2020
Dronabinol	NCT02792257	II	Diagnosis of dementia due to AD	160	Randomized, double-blind, placebo-controlled, parallel-group	5–10 mg/day	3 weeks	Agitation	Symptoms of agitation over a 3-week time frame	December 2020

Table 1 (continued)

Agent	Clinical trial identifier	Phase	Participant diagnosis	Number of participants	Study design	Dose	Study duration	Behavioural or psychiatric symptom targeted	Primary outcome	Tentative study completion date
AVP-786	NCT03393520	III	Diagnosis of probable AD based on NIA-AA criteria	412	Randomized, double-blind, placebo-controlled, parallel-group	2 unspecified daily AVP-786 doses	12 weeks	Agitation	Change in CMAI from baseline to week 12	June 2021
	NCT02442778	III	Diagnosis of probable AD based on NIA-AA criteria	470	Randomized, double-blind, placebo-controlled, parallel-group	2 unspecified daily AVP-786 doses	12 weeks	Agitation	Change in CMAI from baseline to week 12	December 2019
	NCT02442765	III	Diagnosis of probable AD based on NIA-AA criteria	380	Randomized, double-blind, placebo-controlled, parallel-group	2 unspecified daily AVP-786 doses	12 weeks	Agitation	Change in CMAI from baseline to week 12	April 2019
Methylphenidate	NCT02346201	III	Possible or probable AD, based on NINCDS-ADRDA criteria	200	Randomized, double-blind, placebo-controlled, parallel-group	20 mg/day	6 months	Apathy	Change in NPI-Apathy Subscale score from baseline to 6 months	August 2020
Lithium	NCT02862210	II	Behavioral variant FTD or semantic variant, primary progressive aphasia, which is generally accompanied by a behavioral syndrome, or agrammatic/non-fluent primary progressive aphasia with behavioral symptoms	60	Randomized, double-blind, placebo-controlled, parallel-group	600 mg/day	12 weeks	Agitation and aggression	Change in NPI score over 12 weeks	March 2020
	NCT02129348	II	Possible or probable AD by standard NIA criteria	80	Randomized, double-blind, placebo-controlled, parallel-group	600 mg/day	12 weeks	Agitation	Change in NPI score over 12 weeks	April 2019

Table 1 (continued)

Agent	Clinical trial identifier	Phase	Participant diagnosis	Number of participants	Study design	Dose	Study duration	Behavioural or psychiatric symptom targeted	Primary outcome	Tentative study completion date
Carbamazepine Mirtazapine	NCT03031184	III	Possible or probable AD based on NINCDS-ADRDA criteria	471	Randomized, double-blind, placebo-controlled, parallel-group	100 mg/day 15 mg/day	12 weeks	Agitation	Change in CMAI score from baseline to 12 weeks	August 2019
MP-101	NCT03044249	II	Dementia associated with Parkinson's disease, dementia with Lewy bodies, possible or probable AD, frontotemporal degeneration spectrum disorders, vascular dementia	100	Randomized, double-blind, placebo-controlled, parallel-group	60 mg/day	10 weeks	Psychosis and/or agitation and aggression	Change from baseline to week 10 in NPI-Psychosis Subscale	January 2021
AXS-05	NCT03226522	II/III	Diagnosis of probable AD, based on NIA-AA criteria	435	Randomized, double-blind, placebo-controlled, 3-arm, parallel-group	Unspecified	5 weeks	Agitation	Change from baseline to week 10 in the CMAI	September 2019
Intranasal oxytocin (Syntocinon®)	NCT03260920	II	Diagnosis of probable FTD (behavioural variant FTD, FTD-semantic subtype, or FTD-progressive non-fluent aphasia)	112	Randomized, double-blind, controlled, crossover, adaptive	Unspecified low, medium, and high dose	20 weeks	Apathy	Change in NPI apathy score over 20 weeks	September 2021

AD Alzheimer's disease, *CBD* cannabidiol, *CMAI* Cohen Mansfield Agitation Inventory, *DSM-V* Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, *FTD* frontotemporal dementia, *NCD* neurocognitive disorder, *NIA* National Institute on Aging, *NIA-AA* National Institute on Aging and Alzheimer's Association *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, *NPI* Neuropsychiatric Inventory, *THC* tetrahydrocannabinol

were 66 deaths occurring during the trial; however, those were judged to be unrelated to treatment [33]. A phase III randomized, double-blind, placebo-controlled trial is currently underway ($n=407$) where participants with probable AD will receive 1 or 2 mg/day of brexpiprazole or placebo over 10 weeks to treat agitation with the primary outcome measure being mean change in CMAI scores from baseline at week 10 (ClinicalTrials.gov Identifier: NCT03620981).

Lumateperone is a newer investigational atypical antipsychotic. It is a potent antagonist at 5-HT_{2A} receptors, and a serotonin reuptake inhibitor. It further exhibits presynaptic agonism and postsynaptic antagonism at D_2 receptors, which allows it to act as a mesolimbic/mesocortical dopamine phosphoprotein modulator [34–36]. Furthermore, it binds with high affinity to D_1 receptors [36, 37]. It indirectly enhances glutamatergic modulation through N-methyl-D-aspartate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid channels in the prefrontal dorsolateral cortex by D_1 receptor activation and increases protein phosphorylation in the mammalian target of rapamycin pathway [35, 38].

Its ability for indirect glutamatergic modulation, and multiple receptor pathway activity, suggests its potential use as a rapid treatment agent in treating a broad range of BPSD such as agitation, aggression, and sleep disturbances with a reduced incidence of side effects compared with other atypical antipsychotics. Initial phase II trial results showed it was well tolerated across a range of low dosages with improved cognition and reductions in sleep disturbances, agitation, and depression [37, 39]. A phase III, double-blind, placebo-controlled, multicenter trial is currently underway looking at the efficacy and safety of a 9-mg/day dosage in patients with AD ($n=360$) for 4 weeks (ClinicalTrials.gov identifier: NCT02817906). Patients recruited will have a clinical diagnosis of probable AD and clinically significant symptoms of agitation, with the primary outcome measure being the change in CMAI score.

Pimavanserin was approved in 2016 for treating hallucinations and delusions with psychosis in Parkinson's disease, showing greater efficacy in patients with more severe psychotic symptoms [40]. Interestingly, it works as an inverse agonist and antagonist at 5-HT_{2A} receptors, reducing the baseline activity of the 5-HT_{2A} receptor and blocking the actions of agonists. More recently, pimavanserin has been shown to mediate effects at 5-HT_{2C} receptors without any antagonistic properties at D_2 receptors—in contrast to many antipsychotics in treating psychosis [40, 41]. Because an upregulation of 5-HT_{2A} receptors is implicated in psychotic symptoms, pimavanserin working as an inverse agonist at 5-HT_{2A} receptors may lead to a preservation in cognition and a reduction in psychotic symptoms, with the minimized 5-HT_{2C} activity mitigating side effects associated with atypical use [40, 42].

Pimavanserin has recently been examined as a treatment for neuropsychiatric symptoms in AD. A phase II, randomized, double-blind, placebo-controlled trial across the UK included patients ($n=181$; 90 receiving pimavanserin) with possible or probable AD and psychotic symptoms such as delusions or hallucinations, who received either 34 mg/day of pimavanserin or placebo. Primary outcome measures focused on change from baseline at week 6 measured by the NPI-NH, as well as maintained efficacy and safety at week 12. At week 6, the pimavanserin group had a significantly greater mean change (39.5%) in their NPI-NH psychosis score from baseline compared with the control group (19.3%) [41]. Fifty-five percent of pimavanserin-treated individuals saw a clinically relevant response of greater than 30% improvement in psychosis subscale scores and this was significantly different compared to 37% of controls [41]. Results in other individual domains of NPI were not significant. The data were also stratified by comparing patients who scored either <6 and ≥ 6 on the Mini-Mental State Examination and <12 and ≥ 12 on the NPI-Psychosis Subscale at baseline. The high-psychosis group saw significantly more improvement in symptoms as demonstrated by a greater mean change in the NPI-NH psychosis score in the pimavanserin vs. placebo group [41]. Pimavanserin did not significantly reduce NPI-NH psychosis scores compared to baseline scores in patients with less severe psychotic symptoms at baseline (<12 on the NPI-Psychosis Subscale) compared to placebo [41]. The NPI total score was not significantly different between treatment and control groups. Unfortunately, there was no observable difference between treatment and control groups at week 12, which could represent a lack of sustained benefit, but could also be attributable to the heterogeneous and dynamic nature of psychosis over time [30, 41].

Common side effects in the active vs. control groups included falls (23% and 23%), urinary tract infections (22% and 28%), and agitation (21% and 14%), with eight participants in the active group and 11 participants in the control groups discontinuing because of adverse events [41]. Currently, a double-blind, placebo-controlled, relapse-prevention study of pimavanserin ($n=356$) is underway to evaluate the efficacy of pimavanserin in preventing a relapse of psychotic symptoms in subjects with dementia-related psychosis who were stabilized after 12 weeks of an open-label pimavanserin treatment of either 20 mg, 34 mg, or placebo.

3 Selective Serotonin Reuptake Inhibitors

Substantial evidence shows that monoaminergic systems are affected in the pathogenesis of AD [43], and this has been proposed as a target for BPSD [44–47]. In particular, the serotonergic system [44, 48, 49] has been targeted in recent clinical trials using selective serotonin reuptake inhibitors (SSRIs) as an alternative to antipsychotics to treat

neuropsychiatric symptoms such as psychosis, agitation, aggression, and depression. Selective serotonin reuptake inhibitors are generally well tolerated in patients with AD, resulting in fewer safety concerns and decreased risks to mortality compared with antipsychotics and other antidepressant medications [50].

Citalopram is one of the most selective inhibitors of the SSRI class and demonstrates a low incidence of side effects compared with other SSRIs, good patient compliance, and a low potential for interactions with other concomitant medications [51]. Based on these factors, citalopram has been compared to the antipsychotics perphenazine, risperidone, quetiapine, and olanzapine for the treatment of BPSD, particularly agitation and aggression. Patients who received citalopram or perphenazine showed statistically significant improvements on several Neurobehavioral Rating Scale factor scores compared with placebo, though only patients treated with citalopram showed significantly increased improvement in both their total Neurobehavioral Rating Scale and agitation/aggression scores compared with the placebo group [52]. In the study by Pollock et al., agitated/aggressive and psychotic symptoms decreased in both the citalopram and risperidone groups, though the improvement between the two groups did not differ significantly and the study lacked a placebo group. Notably, there was a significant increase in side-effect burden with risperidone but not with citalopram [53].

Similarly, Viscogliosi et al. found similar efficacy between citalopram, quetiapine, and olanzapine in reducing agitation with less adverse outcomes in the citalopram group compared with the atypical antipsychotics [54]. Based on these studies, the evidence supporting the efficacy of SSRIs in treating BPSD was intriguing but limited and required continued investigation.

The CitAD study was conducted to further explore the efficacy of citalopram for treating agitation in non-depressed patients with dementia [19]. The CitAD study was a phase III, randomized, double-blind, placebo-controlled, multicenter, parallel-group clinical trial in which participants with probable AD and clinically significant agitation received standardized psychosocial interventions combined with either citalopram up to 30 mg daily ($n=94$) or placebo ($n=92$). The citalopram group showed a significant reduction in agitation compared with placebo after 9 weeks of treatment; specifically, the citalopram group had significant improvements on the NBRS Agitation Subscale, CMAI, and total NPI [19]. Overall, there was no difference between the citalopram and placebo groups in terms of adherence or serious adverse events, though the citalopram group did show a significantly increased frequency of adverse events such as anorexia and fever. The citalopram group demonstrated a significantly greater decline in cognition as measured by lower Mini-Mental State Examination scores and an increase in the corrected QT interval by electrocardiogram [19]. Because of concerns regarding prolonged corrected QT intervals in the elderly caused by citalopram, the US Food and Drug Administration recommended dose restrictions while the CitAD study was ongoing [19]. As the CitAD study and previous studies utilized higher doses of citalopram, it was deemed difficult to determine if lower doses of citalopram would be efficacious in clinical practice [50]. Nonetheless, patients and their caregivers may find citalopram to be a more desirable pharmacological intervention compared to antipsychotics; the potential decline in cognition and increase in corrected QT intervals associated with citalopram are less severe than the heightened risk of cerebrovascular problems and mortality linked to antipsychotics [55].

Citalopram enantiomers have different affinities for the serotonin transporter; (S)-citalopram has about a 40-fold greater affinity compared with (R)-citalopram [56]. Microdialysis data have demonstrated that (S)-citalopram but not (R)-citalopram increases extracellular 5-HT levels in the rat frontal cortex [57]. Because (R)-citalopram blocks (S)-citalopram from binding at the transporter in vitro, it is hypothesized that (R)-citalopram may reduce the therapeutic benefit of citalopram if in fact the SSRI treats agitation by targeting the serotonergic system [55]. Through population-pharmacodynamic models based on data from the CitAD study, (R)-citalopram is speculated to have accounted for a greater amount of the adverse effects associated with citalopram while (S)-citalopram (escitalopram) exposure was more efficacious for the treatment of agitation [56]. Wu et al. found that when treated for major depressive disorder, geriatric patients who received escitalopram experienced superior treatment persistence and less hospitalizations compared with patients who received citalopram [57].

Escitalopram was compared to the atypical antipsychotic risperidone for the treatment of BPSD associated with AD in a pilot, 6-week randomized, double-blind, controlled trial for in-patients hospitalized owing to behavioral symptoms of AD ($n=40$) [58]. Patients received either 1 mg of risperidone or 10 mg of escitalopram per day. The NPI total score improved in both groups, successfully reducing psychotic symptoms and agitation with no significant differences between groups. Completion rates were higher for escitalopram (75%) compared with risperidone (55%) as a result of adverse events, of which there were none reported for the escitalopram group [58]. A 12-week, randomized, double-blind trial for patients with depression associated with AD (final $n=60$) found no significant differences in measures of depression between the escitalopram and placebo groups as indicated by scores on the Cornell Scale for Depression in Dementia [53]. Adverse events related to treatment did not significantly differ between the two groups and no serious adverse events related to treatment were reported. Despite

the promising results found by An et al., 29% of participants enrolled did not finish the study; future studies will require increased statistical power before meaningful conclusions can be drawn [59]. Additionally, An et al. discussed the need to recruit patients whose depressive symptoms are characterized more robustly or as more severe to improve statistical power [59].

Findings regarding the efficacy of escitalopram indicate a potential alternative with less adverse effects compared to antipsychotics in treating agitation, psychotic symptoms, and depression. These findings must be replicated in future studies for longer durations and in larger samples before escitalopram can be recommended as an alternative to antipsychotics in clinical practice [50]. Currently, a phase III, 12-week, randomized, double-blind study using escitalopram for the treatment of clinically significant agitation in patients with AD is underway with a projected sample size of 392 patients (ClinicalTrials.gov identifier: NCT03108846).

4 Cannabinoids

It has recently been postulated that cannabinoids may be useful for treating agitation/aggression symptoms in dementia populations, based on case reports and retrospective and open-label clinical studies [60, 61]. They act on CB_1 and CB^-_2 cannabinoid receptors in the central nervous system mediating appetite, sedation, motor activity and coordination, and anti-anxiety effects [62–64]. However, previous clinical trial results have been mixed, warranting the need for larger, more robust studies to warrant the use of these agents for treating neuropsychiatric symptoms.

Delta-9-tetrahydrocannabinol (THC) itself has been explored for treating agitation in patients with AD. In a placebo-controlled, parallel-assignment trial where 24 participants were taking either a low dose of THC (1.5 mg) or a high dose of THC (4.5 mg) daily for 3 weeks, there was no difference in NPI or CMAI scores between the treatment groups [65]. Currently, there is an ongoing 16-week, randomized, double-blind, placebo-controlled trial investigating the efficacy of a different formulation of THC in the form of cannabis oil, containing 12 mg of cannabidiol and 0.6 mg of delta-9-THC per drop taken three times daily, in reducing agitation/aggression in patients defined as having dementia based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (ClinicalTrials.gov identifier: NCT03328676). The trial intends to recruit 60 patients with dementia with an NPI-NH agitation/aggression score of ≥ 3, and the primary endpoint is the proportion of subjects achieving a decreased score of 4 or more on the CMAI at the end of 16 weeks. Prior to this study, an open-label 4-week trial found that medical cannabis oil at a 2.5-mg dose taken twice daily significantly reduced delusions, agitation/aggression, irritability, apathy, and sleep and caregiver distress on the NPI in patients with AD [66].

Dronabinol, a synthetic THC analog and full CB_1 and CB^-_2 agonist, was the first cannabinoid explored in a randomized, placebo-controlled, crossover trial for this indication. A twice-daily dose of 2.5 mg was found to be efficacious in reducing disturbed behavior measured by the CMAI in patients with AD who were refusing food [67]. A similar clinical trial with 2.5 mg of dronabinol resulted in decreased night-time activity, as measured by wrist actigraphy, in the two patients enrolled in the trial [68]. Additionally, NPI scores decreased in both patients [68]. In both trials, there were carry-over effects of dronabinol as there were no washout periods. In the first dronabinol trial by Volicer et al [67] adverse events such as euphoria and fatigue were more frequently reported during dronabinol treatment; whereas the two patients in the latter trial reported no adverse effects [67, 68]. The dronabinol trials had promising results but are limited by their small sizes and carry-over effects. Forester et al. are currently recruiting for a larger double-blind, placebo-controlled, parallel-group trial to explore the efficacy of this agent further in agitated inpatients with AD (ClinicalTrials.gov identifier: NCT02792257). They are employing a larger dose than used in previous trials (10 mg daily) as it may be more effective in reducing agitation, which will be measured using the Pittsburgh Agitation Scale and NPI-Clinician Rating Scale [69].

Recently, nabilone, a synthetic cannabinoid and partial CB_1 and CB^-_2 agonist, significantly improved CMAI and NPI-agitation/aggression scores in agitated patients with AD in a randomized, placebo-controlled, crossover trial with 39 participants [70]. Overall NPI scores significantly improved during nabilone treatment and the Clinical Global Impression Scale indicated that patients had greater improvement while taking nabilone [70]. Nabilone was well tolerated in these patients. Sedation was a more common adverse effect while taking nabilone but was not significantly different between the treatment groups [70]. Presently, based on clinical trial results, nabilone appears to be a promising therapeutic cannabinoid for treating agitation and aggressive symptoms due to AD, given its advancement in the drug development pipeline. The results of the nabilone trial warrant the implementation of a larger multi-center study to further validate these results.

5 Dextromethorphan/Quinidine Agents

Dextromethorphan/quinidine, formulated in combination with low-dose quinidine, was examined to treat agitation and aggression in patients with probable AD. Normally marketed as an antitussive, dextromethorphan is a low-affinity N-methyl-D-aspartate receptor antagonist, σ1 receptor

agonist, serotonin and norepinephrine reuptake inhibitor, and neuronal nicotinic α3β4 receptor antagonist [71]. The ability for dextromethorphan to exert its effects in the central nervous system is limited because it is metabolized by the liver enzyme cytochrome P450 2D6; hence, the rationale for formulating it with quinidine. Quinidine, an anti-arrhythmic agent that blocks voltage-gated sodium channels, inhibits cytochrome P450 2D6; thus, increasing the bioavailability of dextromethorphan and making its effects longer lasting [72, 73].

Cummings et al. found that dextromethorphan/quinidine improved NPI agitation/aggression scores compared with placebo in a randomized, placebo-controlled, 10-week, sequential parallel-comparison trial [74]. The premise of the trial design was to improve the power of the study by offsetting placebo effects [74]. In stage 1, 93 participants were randomized to receive 20 mg/10 mg of dextromethorphan/quinidine once a day for the first week followed by twice a day for weeks 2 and 3, while 127 participants received placebo. From week 4 onward, stage 2 of the trial commenced. Patients who received dextromethorphan/quinidine continued their treatment while participants who did not respond to placebo were once again randomized in a 1:1 ratio to receive either 30 mg/10 mg of dextromethorphan/quinidine twice daily or placebo. In both stages, NPI agitation/aggression scores significantly decreased from baseline in the dextromethorphan/quinidine groups compared with the placebo group [74]. Furthermore, when simulating a parallel-group design comparing participants only randomized to dextromethorphan/quinidine ($n=93$) and those only randomized to placebo ($n=66$) across the 10 weeks, dextromethorphan/quinidine was superior in improving agitation/aggressive symptoms [74]. There was a significantly greater proportion of participants having clinically meaningful results of at least a 30% reduction in their NPI agitation/aggression scores over 10 weeks when only receiving dextromethorphan/quinidine (65.6%), compared with 47% of patients who only received placebo [74]. Additionally, dextromethorphan/quinidine significantly improved caregiver distress scores on the caregiver strain index, NPI total scores, NPI irritability/lability domain scores, and Cornell Scale for Depression in Dementia scores. Dextromethorphan/quinidine was generally well tolerated by participants, although there was a greater incidence of falls while taking this treatment. Larger trials investigating dextromethorphan/quinidine should be conducted to corroborate their findings and further establish the safety profile of this agent.

Deudextromorphan is a newer modified version of dextromethorphan/quinidine. It consists of deuterated dextromethorphan formulated with a low dose of quinidine. By modifying dextromethorphan with deuterium atoms, the chemical bonds are stronger; thus, making this agent less susceptible to enzyme cleavage by cytochrome P450 2D6. With lower first-pass liver metabolism, a much lower dose of quinidine is required in the overall formulation, resulting is a lower potential for drug interactions and cardiac effects induced by quinidine [75]. The drug manufacturer has demonstrated that deudextromorphan has a similar pharmacological profile to dextromethorphan/quinidine [76]. The safety, tolerability, and efficacy of deudextromethorphan is currently being investigated in phase II, placebo-controlled, multi-center clinical trials (ClinicalTrials.Gov Identifiers: NCT02442765, NCT02442778, NCT03393520). The TRIAD-1 and TRIAD 2 studies are currently recruiting participants to investigate two different doses of deudextromorphan and are expected to enrol 380 and 325 patients, respectively [77]. The endpoints are changes in CMAI scores and NPI agitation/aggression scores over 12 weeks [77].

6 Miscellaneous Agents

6.1 Scyllo-inositol

Scyllo-inositol is an endogenous inositol stereoisomer that is hypothesized to bind and inhibit Aβ42 peptide aggregates and Aβ fibrillogenesis, thereby potentially preventing Aβ deposition and Aβ-induced toxicity in patients with AD [78]. This drug exhibited promising therapeutic implications for improving symptoms associated with AD in preclinical mice models in which exposure to scyllo-inositol resulted in lower brain Aβ levels and plaque burden, preserved synaptic density, and improvement in existing learning deficits, and subsequently entered clinical trials [79].

In a 78-week, phase II, double-blind trial, 353 patients with mild-to-moderate AD were randomized to scyllo-inositol (250, 1000, or 2000 mg) or placebo twice daily to investigate the safety, efficacy, and biomarker effects of scyllo-inositol. No significant difference between the scyllo-inositol 250-mg and placebo groups was found on the Neuropsychological Test Battery after 78 weeks. The 1000- and 2000-mg groups were not included in the primary analysis because of greater rates of serious adverse events, including nine deaths, leading to an early discontinuation of the two higher dosage groups [80]. In addition to observing the 250-mg dose to be safe, scyllo-inositol had favorable pharmacokinetic measures with concentrations found to be higher in cerebrospinal fluid and the brain while cerebrospinal fluid Aβ42 levels significantly decreased compared with the placebo-group. The authors concluded that their study was limited by small sample sizes, rendering the results inadequate in supporting or refuting the efficacy of scyllo-inositol.

A subsequent study evaluated three scyllo-inositol doses (250 mg, 1000 mg, and 2000 mg) in comparison to a placebo in 351 patients with neuropsychiatric symptoms in a 78-week, phase II study for individuals with

mild-to-moderate AD. Though differences between treatment and control groups were not significant, the treatment group did experience improved neuropsychiatric symptoms that appeared to be partially mediated by brain myo-inositol regulation [81]. There are no current trials in progress for scyllo-inositol owing to a lack of efficacy during trials leading to termination; however, future studies may target earlier stages of AD and be useful in preventing neuropsychiatric symptoms associated with AD altogether [80].

6.2 Methylphenidate

Methylphenidate is a central nervous stimulant that blocks the dopamine transporter and norepinephrine transporter [82]. Dysfunction in the dopaminergic mesolimbic brain reward system is associated with symptoms of apathy in patients with AD, thus increasing dopamine levels at the level of the synapse may facilitate increases in motivation [83]. In a 12-week open-label study with 23 patients, a significant improvement in apathy was observed as measured on the AES [84]. A prospective, randomized, double-blind, placebo-controlled trial conducted in community-dwelling veterans ($n=60$) with mild AD demonstrated significantly greater improvements in apathy as measured by AES scores in the methylphenidate vs. the placebo group. Notably, patients in the methylphenidate group experienced greater improvement in functional status and depression when compared with the placebo group [85]. In a 6-week double-blind, multicenter trial (ADMET), 60 patients with AD with apathy were randomized into groups receiving 20 mg of methylphenidate per day or placebo. The methylphenidate group demonstrated significant improvements in NPI apathy scores over 6 weeks of treatment with potential clinically significant effects [86]. Apathy Evaluation Scale scores improved in the methylphenidate group compared with the placebo group though the results were not significant. This may be because of greater variance than seen in prior trials, resulting in a lack of power to detect AES changes within the current study design [86]. Additionally, a trend in global cognition improvements and limited adverse events and side effects were observed in the methylphenidate group. Because of the small sample size and a brief period for follow-up, further research on methylphenidate to treat apathy is planned to determine long-term clinical efficacy in heterogeneous populations [86]. While there is currently limited high-quality evidence for methylphenidate in effectively treating apathy, this agent seems promising as a potential pharmacotherapy for apathy in AD [87]. A follow-up, phase III, double-blind multicenter trial is in progress (ADMET 2) to compare the mean difference in NPI apathy scores from baseline to 6 months in 200 patients with AD randomly assigned to a target dose of 20 mg of methylphenidate daily or a matching placebo (ClinicalTrials.gov identifier: NCT02346201) [88].

6.3 Prazosin

In AD, a significant reduction in norepinephrine-producing locus coeruleus neurons has been observed, resulting in noradrenergic deficits in the hippocampus and frontal cortex of AD brains [89]. In transgenic APP23 mice who develop extensive Aβ pathology, the alpha 1-adrenoceptor antagonist prazosin reduced the generation of Aβ in N2a cells and prevented memory deficits over time, potentially owing to the anti-inflammatory response induced by prazosin [90]. Prazosin antagonizes norepinephrine effects at brain postsynaptic alpha-1 adrenergic receptors, leading to the compensatory upregulation of existing locus coeruleus neurons that maintain age-appropriate increased levels of norepinephrine outflow in the central nervous system [90]. Due to the relevance of noradrenergic systems in AD and the potential effects on BPSD, Wang et al. investigated the tolerability and efficacy of prazosin for behavioral symptoms in patients with agitation/aggression in patients with AD. In a double-blind, parallel-group study, 22 patients were randomized to receive either 1–6 mg of prazosin daily or a placebo. After 8 weeks, participants who received prazosin demonstrated significant improvements in their agitated/aggressive symptoms compared with those in the placebo group [91]. The onset of action with prazosin occurred rapidly, appeared to be clinically significant, and the degree of behavioral improvement matched changes observed in atypical antipsychotic randomized controlled trials [91]. Though symptoms were reduced and adverse effects were similar between the prazosin and placebo groups, the small sample size and high dropout rate during follow-up are constraints that limit interpretation of the study. Nonetheless, this study provides a rationale for further studies with larger samples, increased follow-up times, and analysis of efficacy for specific behavioral symptoms. There are currently no studies in progress for this purpose though prazosin is being used in a phase IV trial to increase the removal of tau and Aβ from the brains of veterans who have experienced mild traumatic brain injuries and have an increased risk of developing AD (NCT03221751). Additionally, Wang and colleagues undertook a 12-week, randomized, double-blind, controlled trial for agitated patients with AD and suggested that prazosin use may aid in treating behavioral problems by reducing excess adrenaline in the brain (NCT01126099). No results from this latter study have been reported.

6.4 Lithium

Lithium salts are a mood stabilizer with anti-manic properties often used to treat bipolar disorder and other psychiatric disorders [92]. Despite the extensive use of lithium within the past 50 years, there remains ambiguity surrounding the general mechanisms producing the observed effects of the

salts [93]. In the context of treating AD-related pathologies, lithium treatment potentially inhibits glycogen synthase kinase-3β, which blocks the accumulation of Aβ peptides in the brains of transgenic mice otherwise programmed to experience an overproduction of amyloid precursor protein [94]. The inhibition of glycogen synthase kinase-3β has been shown to reduce phosphorylated tau and inflammation in addition to increasing signaling activity of a serine/threonine kinase that regulates vital cellular functions such as growth and survival, protein synthesis, and transcription [94, 95]. Another potential mechanism postulates that lithium inhibits inositol monophosphatase, thereby reducing inositol triphosphate and altering the phosphatidylinositol signaling pathway needed for cell growth, death, secretion, and information processing [96]. This process upregulates autophagy and assists in the elimination of aggregate-prone cytosolic proteins [97]. Lithium treatment in animal models has been shown to improve or reverse aggression and learned helplessness behavior proposed to be related to depression, while reducing cognitive impairments [98–101]. Consequently, lithium may be a viable treatment for treating and preventing further AD-related neuropathologies. As lithium has been shown to significantly improve agitation, aggression, and restlessness in studies of psychiatric disorders, lithium may also benefit neuropsychiatric symptoms in AD. A phase II, 12-week, randomized, double-blind, controlled trial is currently in progress investigating the efficacy and side effects of low-dose lithium compared to a placebo in treating agitation in AD using changes in NPI scores as the primary outcome (NCT02129348). Additionally, another phase II, 12-week, double-blind, placebo-controlled trial is investigating the effects of a 600-mg/day dose of lithium in reducing agitation and aggression in patients with frontotemporal dementia as measured by the NPI (ClinicalTrials.gov identifier: NCT02862210).

6.5 Carbamazepine and Mirtazapine

Carbamazepine and mirtazapine are simultaneously being investigated for treatment of agitation and aggression associated with patients with AD in a large, phase III, multi-center study undergoing participant recruitment (Clinicaltrials.gov identifier: NCT03031184). Patients enrolled must be clinically diagnosed with AD according to the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria and have a CMAI score of 45 at baseline. Carbamazepine, whose mechanism of action is not fully elucidated, is an antiepileptic medication also prescribed for neuropathic pain and psychiatric disorders [102]. Mirtazapine is an antidepressant that acts by antagonizing noradrenergic and serotonergic receptors and is often prescribed to treat anxiety, insomnia, vomiting, and nausea [103]. Both drugs have previously demonstrated efficacious results for the indication being studied. A 12-week open-label pilot study found that a 15- to 30-mg daily dose of mirtazapine significantly reduced scores on the short-form CMAI [104]. Similarly, an open-label study found that carbamazepine was helpful in reducing agitated behavior in 15 patients with AD, who were not responsive to antipsychotics, based on measures of the Brief Psychiatric Rating Scale, although two patients discontinued because of adverse effects of leukopenia and allergic reactions [105]. Carbamazepine also improved agitation in patients with dementia as a secondary measure in a 6-week, randomized, single-blind, parallel-group study that enrolled 51 nursing home patients studying a daily dose of 300 mg [106]. The present study is examining the effects of 15 mg of mirtazapine per day and 100 mg of carbamazepine per day on changes in CMAI scores over 6 and 12 weeks.

6.6 Mp 101

MP-101 is currently in phase II clinical trials for the treatment of dementia-related psychosis and/or agitation, as defined as meeting clinical criteria for either AD, dementia with Lewy bodies, dementia associated with Parkinson's disease, frontotemporal lobe dementia, or vascular dementia, in addition to having a score of ≥ 4 in either the hallucinations or delusions items of the NPI, a score of ≥ 6 on the NPI Psychosis Subscale, or a score ≥ 6 in the NPI agitation/aggression domain. The primary endpoint for this study is the change in NPI-Psychosis Subscale score from baseline (ClinicalTrials.gov identifier: NCT03044249). As a mitochondrial modulator, MP-101 represents a novel mechanism of action being studied for this indication. Preclinical studies conducted by the drug manufacturer reported that a daily dose of MP-101 restored mitochondrial function by reducing free radicals, increased brain-derived neurotrophic factor levels, and had protective effects on dopamine neurons in Parkinson's disease models [107]. The manufacturer also reported that MP-101 significantly reduced oxidative stress, preserved brain volume, and improved motor symptoms in preclinical models of Huntington's disease [108]. Given that mitochondrial deregulation has been implicated in neurodegenerative processes, MP-101 represents another potential treatment for reducing neuropsychiatric symptoms in dementia [108].

6.7 Bupropion/Dextromethorphan

Another agent currently being studied for treating agitation/aggression in patients with AD is bupropion/dextromethorphan. A combination of bupropion and dextromethorphan, the mechanism of action and rationale is similar to dextromethorphan/quinidine and deudextromorphan [109]. The primary purpose is for dextromethorphan to exert its effects

on *N*-methyl-D-aspartate receptors, σ1 receptors, serotonin/norepinephrine reuptake transporters, and neuronal nicotinic α3β4 receptors in the central nervous system, mediated by bupropion inhibiting its metabolism [70, 109]. Bupropion is an antidepressant and is also indicated for smoking cessation [110, 111]. It blocks norepinephrine and dopamine reuptake, seeming to have synergistic effects in formulation with dextromethorphan [109]. The study is a phase II/III, double-blind, placebo-controlled trial with three separate treatment arms comparing the efficacy of bupropion/dextromethorphan, bupropion, and placebo over 5 weeks (Clinicaltrials.gov identifier: NCT03226522). The primary endpoint is change in the CMAI score from baseline at 5 weeks.

6.8 Oxytocin

An ongoing trial is currently recruiting participants diagnosed with frontotemporal dementia. This phase II multicenter study is exploring the tolerability and efficacy of an intranasal formulation of the neuropeptide oxytocin (Syntocinon®), on reducing apathy in these patients over 20 weeks (ClinicalTrials.gov identifier: NCT03260920). Oxytocin has previously been shown to have prosocial effects in humans and to improve measures of social cognition in patients with schizophrenia [112]. A double-blind placebo-controlled trial of intranasal oxytocin showed that one dose of 24 IU significantly improved NPI scores in patients with behavioral variant frontotemporal dementia 8 h and 1 week after administration [113]. Doses of 24, 48, and 72 IU of this oxytocin formulation have also been shown to be safe in another phase I study [114]. Thus, intranasal oxytocin appears to be tolerable and has exciting implications for improving apathetic symptoms by way of its demonstrated prosocial effects. The study is investigating the effects of a low, medium, and high dose of intranasal oxytocin and is expected to be completed in 2021.

7 Conclusions

The comparative efficacy of the new compounds being evaluated in this review remains unclear because of significant variance between trials regarding inclusion criteria, target symptoms, study designs, and selected outcomes. Of the investigative agents outlined in this review though, the behavioral disturbance most widely targeted in clinical trials thus far has been agitation/aggression in patients with AD. The agents explored that have demonstrated efficacy belong to a diverse range of drug classes, from atypical antipsychotics, SSRIs, cannabinoids, dextromethorphan combinatory formulations, and others with miscellaneous mechanisms of action. For this indication, the newer atypical antipsychotics investigated, brexpiprazole and lumateperone, have progressed quite far in the drug development pipeline. Both are currently being evaluated in phase III clinical trials. As the use of currently available atypical antipsychotics appears associated with increased risks of cerebrovascular events and mortality in elderly populations, these newer agents may represent safer options in this drug class for treating agitation/aggressive symptoms in patients with AD, but this must be demonstrated through larger, appropriately powered, randomized controlled trials before widespread use can be recommended [19, 20]. Selective serotonin reuptake inhibitors are considered safer than antipsychotics, which is why they may be preferentially prescribed to treat agitated/aggressive symptoms in patients with AD [54]. Currently being studied in a large phase III trial, escitalopram is a promising advancement to this class of agents commonly prescribed for treating agitation. Targeting the endocannabinoid system, the synthetic cannabinoids dronabinol and nabilone have been efficacious in reducing behavioral symptoms associated with dementia on the CMAI and NPI in placebo-controlled crossover trials [66, 67, 69]. Of the agents explored, the results of the most recent nabilone trial have had promising results in reducing agitated symptoms. The dextromethorphan/quinidine agents dextromethorphan/quinidine and deudextromethorphan are novel additions to the treatments being explored for agitation associated with dementia. Additionally, the dextromethorphan/bupropion combination agent is also being explored in a phase II/III trial. Prazosin was first shown to significantly reduce NPI scores in a small cohort of agitated patients with AD after 8 weeks; it remains a valuable candidate for the treatment of agitation and aggression associated with dementia to explore in larger studies [89]. Furthermore, a phase III trial of carbamazepine in conjunction with mirtazapine is the only ongoing trial comparing the efficacy of two agents on reducing agitated symptoms. Last, MP-101 is a novel addition as the studies launched for the treatment of agitation are addressing a mitochondrial basis for behavioral issues in AD for the first time [106].

With the advent of newer atypical antipsychotics for treating BPSD, few have been explored for treating psychotic symptoms in patients with dementia. Pimavanserin has demonstrated efficacious results for improving symptoms of psychosis in participants with AD after 6 weeks [41]. Furthermore, pimavanserin was found to selectively improve NPI-NH psychosis subscores in patients who had more severe symptoms at baseline [41]. This suggests that pimavanserin may represent a safer alternative to traditional antipsychotics arguably for patients who will most likely require such pharmacotherapy. The ongoing phase III trial exploring the effects of pimavanserin for up to 26 weeks is currently underway and may help further elucidate the therapeutic efficacy of this agent over a longer period of time.

Other symptoms associated with dementia explored as a primary outcome in clinical trials were apathy, in which methylphenidate and intranasal oxytocin are currently being investigated in clinical trials. These agents have different neural bases: methylphenidate being used to improve motivation and oxytocin influencing prosocial behavior as a neuropeptide [111]. Oxytocin is being studied for frontotemporal dementia in which diminished prosocial behavior is characteristic of this condition, whereas methylphenidate is being studied for AD. ADMET-2 will further elucidate the therapeutic benefit of methylphenidate in a longer period of 6 months of treatments in a larger cohort of participants.

The diversity of the agents for BPSD summarized in this review indicates the potential for more agents for treating BPSD to be approved in the future. With the plethora of information becoming available, numerous considerations must be made to the application of these results in clinical practice. Treatment protocols must be personalized. First, contributing social and psychological factors must be given weight in the treatment plan selection process. If non-pharmacological treatments are unsuccessful or not feasible, then pharmacological agents can be considered using emerging biomarker evidence to determine what might work best for each patient. In this way, clinical trials must be receptive to the heterogeneity of neuropsychiatric and behavioral symptoms of dementia, incorporating opportunities for the development of biomarkers that can aid as predictors for treatment response.

Future studies should continue to use appropriate, validated, behavioral outcome measures when assessing the efficacy of the treatments being studied. Clinical trials investigating treatments for neuropsychiatric symptoms could also benefit from the incorporation of a psychosocial intervention; for instance, the S-CitAD study currently includes a structured psychosocial intervention for participants with clinically significant agitation. Participants who do not show a response to the intervention are then randomized to receive either escitalopram or placebo. Additionally, the ADMET-2 study includes a psychosocial intervention for both its methylphenidate and placebo arms. The inclusion of psychosocial interventions in trials mimics the management in neuropsychiatric settings; thus, relating the efficacy of the agent to the clinical setting in which they will ultimately occur.

Compliance with Ethical Standards

Funding No sources of funding were provided for the preparation of this review article.

Conflict of Interest Krista L. Lanctôt has received research grants from the National Institute of Aging for "Apathy in Alzheimer's Disease Methylphenidate Trial II (ADMET II)" and "Escitalopram for Agitation in Alzheimer's Disease (S-CitAD)", Alzheimer Drug Discovery Fund, the Alzheimer Society of Canada (Grant 15–17), Alzheimer's Association, Canadian Institutes of Health Research, AbbVie, Lundbeck, Pfizer, Sanofi-Aventis, Janssen-Ortho Inc., Roche, and Wyeth; and honoraria from Abbvie and Lundbeck. Nathan Herrmann has received research grants from the Alzheimer Drug Discovery Fund, the Alzheimer Society of Canada, the National Institutes of Health, Canadian Institute of Health Research, Lundbeck, and Roche; and consultation fees from Lilly, Merck, and Astellas. Mehnaz Ahmed, Marlene Malik and Johannes Teselink declare they have no conflicts of interest relevant to the content of this review article.

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