Curr Treat Options Psych (2020) 7:489–507
DOI 10.1007/s40501-020-00233-9

Geriatric Disorders (M Sajatovic and A Aftab, Section Editors)

Pharmacological Management of Neuropsychiatric Symptoms of Dementia

Lauren B. Gerlach, DO, MS[1,2,*]
Helen C. Kales, MD[3]

Address
[1]Department of Psychiatry, University of Michigan, 4250 Plymouth Road, Ann Arbor, MI, 48109, USA
[*,2]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI, USA
Email: glauren@umich.edu
[3]Department of Psychiatry, University of California, Davis, CA, USA

Published online: 2 September 2020

This article is part of the Topical Collection on *Geriatric Disorders*

Keywords Neuropsychiatric symptoms · Pharmacologic treatment · Dementia

Abstract

Purpose Neuropsychiatric symptoms are universal across all stages and types of dementia and can cause significant challenges for patients and caregivers. While there are currently no approved medications for treatment of neuropsychiatric symptoms of dementia, a variety of psychotropic medications such as antipsychotics, benzodiazepines, anticonvulsants, and antidepressants are used off-label to treat these symptoms. This systematic review evaluated the available evidence for effectiveness and tolerability of pharmacologic treatments in addressing behavioral disturbances in dementia.

Recent findings Inclusion criteria were placebo-controlled, randomized controlled clinical trials (RCTs) or meta-analyses; a total of 38 studies and 3 meta-analyses representing an additional 27 RCTs met the inclusion criteria. Of the medication classes evaluated, atypical antipsychotics had the greatest available evidence for use; however, the treatment effect size was modest. Nine trials of antidepressants were included; 3 trials supported use in dementia. Eight trials of anticonvulsants were included; only one showed benefit. For benzodiazepines, 2 RCTs were included; only one trial of lorazepam showed improvement. Six trials of melatonin agonists were included; none showed efficacy outside of improved sleep measures. Evidence for effectiveness of pimavanserin and dextromethorphan-quinidine was limited to one study each, both of which showed benefit.

Summary Despite the widespread off-label use of psychotropic medications for treatment of neuropsychiatric symptoms in dementia, there are relatively few RCTs to

evaluate their use with treatment effect sizes absent or modest for most medication classes. Of the medication classes reviewed, atypical antipsychotics have the best evidence for effectiveness; however, the overall magnitude of treatment effect is modest and must be balanced with risk of serious adverse events including death.

Introduction

Although memory impairment is typically thought of as the cardinal feature of dementia, neuropsychiatric or behavioral and psychological symptoms of dementia are nearly universal across all types and stages of dementia. Longitudinal studies of patients with dementia demonstrate that 97% of patients will develop one or more behavioral disturbances during the course of their disease [1•]. Neuropsychiatric symptoms can include a variety of behaviors including depression, psychosis (delusions and hallucinations), agitation, aggression, apathy, sleep disturbances, and socially inappropriate behaviors [2••]. These distressing symptoms can often create the most challenges for patients, their caregivers, and providers. The presence of these behaviors is associated with poor outcomes for both patients and their caregivers including increased morbidity, greater risk of hospitalization for patients, and high caregiver strain [3–5].

Currently there are no US Food and Drug Administration (FDA)-approved medications for the treatment of neuropsychiatric symptoms of dementia. Despite numerous expert bodies recommending non-pharmacological treatment strategies as first-line treatment, psychotropic medications such as antipsychotics are often prescribed off-label as the primary treatment of behavioral disturbances of dementia in real-world practice [6, 7]. Recent studies of Medicare beneficiaries with dementia demonstrate that upwards of 60–70% of patients are prescribed a psychotropic medication with 22% of community dwelling patients with dementia receiving antipsychotics [8•, 9]. Commonly utilized psychotropic medication classes for the treatment of neuropsychiatric symptoms include antipsychotics, antidepressants, anticonvulsants, and benzodiazepines. Of these medication classes, previous meta-analyses and systematic reviews suggest that antipsychotics likely have the strongest evidence base; however, the effect size of treatment is moderate (0.13–0.16) [10••, 11••]. Further, treatment with antipsychotic medications is coupled with concerns for significant side effects including increased mortality as highlighted by the US FDA black box warnings regarding antipsychotic use for dementia-related psychosis [12].

In light of the high prevalence of psychotropic medication use among patients with dementia and known associated harms with antipsychotic use, we sought to evaluate the available evidence for the effectiveness and tolerability of pharmacotherapy in treatment of neuropsychiatric symptoms of dementia. For the purpose of this review, we chose to focus on the following psychotropic medication classes: antipsychotics, antidepressants, anticonvulsants, and benzodiazepines. Cholinesterase inhibitors and memantine were excluded from this review given that there are several previously published meta-analyses and systematic reviews evaluating the role of these medications in treating neuropsychiatric symptoms of dementia [11••, 13••]. We also evaluated the available evidence evaluating use of newer agents including dextromethorphan-quinidine and melatonin receptor agonists.

Within each psychotropic medication class, we reviewed the available evidence to inform treatment and consider medication side effects. Studies were selected for inclusion in our review if they (1) included patients ≥ 50 years of age; (2) focused on patients diagnosed with Alzheimer's disease or related dementia; (3) were a randomized, placebo-controlled trial (RCT) or a meta-analysis of RCTs; and (4) primary study outcomes focused on neuropsychiatric symptoms of dementia. In order to summarize the large body of evidence, meta-analyses were included along with any published RCTs since that time. Electronic databases including PubMed/MEDLINE were searched from inception through June 2020 to identify studies that met our inclusion criteria. The final search was completed on June 30, 2020.

All treatments reviewed in this article are summarized in Tables 1 and 2.

Table 1. Antipsychotic (typical and atypical) use for treatment of neuropsychiatric symptoms of dementia

Typical antipsychotics						
Study	**Medication**	**N**	**Study design**	**Follow-up**	**Summary of findings**	**Favors medication**
Stotsky 1984 [14]	Thioridazine, diazepam	358	RCT	4 wk	Patients taking thioridazine had greater improvement on the Hamilton Anxiety Scale as well as decreased agitation and behavioral changes as compared with placebo and diazepam	Yes
Auchus and Bissey-Black 1997 [15]	Haloperidol, fluoxetine	15	RCT	6 wk	No significant reduction in CMAI or BEHAVE-AD among groups. Also had a fluoxetine group (Table 2)	No, adverse events were greater for haloperidol.
Schneider et al. 1990 [10••]	Haloperidol, thioridazine, thiothixene, chlorpromazine, trifluoperazine, acetophenazine	252	Meta-analysis of 7 RCTs	3–8 wk	Antipsychotics were significantly more effective than placebo but had a small effect size ($r = 0.18$); 18 of 100 patients with dementia benefited from antipsychotics over placebo. In 11 studies comparing thioridazine or haloperidol with another antipsychotic, neither differed significantly from the comparison medication	Yes
Teri et al. 2000 [17]	Haloperidol, trazodone	73	RCT	16 wk	No difference between haloperidol and placebo on CGI-C or CMAI. Also had a trazodone group (Table 2)	No, also included a behavioral management therapy arm that performed as well as medications
Lonergan et al. 2002 [40•]	Haloperidol	573	Meta-analysis of 5 RCTs	3–16 wk	Four trials assessing behavioral symptoms found no improvement with treatment of haloperidol compared with placebo on primary outcome	No, participants receiving haloperidol were more likely to discontinue

Table 1. (Continued)

Study	Medication	N	Study design	Follow-up	Summary of findings	Favors medication
Typical antipsychotics						
					measures. Only aggression was significantly different for haloperidol versus placebo in three trials	treatment due to side effects
Pollock et al. 2002 [18]	Perphenazine, citalopram	85	RCT	17 days	No difference between perphenazine and placebo on the NBRS. Also contained citalopram group (Table 2)	No
Atypical antipsychotics						
Meehan et al. 2002 [25]	Olanzapine (IM, lorazepam (IM)	272	RCT	24 h	Significant improvement with intramuscular olanzapine over placebo on the CMAI and PANSS-EC. Also included a lorazepam group (Table 2)	Yes
De Deyn et al. 2005 [41]	Aripiprazole	208	RCT	10 wk	Aripiprazole showed no benefit over placebo in the NPI Psychosis subscale or BPRS total score. Aripiprazole showed improvement over placebo in the BPRS psychosis and core subscale scores	No
Mintzer et al. 2006 [42]	Risperidone	473	RCT	8 wk	No significant difference between risperidone and placebo on the BEHAVE-AD Psychosis subscale or CGI-C	No, more side effects were observed with risperidone
Schneider et al. 2006 [43••]	Olanzapine, quetiapine, risperidone	421	RCT	32 wk	No significant differences in improvement on CGI-C scores. No significant differences in terms of time to discontinuation of treatment for any reason	No
Schneider et al. 2006 [44•]	Aripiprazole, olanzapine, quetiapine, risperidone	5110	Meta-analysis of 15 RCTs	6–26 wk	3 RCTs for aripiprazole, 5 RCTs for olanzapine, 3 RCTs for quetiapine, and 4 RCTs for risperidone were identified.	Yes, however, positive treatment effect only identified

Table 1. (Continued)

Typical antipsychotics						
Study	**Medication**	**N**	**Study design**	**Follow-up**	**Summary of findings**	**Favors medication**
					Among these trials, improvement on neuropsychiatric symptom rating scales (NPI, CGI-S, CAMI, PANSS-EC, BEHAVE-AD) was observed for aripiprazole and risperidone, but not for quetiapine or olanzapine	for aripiprazole and risperidone
Tariot et al. 2006 [45]	Quetiapine, haloperidol	284	RCT	10 wk	No benefit was seen with primary outcomes of BPRS and CGI-S	No
Kurlan et al. 2007 [46]	Quetiapine	40	RCT	10 wk	No significant improvement in the BPRS as compared with placebo.	No, study done in subjects with Lewy Body Dementia and Parkinson disease dementia
Mintzer et al. 2007 [47]	Aripiprazole (2, 5, or 10 mg)	487	RCT	10 wk	Only aripiprazole 10 mg/day showed improvement on the NPI-NH Psychosis subscale score	No, cerebrovascular adverse events were reported
Zhong et al. 2007 [48]	Quetiapine (100, 200 mg)	333	RCT	10 wk	Only quetiapine 200 mg was associated with reductions in the PANSS-EC. Quetiapine 100 mg did not differentiate from placebo	No, mortality rates were higher in quetiapine group
Paleacu et al. 2008 [49]	Quetiapine	40	RCT	6 wk	Significant reductions in the CGI-C score among quetiapine group, however, no differences in NPI	Yes
Streim et al. 2008 [50]	Aripiprazole	256	RCT	10 wk	No significant differences in NPI-NH Psychosis score or CGI-S	No

Table 1. (Continued)

Typical antipsychotics						
Study	**Medication**	**N**	**Study design**	**Follow-up**	**Summary of findings**	**Favors medication**
Rappaport et al. 2009 [51]	Aripiprazole (5, 10, or 15 mg IM)	129	RCT	24 h	Improvement in PANSS-EC with 10 mg and 15 mg IM aripiprazole compared with placebo	Yes, but associated with higher side effects including sedation
Ballard et al. 2018 [52•]	Pimavanserin	181	RCT	12 wk	Showed reduction in NPI-NH Psychosis score at 6 weeks, no difference was seen at 12 weeks	Yes, but improvements were not sustained at 12 weeks

IM Intramuscular, *RCT* randomized controlled trial, *wk* week
BEHAVE-AD Behavioral Rating Scales: Behavioral Pathology in Alzheimer's Disease rating scale, *BPRS* Brief Psychiatric Rating Scale, *CGI-C* Clinical Global Impression of Change, *CGI-S* Clinical Global Impression-Severity, *CMAI* Cohen-Mansfield Agitation Inventory, *NBRS* Neurobehavioral Rating Scale, *NPI* Neuropsychiatric Inventory, *NPI-NH* Neuropsychiatric Inventory-Nursing Home Version, *PANSS-EC* Positive and Negative Syndrome Scale-Excitement Component

Treatment

Antipsychotics

Typical antipsychotics

Two meta-analyses including 12 RCTs [10••, 40•] and 4 additional RCTs [14, 15, 17, 18] were identified evaluating the use of typical antipsychotics in treatment of neuropsychiatric symptoms of dementia. Study sample sizes ranged from 85 to 573 participants with follow up ranging from 17 days to 16 weeks (Table 1).

A meta-analysis conducted by Schneider et al. in 1990 evaluated 7 RCTs comparing several typical antipsychotic medications with placebo [10••]. The results of the meta-analysis demonstrated that typical antipsychotics were significantly more effective than placebo, however, had overall a relatively small treatment effect size ($r = 0.18$) in improving neuropsychiatric symptoms. In 2002, a meta-analysis evaluating 5 RCTs evaluating the efficacy of haloperidol in treating behavioral symptoms of dementia found only one trial that demonstrated a favorable response with haloperidol over placebo [40•]. Further, patients receiving haloperidol were more likely to discontinue treatment due to intolerable side effects. A placebo-controlled trial of thioridazine found that patients receiving the antipsychotic had greater improvement in agitation scores [14]. Lastly, an RCT evaluating perphenazine found no difference from placebo at 17 days in reducing behavioral symptoms as measured by the Neurobehavioral Rating Scale [18].

Atypical antipsychotics

One meta-analysis including 15 RCTs as well as an additional 12 RCTs was identified comparing the use of atypical antipsychotics with placebo for treatment of neuropsychiatric symptoms of dementia (Table 1). Study sample sizes ranged from 40 to 5110 participants with follow-up time of 24 h to 32 weeks. A meta-analysis by Schneider et al. in 2006 evaluated the efficacy of available atypical antipsychotic medications including 3 RCTs for aripiprazole, 5 RCTs for olanzapine, 3 RCTs for quetiapine, and 4 RCTs for risperidone [44•]. Among these trials, improvement on neuropsychiatric symptom rating scales were observed for aripiprazole and risperidone, but not for quetiapine or olanzapine. As with typical antipsychotics, the overall magnitude of benefit from treatment was considered to be modest. Additionally, adverse events with atypical antipsychotic medication use included somnolence, urinary tract infections, and extrapyramidal symptoms as well as a significant risk for cerebrovascular events, especially with use of risperidone [44•].

Among the additional 12 trials identified, only 4 studies demonstrated greater improvement on behavioral symptom scales with use of atypical antipsychotics versus placebo (Table 1) [25, 49, 51, 52•]. Improvements were generally seen in scales of aggression, psychosis, and overall impression of change. However, these studies concluded that the potential for benefit needed to be weighed against the risk of adverse effects including sedation, falls, and extrapyramidal side effects. In 2006, the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study evaluated the use

Table 2. Other pharmacotherapy for treatment of neuropsychiatric symptoms of dementia

Study	Medication	N	Study design	Weeks	Summary of findings	Favors medication
Antidepressants						
Auchus and Bissey-Black 1997 [15]	Fluoxetine, haloperidol	15	RCT	6 wk	No significant reduction in CMAI or BEHAVE-AD among groups. Also had a haloperidol group (Table 1)	No, adverse events were greater for fluoxetine
Lawlor et al. 1997 [16]	Selegiline	25	RCT	14 wk	No improvement on BPRS score with selegiline	No
Teri et al. 2000 [17]	Trazodone, haloperidol	73	RCT	16 wk	No difference between trazodone and placebo on CGI-C or CMAI. Also had a haloperidol group (Table 1)	No
Pollock et al. 2002 [18]	Citalopram, perphenazine	85	RCT	17 days	Citalopram showed improvement in NBRS as compared with placebo. Also had a perphenazine group (Table 1)	Yes
Lyketsos et al. 2003 [19]	Sertraline	44	RCT	12 wk	No difference between sertraline and placebo on NPI. Did see improvement in depressive symptoms	No
Finkel et al. 2004 [20]	Sertraline	245	RCT	12 wk	No significant differences between groups on NPI or CGI-C	No, all subjects were taking donepezil as well
Camargos et al. 2014 [21]	Trazodone	30	RCT	2 wk	Trazodone users slept 42.5 more minutes per night and nighttime percent sleep increased 8.5%	Yes
Porsteinsson et al. 2014 [22••]	Citalopram	186	RCT	9 wk	Participants receiving citalopram showed reduced in the NBRS-Agitation subscale and modified Alzheimer Disease Co-operative Study-CGIC	Yes, worsening cognition and QT interval prolongation (18.1 ms) seen in citalopram group
Scoralick et al. 2017 [23•]	Mirtazapine	24	RCT	2 wk	Mirtazapine showed no benefit over placebo in improving sleep duration or efficiency	No, mirtazapine group had increased daytime sleepiness
Benzodiazepines						
McCarten et al. 1995 [24]	Triazolam 0.125 mg	7	RCT	8 days	Triazolam had no significant improvement across sleep measures	No
Meehan et al. 2002 [25]	Lorazepam (IM) olanzapine (IM)	272	RCT	24 h	Significant improvement with lorazepam 1 mg on the CMAI. Results were not sustained on the PANSS-EC at 24 h	Yes, included an olanzapine group as well (Table 1)—effect of olanzapine lasted longer

Table 2. (Continued)

Study	Medication	N	Study design	Weeks	Summary of findings	Favors medication
Mood Stabilizers						
Tariot et al. 1998 [26]	Carbamazepine	51	RCT	6 wk	Improvement on both BPRS and CGI for carbamazepine group.	Yes, side effects more common in carbamazepine group
Olin et al. 2001 [27]	Carbamazepine	21	RCT	6 wk	No improvement on the CGI-C or BPRS for carbamazepine	No
Porsteinsson et al. 2001 [22]	Divalproex	56	RCT	6 wk	No improvement on the BPRS agitation or CGI. Side effects more common in divalproex group	No
Sival et al. 2002 [28]	Valproate	42	RCT	3 wk	No difference between groups on Social Dysfunction and Aggression scale-9 or CGI-S	No
Tariot et al. 2005 [29]	Divalproex	153	RCT	6 wk	BPRS agitation factor scores did not differ between divalproex and placebo	No
Herrmann et al. 2007 [30]	Valproate	14	RCT	6 wk	NPI scores significantly worsened during valproate treatment compared with placebo	No, greater number of adverse events with valproate
Sommer et al. 2009 [31]	Oxcarbazepine	103	RCT	8 wk	No difference among groups on NPI agitation and aggression scores	No
Tariot et al. 2011 [32]	Valproate	313	RCT	26 months	Trial in individuals with Alzheimer disease who had not experienced agitation or psychosis. No difference between groups in time to emergence of symptoms (NPI, CMAI)	No, valproate group had higher rates of somnolence, gait disturbance, and tremor
Dextromethorphan-quinidine						
Cummings et al. 2015 [33•]	Dextromethorphan-quinidine	220	RCT	10 wk	Patients treated with dextromethorphan-quinidine showed reduction on the NPI agitation and aggression scores, however, experienced more side effects including falls	Yes
Melatonin agonists						
Serfaty et al. 2002 [34]	Melatonin 6 mg	44	RCT	6 wk	Melatonin had no effect on median total sleep time, number of awakenings, or sleep efficiency	No
Asayama et al. 2003 [35]	Melatonin 3 mg	20	RCT	4 wk	Melatonin significantly increased sleep time and decreased activity at night	Yes
Singer et al. 2003 [36]	Melatonin 2.5 mg, 10 mg	157	RCT	8 wk	No statistically significant differences in objective sleep	No

Table 2. (Continued)

Study	Medication	N	Study design	Weeks	Summary of findings	Favors medication
					measures were seen among melatonin groups relative to placebo	
Riemersma-van der Lek et al. 2008 [37]	Melatonin 2.5 mg, light therapy	189	RCT	15 months	Melatonin shortened sleep onset latency by 8.2 min and increased total sleep duration by 27 min. No improvement in agitation scales (NPI, CMAI); melatonin group had worse scores on mood symptoms	No, trial also include a group randomized to combined light therapy and melatonin treatment
Gehrman et al. 2009 [38]	Melatonin 1.5 mg, 8.5 mg	41	RCT	18 days	There were no significant effects of melatonin compared with placebo on sleep measures or agitation as rated by the Agitated Behavior Rating Scale (ABRS) and CMAI	No
Wade et al. 2014[39]	Melatonin 2 mg prolonged release	80	RCT	28 wk	Patients treated with melatonin had improved sleep efficiency and was generally well tolerated with an adverse event profile similar to placebo	Yes

BEHAVE-AD Behavioral Rating Scales: Behavioral Pathology in Alzheimer's Disease rating scale, *BPRS* Brief Psychiatric Rating Scale, *CGI-C* Clinical Global Impression of Change, *CGI-S* Clinical Global Impression-Severity, *CMAI* Cohen-Mansfield Agitation Inventory, *NBRS* Neurobehavioral Rating Scale, *NPI* Neuropsychiatric Inventory, *NPI-NH* Neuropsychiatric Inventory-Nursing Home Version, *PANSS-EC* Positive and Negative Syndrome Scale-Excitement Component

of atypical antipsychotics in treating neuropsychiatric symptoms of dementia [43••]. The study was a 42-site, double-blind, placebo-controlled trial of 421 outpatients with Alzheimer's disease with symptoms of psychosis, aggression, or agitation. Participants were randomized to treatment with olanzapine, risperidone, quetiapine, or placebo. The trial failed to find improvement on behavioral outcomes with any atypical antipsychotic over placebo at 12 weeks [43••].

In 2016 pimavanserin was approved by the US FDA for treatment of Parkinson's disease psychosis. This atypical antipsychotic has a novel mechanism of action working as a selective inverse agonist at the serotonin receptor with no appreciable dopamine blockade or subsequent risk of extrapyramidal symptoms [53]. To date, there has been only one study evaluating the use of pimavanserin in treatment of behavioral disturbances in patients with Alzheimer's disease. In 2018, Ballard et al., in a phase 2, single-center study of nursing home residents, found that participants treated with pimavanserin had significantly reduced Neuropsychiatric Inventory-Nursing Home (NPI-NH) psychosis scores at 6 weeks [52•]. However, these improvements were not sustained at 12 weeks as compared with placebo. Pimavanserin carries a similar side effect profile to other atypical antipsychotic medications including the black box warning for increased mortality in patients with dementia-related psychosis and QT prolongation [53].

Antidepressants

A total of 9 studies met eligibility criteria, with sample sizes ranging from 15 to 245 and follow-up ranging from 17 days to 16 weeks (Table 2) [15–18, 20, 21, 22••, 23•, 54]. Of these studies, only 3 showed benefit of antidepressant treatment over placebo [18, 21, 22••]. In 2014, the Citalopram for Agitation in Alzheimer's Disease (CitAD) study randomized participants to receive citalopram or placebo. The study found that patients treated with citalopram had significant improvement in agitation and on measures of caregiver stress [22••]. Participants in the citalopram group also had improved performance on activities of daily living and reduction in use of a rescue medication (lorazepam) as compared with placebo. However, participants treated with citalopram were found to have side effects which may limit its use including worsening cognition and QT prolongation (overall increase in the QT interval of 18 milliseconds) [22••]. In 2002, Pollock et al. also found that use of citalopram was associated with reductions in behavioral symptoms including agitation and aggression as compared with placebo [18]. Lastly, a 2014 study of trazodone demonstrated that participants receiving trazodone had better sleep outcomes as compared with participants taking placebo [21]. Participants with dementia receiving trazodone obtained on average 42.5 more minutes of sleep per night, however, with a total sleep time of only 4–5 h per night. The study did not evaluate neuropsychiatric symptoms other than sleep.

More recently in 2017, a trial of mirtazapine found that users had no benefit over placebo in improving sleep duration or efficiency among patients with dementia [23•]. Further the mirtazapine group experienced increased daytime sleepiness limiting its use. In 2004, a large RCT of 245 subjects with dementia were randomized to receive treatment with either sertraline or placebo [20]. The study found no significant differences between groups on the Neuropsychiatric

Inventory (NPI). A smaller study in 1997 found that there was no positive treatment effect with fluoxetine among patients with dementia, with fluoxetine users experiencing more side effects [15]. Further a 2003 study comparing sertraline and placebo found no improvement in behavioral symptoms with use of the antidepressant [54]. However, there were significant improvements noted in depression scores among patients with dementia.

Anticonvulsants

A total of 8 studies were found to meet eligibility criteria including 5 studies evaluating valproate derivatives, 2 studies evaluating carbamazepine, and 1 study evaluating oxcarbazepine (Table 2) [26–32, 55]. Of the 5 studies investigating valproate derivatives, with sample sizes ranging from 14 to 313, no study found improvement in neuropsychiatric symptoms with valproate as compared with placebo. Treatment with valproate was associated with increased side effects including sedation, gait disturbance, and tremor. Among two small studies evaluating use of carbamazepine for treatment of neuropsychiatric symptoms, only one study favored use of carbamazepine; however, the medication was associated increased side effects as compared with placebo [26, 27]. Only one RCT evaluating the use of oxcarbazepine met eligibility criteria which showed no improvement in treating agitation or aggression in patients with dementia as compared with placebo [31]. Despite frequently being used for off-label treatment of neuropsychiatric symptoms in dementia [8•, 56], there are currently no published placebo-controlled, RCTs evaluating the use of gabapentin. While there are currently no RCTs evaluating the use of lithium, the Lithium Treatment for Agitation in Alzheimer's disease (Lit-AD) [57] clinical trial recently completed recruitment; however, the study results are not yet published. This study will serve as the first randomized, double-blind, placebo-controlled trial to assess the efficacy of lithium treatment for symptoms of agitation or aggression in older adults diagnosed with Alzheimer's disease.

Benzodiazepines

A total of 2 studies met eligibility criteria; one demonstrated benefit over placebo. Study follow-up periods ranged from 24 h to 8 days [24, 25]. Meehan et al. randomized 272 patients with dementia to receive intramuscular injections of lorazepam, olanzapine, or placebo. At 24 h, they found that intramuscular lorazepam led to significant reductions on the Positive and Negative Symptom Scale (PANSS), Cohen-Mansfield Agitation Inventory (CMAI), and the Agitation-Calmness Scale. However, the effect of treatment was greater with intramuscular olanzapine with longer lasting results. A 1995 study by McCarten et al. limited to 7 patients found that use of triazolam had no significant improvement across sleep measures among patients with dementia.

Dextromethorphan-quinidine

In 2010, the US FDA approved dextromethorphan-quinidine for the treatment of pseudobulbar affect [58]. Only one study has evaluated the potential impact of off-label use of dextromethorphan-quinidine for treatment of agitation in patients with Alzheimer disease [33•].• In this phase 2 study, 220 participants were randomized to receive either dextromethorphan-quinidine or placebo over 10 weeks. The study found that patients treated with dextromethorphan-

quinidine showed significant reduction on the Neuropsychiatric Inventory agitation and aggression scores. However, significant adverse events were seen with treatment including falls (8.6%), diarrhea (5.9%), and urinary tract infection (5.3%) [33•].

Melatonin agonists

A total of 6 studies met eligibility criteria, with sample sizes ranging from 20 to 189 and follow-up periods ranging from 18 days to 15 months (Table 2) [34–39]. Of these studies, only 2 trials showed benefit of melatonin treatment over placebo in improving sleep measures in dementia [35, 39]. In 2003, a small study by Asayama et al. found that melatonin significantly increased total sleep time and decreased nighttime activity among 11 patients with Alzheimer's disease as compared with placebo [35]. Additionally, a 2014 study by Wade et al. found that melatonin resulted in improved sleep efficacy as compared with placebo [39]. Lastly, an RCT of 189 patients with dementia followed over 15 months found that patients treated with melatonin had limited improvement on sleep measures and worsening mood symptoms as compared with placebo [37]. No studies meeting eligibility criteria found that melatonin improved behavioral outcomes other than sleep, finding no difference over placebo on measures neuropsychiatric symptoms including agitation and aggression.

Discussion

This systematic review highlights several key features regarding psychotropic medication use for treatment of neuropsychiatric symptoms of dementia. First, the high rates of psychotropic medication prescribing among patients with dementia are notably out of proportion to the body of evidence supporting such use. Of the pharmacologic classes included, our search found that atypical antipsychotic medications have the strongest evidence for efficacy in treating neuropsychiatric symptoms; however, the overall magnitude of treatment effect is modest [10••, 43••]. One of the largest trials evaluating atypical antipsychotic use in dementia to date, the Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study, failed to find any benefit of treatment with olanzapine, quetiapine, and risperidone in improving neuropsychiatric symptoms over placebo [43••]. Despite a modest evidence for benefit, atypical antipsychotics have a concerning side effect profile including a 1.6- to 1.7-fold increase in mortality as highlighted by the 2005 and 2008 black box warnings for treatment of dementia-related behaviors [12]. Additionally, antipsychotic medications are associated with other significant side effects including somnolence, falls, cognitive worsening, QTc prolongation, and stroke which need to be accounted for when considering their use [59].

Antidepressant medications may have benefit in reducing agitation in dementia but results from RCTs have been inconsistent. While the Citalopram for Agitation in Alzheimer's Disease (CitAD) study found that treatment with citalopram led to reductions in agitation, these benefits were countered by serious side effects including worsening cognition and QT prolongation [22••]. The largest study evaluating use of sertraline in dementia found no benefit over placebo [20]. Recent pharmacoepidemiologic data demonstrate

growth in off-label use of sedative antidepressants among long-term care residents with dementia—finding a 15% increase in prescribing from 2004 to 2015 [60, 61]. Trials evaluating use of trazodone for treatment of neuropsychiatric symptoms of dementia have been inconsistent in showing benefit, and we were able to identify only one trial of mirtazapine use among patients with dementia which showed no improvement in behavioral rating scales over placebo [17, 21, 23•].

Nearly a quarter of patients with dementia are prescribed benzodiazepines and sedative hypnotics [8•]—thus it is surprising that we were only able to find 2 trials evaluating use of benzodiazepines in dementia. Of these trials, only one showed benefit with use of intramuscular lorazepam over placebo, with benzodiazepines performing worse than antipsychotics in reducing agitation [25]. Use of benzodiazepines and sedative hypnotics can lead to significant side effects for patients with dementia including increased confusion, worsening agitation, and paradoxical disinhibition [62]. Given the high rates of use of these medications among patients with dementia, it is concerning that there is such limited evidence to support their use.

While there has been a large focus on reducing antipsychotic prescribing to patients with dementia with efforts such as the Centers for Medicare and Medicaid Services' (CMS) National Partnership to Improve Dementia Care, and use of antipsychotic medications in dementia has declined [63], pharmacoepidemiologic studies demonstrate that there has been a shift to use of other psychotropic medication classes or "substitution" [8•]. In particular, there has been recent growth in off-label anticonvulsant prescribing among patients with dementia in long-term care, largely contributed by growth in gabapentin and valproate prescribing [8•, 56]. As such, it is notable that we were unable to find any studies evaluating the efficacy and safety of gabapentin use in dementia. Of the 5 studies including valproate identified for this review, no study found improved symptom control for neuropsychiatric symptoms with medication use as compared with placebo. RCTs of use of other agents such as melatonin agonists and dextromethorphan-quinidine have been limited. Melatonin has shown limited benefit over placebo on sleep measures with no studies demonstrating improvement in agitation or aggression. Despite only one study being completed evaluating dextromethorphan-quinidine which showed modest improvement in agitation and significant side effects including falls, concerns have been raised regarding the wide spread off-label prescribing of this medication among long-term care residents [33•, 58].

This study has several limitations. Our inclusion of only RCTs limits our sample size of included studies. Additionally, we did not assess for potential publication bias or perform a search for unpublished data. The majority of studies included evaluated the long-term control of neuropsychiatric symptoms over weeks to months, while relatively few studies were designed to evaluate the short-term efficacy of these medications to address agitation over the span of hours, where there use may be clinically useful for prompt control of agitated behaviors. Further, most studies included in this review evaluated primary outcomes assessing patients total score reduction on behavioral rating scales such as the Neuropsychiatric Inventory (NPI) or Cohen-Mansfield Agitation Inventory (CMAI). Secondary outcomes to assess medication impact on individual behaviors or symptom clusters were often not adequately powered to evaluate such results. Further, few studies included other meaningful clinical

outcomes for patients and caregivers including time to nursing home placement or measures of caregiver burden, which could also help inform provider and caregiver decisions regarding medication use. Additionally, patients enrolled in RCTs generally represent a small subset of the larger population of patients with dementia and the need for caregiver or proxy consent given cognitive decline in dementia may further limit persons with dementia participation in clinical trials and study generalizability. Lastly, we have not included trials of cholinesterase inhibitors and memantine in treating neuropsychiatric symptoms of dementia as several previous systematic reviews and meta-analyses have been published on this topic [11••, 13••]. These reviews highlight that cholinesterase inhibitors have a significant although small reduction in agitation scores, leading to an overall reduction of 1.7 points on the 120-point Neuropsychiatric Inventory (NPI) [13••].

Given the limited evidence supporting use of pharmacotherapy in dementia and concerns for significant side effects, numerous expert bodies and professional organizations, including the American Geriatrics Society, American Association of Geriatric Psychiatry, and American Psychiatric Association, have recommended non-pharmacological treatment strategies as first line in treating neuropsychiatric symptoms of dementia [6, 7]. Such strategies can include a variety of interventions that focus on behavioral, environmental, and caregiver supportive interventions to help prevent or mitigate neuropsychiatric symptoms of dementia. Caregiver-directed interventions have the most evidence to support reduction of behavioral disturbances [64•]. These interventions often focus on helping build caregiver problem-solving abilities to identify modifiable causes of behaviors and improve communication between the person with dementia and caregiver [6, 7]. A meta-analysis of 23 RCTs evaluating non-pharmacological interventions found that these interventions significantly reduced neuropsychiatric symptoms in dementia [64•]. The authors found that the effect size for treatment was greater for caregiver interventions than with antipsychotics for treatment of agitation or cholinesterase inhibitors for treatment of cognitive symptoms.

Despite this, in real-world practice, implementing non-pharmacologic treatment strategies can be challenging due to lack of provider training, time required to implement interventions, and lack of reimbursement [2••]. Evidence-based training programs for caregivers such as the DICE (Describe, Investigate, Create, and Evaluate) approach can assist both providers and caregivers in the prevention, assessment, and management of neuropsychiatric symptoms of dementia, and such strategies should be considered first line [2••]. Further, psychotropic medications rarely help for such behaviors as unfriendliness, poor self-care, memory problems, inattention, repetitive verbalizations, and wandering where behavioral strategies should be prioritized. Psychotropic medications should be considered first line if imminent risk is present related to major depressive disorder with suicidal ideation, psychosis causing harm or potential for harm, and aggression with risk to self or others [65]. While medication choice is targeted to the symptom cluster that is most problematic (e.g., use of antipsychotics for treatment of agitation, anticonvulsants for treatment of disinhibition, antidepressants for depression or apathy), unfortunately there is limited evidence to support such

prescribing across a variety of psychotropic medication classes. Treating clinicians should consider the range of both pharmacologic and non-pharmacologic treatment strategies available to best and safely manage neuropsychiatric symptoms of dementia.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Rozum WJ, Cooley B, Vernon E, Matyi J, Tschanz JT. Neuropsychiatric symptoms in severe dementia: Associations with specific cognitive domains the Cache County Dementia Progression Study. *Int J Geriatr Psychiatry*. 2019;34(7):1087–94

Prospective study evaluating the prevelance and types of neuropsychiatric symptoms experienced in patients with dementia.

2.•• Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369.

Article highlighting the Describe, Investigate, Create, and Evaluate (DICE) non-pharmacological treatment approach to addressing behavioral disturbances in dementia.

3. Wancata J, Windhaber J, Krautgartner M, Alexandrowicz R. The consequences of non-cognitive symptoms of dementia in medical hospital departments. *Int J Psychiatry Med*. 2003;33(3):257–71.

4. Yaffe K, Fox P, Newcomer R, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA*. 2002;287(16):2090–7.

5. Clyburn LD, Stones MJ, Hadjistavropoulos T, Tuokko H. Predicting caregiver burden and depression in Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci*. 2000;55(1):S2–13.

6. American Geriatrics Society. American Association of Geriatric Psyciatry. Consensus statement on improving the quality of mental health care in U.S. nursing homes: management of depression and behavioral symptoms associated with dementia. *Journal of the American Geriatrics Society*. 2003;51(9):1287–98.

7. Choosing Wisely. Five things physicians and patients should question. Arlington (VA): American Psychiatric Association; 2013. Available at: http://www.choosingwisely.org/societies/american-psychiatric-association. Accessed Jun, 2020

8.• Maust DT, Kim HM, Chiang C, Kales HC. Association of the Centers for Medicare & Medicaid Services' National Partnership to Improve Dementia Care With the Use of Antipsychotics and Other Psychotropics in Long-term Care in the United States From 2009 to 2014. *JAMA Intern Med*. 2018;178(5):640–7

Study evaluating recent psychotropic medication prescribing trends among Medicare beneficiaries with dementia in long-term care.

9. Maust DT, Strominger J, Bynum JPW, Langa KM, Gerlach LB, Zivin K, et al. Prevalence of psychotropic and opioid prescription fills among community-dwelling older adults with dementia in the U.S. *JAMA. 2020; in press*.

10.•• Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. *J Am Geriatr Soc*. 1990;38(5):553–63

This meta-analysis reviews the evidence for use of typical antipsychotics in treating neuropsychiatric symptoms.

11.•• Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA*. 2005;293(5):596–608

Comprehensive systematic review evaluating the use of pharmacotherapy in treatment of behavioral disturbances in dementia.

12. U.S. Food and Drug Administration. Public Health Advisory: Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. 2005. Available at: http://psychrights.org/drugs/FDAatypicalswarning4elderly.pdf Accessed on May 25, 2020.

13.•• Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA*. 2003;289(2):210–6

The most recent meta-analysis examining the use of cholinesterase inhibitors in treating neuropsychiatric symptoms of dementia.

14. Stotsky B. Multicenter study comparing thioridazine with diazepam and placebo in elderly, nonpsychotic patients with emotional and behavioral disorders. *Clin Ther*. 1984;6(4):546–59.

15. Auchus AP, Bissey-Black C. Pilot study of haloperidol, fluoxetine, and placebo for agitation in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 1997;9(4):591–3.

16. Lawlor BA, Aisen PS, Green C, Fine E, Schmeïdler J. Selegiline in the treatment of behavioural disturbance in Alzheimer's disease. *Int J Geriatr Psychiatry*. 1997;12(3):319–22.
17. Teri L, Logsdon RG, Peskind E, et al. Treatment of agitation in AD: a randomized, placebo-controlled clinical trial. *Neurology*. 2000;55(9):1271–8.
18. Pollock BG, Mulsant BH, Rosen J, et al. Comparison of citalopram, perphenazine, and placebo for the acute treatment of psychosis and behavioral disturbances in hospitalized, demented patients. *Am J Psychiatry*. 2002;159(3):460–5.
19. Lyketsos CG, Sheppard JM, Steele CD, et al. Randomized, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer's disease: initial results from the Depression in Alzheimer's Disease study. *Am J Psychiatry*. 2000;157(10):1686–9.
20. Finkel SI, Mintzer JE, Dysken M, Krishnan KR, Burt T, McRae T. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. *Int J Geriatr Psychiatry*. 2004;19(1):9–18.
21. Camargos EF, Louzada LL, Quintas JL, Naves JO, Louzada FM, Nóbrega OT. Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, double-blind, and placebo-controlled study. *Am J Geriatr Psychiatry*. 2014;22(12):1565–74.
22.•• Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA*. 2014;311(7):682–91

The Citalopram for Agitation in Alzheimer's Disease (CitAD) study is the largest study evaluating the use of citalopram for treatment of neuropsychiatric symptoms of dementia.

23.• Scoralick FM, Louzada LL, Quintas JL, Naves JO, Camargos EF, Nóbrega OT. Mirtazapine does not improve sleep disorders in Alzheimer's disease: results from a double-blind, placebo-controlled pilot study. *Psychogeriatrics*. 2017;17(2):89–96

Recent study evaluating use of mirtazapine in treating sleep disturbances in dementia.

24. McCarten JR, Kovera C, Maddox MK, Cleary JP. Triazolam in Alzheimer's disease: pilot study on sleep and memory effects. *Pharmacol Biochem Behav*. 1995;52(2):447–52.
25. Meehan KM, Wang H, David SR, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. *Neuropsychopharmacology*. 2002;26(4):494–504.
26. Tariot PN, Erb R, Podgorski CA, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. *Am J Psychiatry*. 1998;155(1):54–61.
27. Olin JT, Fox LS, Pawluczyk S, Taggart NA, Schneider LS. A pilot randomized trial of carbamazepine for behavioral symptoms in treatment-resistant outpatients with Alzheimer disease. *Am J Geriatr Psychiatry*. 2001;9(4):400–5.
28. Sival RC, Haffmans PM, Jansen PA, Duursma SA, Eikelenboom P. Sodium valproate in the treatment of aggressive behavior in patients with dementia–a randomized placebo controlled clinical trial. *Int J Geriatr Psychiatry*. 2002;17(6):579–85.
29. Tariot PN, Raman R, Jakimovich L, et al. Divalproex sodium in nursing home residents with possible or probable Alzheimer Disease complicated by agitation: a randomized, controlled trial. *Am J Geriatr Psychiatry*. 2005;13(11):942–9.
30. Herrmann N, Lanctôt KL, Rothenburg LS, Eryavec G. A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2007;23(2):116–9.
31. Sommer OH, Aga O, Cvancarova M, Olsen IC, Selbaek G, Engedal K. Effect of oxcarbazepine in the treatment of agitation and aggression in severe dementia. *Dement Geriatr Cogn Disord*. 2009;27(2):155–63.
32. Tariot PN, Schneider LS, Cummings J, et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch Gen Psychiatry*. 2011;68(8):853–61.
33.• Cummings JL, Lyketsos CG, Peskind ER, et al. Effect of dextromethorphan-quinidine on agitation in patients with Alzheimer disease dementia: a randomized clinical trial. *JAMA*. 2015;314(12):1242–54

Only study evaluating off-label use of dextromethorphan-quinidine for treatment of agitation in patients with Alzheimer disease.

34. Serfaty M, Kennell-Webb S, Warner J, Blizard R, Raven P. Double blind randomised placebo controlled trial of low dose melatonin for sleep disorders in dementia. *Int J Geriatr Psychiatry*. 2002;17(12):1120–7.
35. Asayama K, Yamadera H, Ito T, Suzuki H, Kudo Y, Endo S. Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia. *J Nippon Med Sch*. 2003;70(4):334–41.
36. Singer C, Tractenberg RE, Kaye J, et al. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep*. 2003;26(7):893–901.
37. Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *Jama*. 2008;299(22):2642–55.
38. Gehrman PR, Connor DJ, Martin JL, Shochat T, Corey-Bloom J, Ancoli-Israel S. Melatonin fails to improve sleep or agitation in double-blind randomized placebo-controlled trial of institutionalized patients with Alzheimer disease. *Am J Geriatr Psychiatry*. 2009;17(2):166–9.
39. Wade AG, Farmer M, Harari G, et al. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-

month, randomized, placebo-controlled, multicenter trial. *Clin Interv Aging.* 2014;9:947–61.

40.• Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. *Cochrane Database Syst Rev.* 2002;(2):Cd002852

This meta-analysis evaluates the evidence for haloperidol in treating neuropsychiatric symptoms of dementia.

41. De Deyn P, Jeste DV, Swanink R, et al. Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease: a randomized, placebo-controlled study. *J Clin Psychopharmacol.* 2005;25(5):463–7.

42. Mintzer J, Greenspan A, Caers I, et al. Risperidone in the treatment of psychosis of Alzheimer disease: results from a prospective clinical trial. *Am J Geriatr Psychiatry.* 2006;14(3):280–91.

43.•• Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med.* 2006;355(15):1525–38

The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) trial is one of the largest randomized controlled trials evaluating use of atypical antipsychotic medications for treatment of behavioral disturbances in dementia.

44.• Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry.* 2006;14(3):191–210

This meta-analysis included 15 randomized controlled trials examining atypical antipsychotic use for treatment of neuropsychiatric symptoms of dementia.

45. Tariot PN, Schneider L, Katz IR, et al. Quetiapine treatment of psychosis associated with dementia: a double-blind, randomized, placebo-controlled clinical trial. *Am J Geriatr Psychiatry.* 142(006):767–76.

46. Kurlan R, Cummings J, Raman R, Thal L. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. *Neurology.* 2007;68(17):1356–63.

47. Mintzer JE, Tune LE, Breder CD, et al. Aripiprazole for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. *Am J Geriatr Psychiatry.* 2007;15(11):918–31.

48. Zhong KX, Tariot PN, Mintzer J, Minkwitz MC, Devine NA. Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study. *Curr Alzheimer Res.* 2007;4(1):81–93.

49. Paleacu D, Barak Y, Mirecky I, Mazeh D. Quetiapine treatment for behavioural and psychological symptoms of dementia in Alzheimer's disease patients: a 6-week, double-blind, placebo-controlled study. *Int J Geriatr Psychiatry.* 2008;23(4):393–400.

50. Streim JE, Porsteinsson AP, Breder CD, et al. A randomized, double-blind, placebo-controlled study of aripiprazole for the treatment of psychosis in nursing home patients with Alzheimer disease. *Am J Geriatr Psychiatry.* 2008;16(7):537–50.

51. Rappaport SA, Marcus RN, Manos G, McQuade RD, Oren DA. A randomized, double-blind, placebo-controlled tolerability study of intramuscular aripiprazole in acutely agitated patients with Alzheimer's, vascular, or mixed dementia. *J Am Med Dir Assoc.* 2009;10(1):21–7.

52.• Ballard C, Banister C, Khan Z, et al. Evaluation of the safety, tolerability, and efficacy of pimavanserin versus placebo in patients with Alzheimer's disease psychosis: a phase 2, randomised, placebo-controlled, double-blind study. *Lancet Neurol.* 2018;17(3):213–22

This recent study evaluates use of pimavanserin in treating neuropsychiatric symptoms of dementia.

53. Cruz MP. Pimavanserin (Nuplazid): a treatment for hallucinations and delusions associated with Parkinson's disease. *P T.* 2017;42(6):368–71.

54. Lyketsos CG, DelCampo L, Steinberg M, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Arch Gen Psychiatry.* 2003;60(7):737–46.

55. Porsteinsson AP, Tariot PN, Erb R, et al. Placebo-controlled study of divalproex sodium for agitation in dementia. *Am J Geriatr Psychiatry.* 2001;9(1):58–66.

56. Gerlach LB, Kales HC, Kim HM, et al. Trends in Antipsychotic and Mood Stabilizer Prescribing in Long-Term Care in the U.S.: 2011–2014. *J Am Med Dir Assoc.* 2020.

57. Devanand DP, Strickler JG, Huey ED, et al. Lithium treatment for agitation in Alzheimer's disease (Lit-AD): clinical rationale and study design. *Contemp Clin Trials.* 2018;71:33–9.

58. Fralick M, Sacks CA, Kesselheim AS. Assessment of use of combined dextromethorphan and quinidine in patients with dementia or Parkinson disease after US Food and Drug Administration approval for pseudobulbar affect. *JAMA Internal Medicine.* 2019;179(2):224–30.

59. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. *BMJ.* 2008;337:a1227.

60. Vasudev A, Shariff SZ, Liu K, et al. Trends in psychotropic dispensing among older adults with dementia living in long-term care facilities: 2004–2013. *Am J Geriatr Psychiatry.* 2015;23(12):1259–69.

61. Ivers NM, Taljaard M, Giannakeas V, Reis C, Williams E, Bronskill S. Public reporting of antipsychotic prescribing in nursing homes: population-based interrupted time series analyses. *BMJ Quality & Safety.* 2019;28(2):121–31.

62. Markota M, Rummans TA, Bostwick JM, Lapid MI. Benzodiazepine use in older adults: dangers, management, and alternative therapies. *Mayo Clin Proc.* 2016;91(11):1632–9.

63. Centers for Medicare and Medicaid Services. Partnership to improve dementia care in nursing homes: antipsychotic drug use in nursing homes trend update. https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2014-Fact-sheets-

items/2014-09-19.html. Published 2014. Accessed Jun 1, 2020.

64.• Brodaty H, Arasaratnam C. Meta-analysis of nonpharmacological interventions for neuropsychiatric symptoms of dementia. *Am J Psychiatry*. 2012;169(9):946–53

Meta-analysis evaluating non-pharmacological interventions including caregiver-focused interventions in addressing neuropsychiatric symptoms of dementia.

65. Kales HC, Gitlin LN, Lyketsos CG. Detroit Expert Panel on Assessment and Mangement of Neuropsychiatric Symptoms of Dementia. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc*. 2014;62(4):762–9.

Publisher's Note