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Geriatric Disorders (D Steffens and K Zdanys, Section Editors)

Antipsychotics, Antidepressants, Anticonvulsants, Melatonin, and Benzodiazepines for Behavioral and Psychological Symptoms of Dementia: a Systematic Review of Meta-analyses

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Opinion statement

The purpose of this systematic review is to evaluate the data on the use of antipsychotics, antidepressants, anticonvulsants, melatonin, and benzodiazepines for the treatment of behavioral and psychological symptoms of dementia (BPSD) from meta-analyses. We performed a literature search of PubMed, MEDLINE, EMBASE, PsycINFO, and Cochrane collaboration databases through August 31, 2016 using the following keywords: dementia, meta-analysis, antipsychotics, antidepressants, anticonvulsants, melatonin, and benzodiazepines. We found a total of 24 meta-analyses that assessed the use of antipsychotics, antidepressants, anticonvulsants, melatonin, and benzodiazepines among individuals with dementia. Sixteen of these meta-analyses evaluated the use of antipsychotics

among individuals with dementia. One of the 16 meta-analyses not only evaluated the use of antipsychotics but also antidepressants and mood stabilizers for BPSD. A total of three meta-analyses assessed the use of antidepressants among individuals with dementia, two meta-analyses evaluated the use of mood stabilizers, two meta-analyses evaluated the use of melatonin, and one meta-analysis evaluated the use of melatonin, trazodone, and ramelteon for sleep disturbances among individuals with dementia. There was no meta-analysis for the use of benzodiazepines among individuals with dementia. Data from this systematic review indicates that antipsychotics demonstrate modest efficacy in the treatment of BPSD. Antidepressants appear to improve symptoms of depression among individuals with dementia and may improve some behavioral symptoms among these individuals. Anticonvulsants appear to have no beneficial effects when used in individuals with dementia. Melatonin appears to improve some sleep parameters and some behavioral symptoms among these individuals. Trazodone appears to improve some sleep parameters among individuals with dementia but has not demonstrated efficacy in managing BPSD. The use of antipsychotics and anticonvulsants in this population is limited by their adverse effect profile.

Introduction

Behavioral and psychological symptoms of dementia (BPSD) include a diverse group of psychological reactions, psychiatric symptoms, and behaviors that are unsafe, disruptive, and impair the care of individuals with dementia in a given environment [1]. BPSD is seen in about one third of community-dwelling individuals with dementia and its prevalence rises to approximately 80% in skilled nursing facilities [2, 3]. BPSD results in greater caregiver burden, faster cognitive and functional decline, and higher rates of institutionalization [4–7]. Additionally, BPSD lowers the quality of life and leads to greater social and economic burden of care for individuals with dementia [8].

Both non-pharmacological and pharmacological interventions have efficacy for the management of BPSD [9, 10]. Pharmacotherapy is often used in combination with non-pharmacological treatments for BPSD that are severe and/or refractory to treatment with non-pharmacological interventions [11]. Medication classes that have shown efficacy in the treatment of BPSD include antipsychotics, antidepressants, anticonvulsants, cholinesterase inhibitors, and melatonin [12]. Current data also indicates that antipsychotics and benzodiazepines are the most prescribed medications for treating BPSD in nursing homes [13].

The 2012 American Geriatrics Society (AGS) Beers Criteria includes antipsychotics and benzodiazepines among the class of potentially inappropriate medications and strongly recommends avoiding their use among older adults especially for the treatment of insomnia, agitation, or delirium [14]. In addition, antipsychotics, antidepressants, and carbamazepine are included among the potentially inappropriate medications to be used with caution among older adults. Furthermore, antipsychotics, antidepressants, and benzodiazepines are included in the potentially inappropriate medications and classes to be avoided in older adults with certain diseases and syndromes as these drugs can exacerbate syncope, seizures, delirium, cognitive impairment, and falls. There is also serious concern among clinicians for using antipsychotics in the treatment of BPSD given their significant adverse effect profile [15].

There are multiple published reviews on the use of psychotropic medications for the treatment of BPSD but none of these reviews have systematically studied the data on the use of antipsychotics, antidepressants, anticonvulsants, melatonin, and benzodiazepines among individuals with dementia exclusively from meta-analyses and have published them in a single document [10–12]. Systematic reviews and meta-analyses of well-designed randomized controlled trials (RCTs) offer the highest levels of evidence to support therapeutic interventions [16]. To fill this void in the literature, we conducted a systematic review of meta-analyses that evaluated the use of antipsychotics, antidepressants, anticonvulsants, melatonin, and benzodiazepines among individuals with dementia.

Our goal was to assess the highest level of evidence on the use of these medications among individuals with BPSD in order to improve the care of these vulnerable individuals. Other medication classes were not included in this review to keep the data manageable and prevent information overload for the readers of this paper.

Search strategy

This systematic review was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. The data on the use of antipsychotics, antidepressants, anticonvulsants, melatonin, and benzodiazepines among individuals with dementia were evaluated from meta-analyses. A literature search was performed of PubMed, MEDLINE, EMBASE, PsycINFO, and Cochrane collaboration databases through August 31, 2016 using the following keywords: dementia, meta-analysis, antipsychotics, antidepressants, anticonvulsants, benzodiazepines, and melatonin. This search was not restricted by the age of the subjects. Only studies involving human subjects that were published in English language journals or had an official English translation were included in the final review. In addition, we reviewed the bibliographic databases of published articles for additional studies.

All three authors (RRT, DJT, and SB) reviewed all the abstracts and full text articles from the citations obtained via the search of the databases. The decision on which studies to be included or excluded from the final analysis was done after a review of the full text articles by all the authors. Disagreements between the authors were resolved by a consensus (Fig. 1).

Results

This systematic review of the literature identified a total of 24 meta-analyses that evaluated the use of antipsychotics, antidepressants, anticonvulsants, benzodiazepines, and melatonin among individuals with dementia [18–26, 27•, 28–30, 31•, 32•, 33–41].

A total of 16 meta-analyses (64%) evaluated the use of antipsychotics among individuals with dementia [18–26, 27•, 28–30, 31•, 32•, 33]. Twelve of the 16 meta-analyses (75%) evaluated the efficacy of antipsychotics among individuals with dementia [18, 19, 21–26, 28, 30, 31•, 32•]. Among the 12 meta-analyses, 8 studies (67%) also assessed adverse effects in addition to efficacy [19, 21, 22, 24, 26, 28, 30, 31•]. Two additional meta-analyses evaluated the adverse effect of death due to the antipsychotics [20, 33]. One of the 16 meta-analyses also evaluated the use of antipsychotics, antidepressants, and mood stabilizers among individuals with BPSD [30]. In addition, two meta-analyses evaluated the discontinuation of antipsychotics among individuals with dementia [27•, 29].

Three meta-analyses evaluated the use of antidepressants among individuals with dementia [34–36]. Two meta-analyses evaluated the use

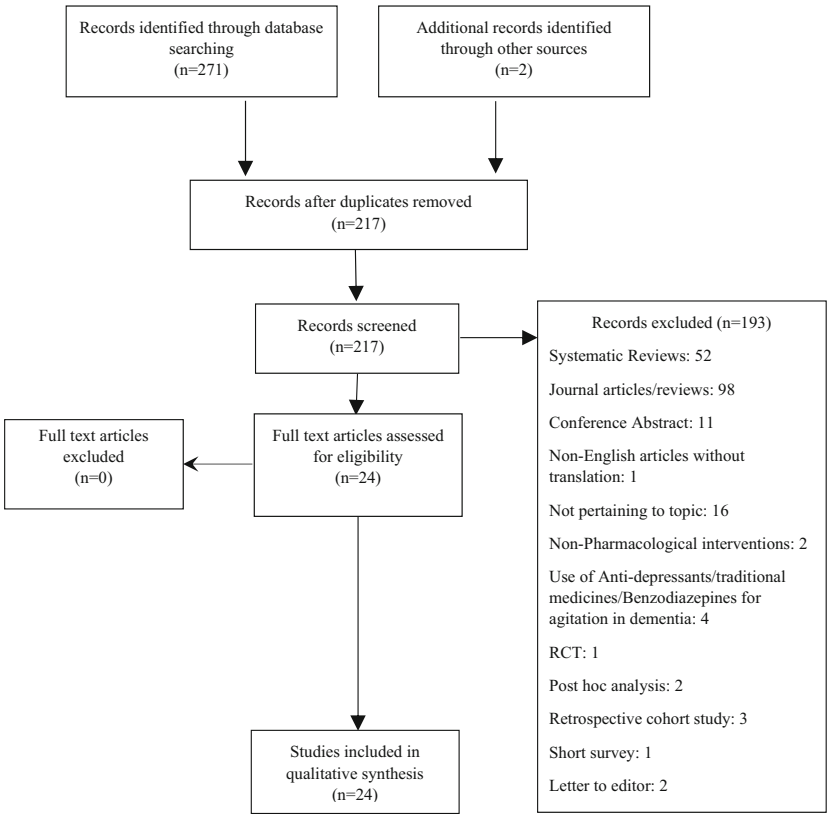

Fig. 1. Flow chart of study selection based on the PRISMA guidelines.

of mood stabilizers among individuals with dementia [37, 38]. Two meta-analyses assessed the use of melatonin among individuals with dementia [39, 40] and one meta-analysis evaluated the use of melatonin, trazodone, and ramelteon among individuals with dementia [41].

Seventeen meta-analyses (68%) included individuals with dementia [18–20, 22, 23, 25, 26, 27•, 28, 29, 31•, 33, 34, 36, 37, 39, 40]. Six meta-analyses (28%) were conducted specifically among individuals with Alzheimer's disease (AD) [21, 24, 30, 35, 38, 41]. One meta-analysis included individuals with Lewy Body Dementia (LBD) [32•]. LBD includes individuals with Dementia with Lewy Bodies (DLB) and Parkinson's-Disease Dementia. Eleven meta-analyses (44%) were completed prior to 2010 [18–24, 36, 37, 39, 41] when compared to 13 studies (56%) after 2010 [25, 26, 27•, 28–30, 31•, 32•, 33–35, 38, 40].

Antipsychotics

As there were many meta-analyses evaluating the use of antipsychotics among individuals with dementia, we decided to summarize the data from these studies. Additional information from these studies have been incorporated into three tables.

Efficacy data

Ten of the 12 meta-analyses [21–26, 28, 30, 31•, 32•] that evaluated the efficacy of antipsychotic medications among individuals with dementia evaluated atypical antipsychotic medications. Only two meta-analyses evaluated the use of typical antipsychotics among individuals with dementia [18, 19]. Among the atypical antipsychotic medications, risperidone, olanzapine, and aripiprazole appear to show modest efficacy when used among individuals with dementia. Quetiapine shows limited efficacy when used in individuals with dementia. Psychosis, aggression, agitation, and more severe behavioral symptoms appear to be better responsive to these drugs. Smaller treatment effects were noted for individuals with less severe dementia and for individuals receiving outpatient treatment. The two meta-analyses that evaluated the use of typical antipsychotics indicate that these medications have modest efficacy when used among individuals with dementia with no superiority noted for any of the medications in this drug-class. There was no meta-analysis that identified on the use of antipsychotic medications among individuals with LBD (Table 1).

Adverse effects

The 10 meta-analyses [19–22, 24, 26, 28, 30, 31•, 33] that reported on the adverse effects of using antipsychotics among individuals with dementia indicated that the use of these medications resulted in greater number of adverse effects when compared to treatment with placebo including an increased risk of cerebrovascular adverse effects (CVAEs) and deaths. The risk of CVAEs appeared to be most prominent among the risperidone-treated group. The risk of death did not appear to be associated with any particular drug and was noted to be significant only when the antipsychotic drugs were pooled together as a group. The risk of death did not appear to be associated with the severity of dementia, the severity of behavioral symptoms, by the sample selection, or by the diagnosis. Sedation, abnormal gait, and extrapyramidal symptoms (EPS) appear to be most prominent with the use of risperidone and olanzapine among individuals with dementia (Table 2).

Discontinuation of antipsychotics

The two meta-analyses [27•, 29] that evaluated the discontinuation of antipsychotic medications indicated that discontinuation of these medications may not necessarily worsen behavioral symptoms among all individuals with dementia. However, those individuals with greater baseline behavioral symptoms may have a worsening of symptoms when these medications are discontinued. One study [29] found that mortality rates among the antipsychotic discontinuation group were lower than the continuation group (Table 3).

Antidepressants

There were three meta-analyses that evaluated the use of antidepressants among individuals with dementia [34–36]. In the first meta-analysis, the investigators included data from seven studies [34]. They were able to combine data from four studies in the meta-analysis. The investigators found that two of the four studies evaluated the properties of tricyclic antidepressants (TCAs), clomipramine, and imipramine that are not commonly used in the older adults. Only two studies

Table 1. Efficacy of antipsychotics

Study	Number of studies and population studied	Outcomes
Schneider et al. [18]	Dementia 7 RCTs Typical antipsychotics versus placebo One typical antipsychotic versus another typical antipsychotic	Modest effect size (0.18) was noted for treating agitation There were no differences between thioridazine and haloperidol and the other medications on outcome measures
Kirchner et al. [19]	Dementia 8 RCTs Thioridazine versus placebo Thioridazine versus no treatment Thioridazine versus alternative pharmacological intervention Thioridazine versus behavioral intervention	Thioridazine was superior to diazepam for the treatment of anxiety symptoms Thioridazine was found to have had no efficacy on global clinical evaluation scales Thioridazine was inferior to chlormethiazole for the treatment of behavioral symptoms Thioridazine was no better than etoperidone, loxapine, or zuclopenthixol for the treatment of behavioral symptoms
Ballard et al. [21]	AD 10 RCTs Atypical antipsychotics versus placebo One atypical antipsychotic medication versus other atypical antipsychotic medication(s)	Risperidone and olanzapine were noted to improve aggression when compared to placebo Risperidone was noted to improve psychotic symptoms among these individuals
Schneider et al. [22]	Dementia 15 RCTs Atypical antipsychotics versus placebo One atypical antipsychotic medication versus other atypical antipsychotic medication(s)	Efficacy was noted for aripiprazole and risperidone but not for olanzapine for the treatment of behavioral symptoms Smaller treatment effects were noted for individuals with less severe dementia, individuals receiving outpatient treatment, and among individuals with psychotic symptoms
Yury and Fisher [23]	Dementia 7 RCTs Atypical antipsychotics versus placebo	The overall mean effect size from the seven placebo-controlled studies for primary outcome measures was 0.45 for the atypical antipsychotic group when compared to 0.32 for the placebo group For all the measures of behavioral problems, the mean effect size was 0.43 for the atypical antipsychotic group when compared to 0.26 for the placebo group

Table 1. (Continued)

Study	Number of studies and population studied	Outcomes
Katz et al. [24]	AD 4 RCTs Risperidone versus placebo	Risperidone improved the scores on the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) Psychosis subscale when compared to placebo (effect size of 0.87 versus 0.57) with an estimated effect size between the two groups at endpoint of 0.15 On the Clinical Global Impression of Change (CGI) scale, the estimated effect size at endpoint between the risperidone and the placebo-treated groups was 0.17 Individuals with more severe symptoms showed better response to risperidone when compared to placebo (effect size 1.14 versus 0.61) with an estimated effect size difference at endpoint of 0.29 between the two groups
Cheug and Stapleberg [25]	Dementia 5 RCTs Quetiapine versus placebo	Mean difference of –3.05 and –0.31 respectively was noted on the Neuropsychiatric Inventory (NPI) total score and the CGI-C score when the quetiapine group was compared to the placebo group
Maher et al. [26]	Dementia 18 RCTs in individuals with dementia Atypical antipsychotics versus placebo	For aripiprazole, olanzapine, and risperidone groups, the effect size for treating behavioral symptoms ranged from 0.12 to 0.20 and for the quetiapine group it was 0.11 For the treatment of psychosis, the effect sizes were 0.20 for the risperidone group, 0.20 for the aripiprazole group, 0.05 for the olanzapine group, and –0.03 for the quetiapine group For the treatment of agitation, the aripiprazole, olanzapine, and risperidone groups had effect sizes between 0.19 and 0.31 whereas the effect size for the quetiapine group was 0.05
Ma et al. [28]	Dementia 16 RCTs Atypical antipsychotics versus placebo	Atypical antipsychotics showed efficacy on the Brief Psychiatric Rating Scale (BPRS) (WMD) [–1.58], the Cohen Mansfield Agitation Inventory (CMAI) (–1.84), the NPI (–2.81), the CGI-C (–0.32), and the CGI-S (–0.19) when compared to placebo
Wang et al. [30]	AD 6 RCTs Atypical antipsychotics versus placebo	Atypical antipsychotics improved the NPI total score [(SMD) –0.21] when compared to placebo Olanzapine improved behavioral symptoms among individuals with AD (SMD –0.18) when compared to placebo Aripiprazole produced improvements on the NPI scale (SMD –0.20) when compared to placebo
Tan et al. [31•]	Dementia 23 RCTs Atypical antipsychotics versus placebo	The WMD in change scores for the NPI total score was only significant for the aripiprazole group (–4.4) when compared to placebo group The WMD change scores for the BEHAVE-AD was only significant for the risperidone (–1.48) when compared to the placebo group
Stinton et al. [32•]	LBD No meta-analysis conducted for antipsychotics but 1 RCT	Individuals treated with olanzapine 5 mg a day showed greater reductions in scores on the NPI subscales for delusions (–3.8 points) and hallucinations (–5.9 points) when compared to placebo

Table 1. (Continued)

Study	Number of studies and population studied	Outcomes
	for olanzapine and 1 RCT for quetiapine were included in the manuscript Antipsychotics versus placebo Antipsychotics versus any treatment	Quetiapine was no better than placebo for the treatment of neuropsychiatric symptoms

SMD standardized mean difference, *WMD* weighted mean difference

Table 2. Adverse effects of antipsychotics

Study	Outcomes
Kirchner et al. [19]	No deaths were reported in any of the studies
Schneider et al. [20]	118 (3.5%) of the deaths were noted in drug-treated group when compared to 40 deaths (2.3%) in the placebo groups, odds ratio (OR) of 1.54 and a risk difference (RD) of 0.01. There was no differential risk for the individual drugs, or based on the severity of dementia, the sample selection or by the diagnosis
Ballard et al. [21]	Somnolence, UTI, falls, extrapyramidal symptoms (EPS), pain, peripheral edema, fever, gait abnormality, urinary incontinence, and asthenia were more among the risperidone group when compared to the placebo group Adverse effects and dropouts were more in the group receiving the risperidone 2 mg dose when compared to the group receiving the 1 mg dose Cerebrovascular adverse events were more in the risperidone group when compared to the placebo group, OR of 3.64 Dropouts due to adverse effects were greater in the olanzapine group when compared to the placebo group Abnormal gait, somnolence, fever, and urinary incontinence were greater in the olanzapine group when compared to the placebo group Somnolence was greater in the aripiprazole group when compared to the placebo group Cognition was worsened in the quetiapine group when compared to placebo group
Schneider et al. [22]	Somnolence was greater in the drug-treated group when compared to the placebo group, OR of 2.84 Somnolence was greater in the olanzapine group when compared to the aripiprazole group and when compared to the placebo group, RD of 0.16 versus 0.06 Risk for EPS was greater in the drug-treated group when compared to the placebo group, OR of 1.51

Table 2. (Continued)

Study	Outcomes
	Highest risk for EPS was in the risperidone group when compared to the placebo group, OR of 1.8 and RD of 0.06. Abnormal gait was seen more often in the risperidone and olanzapine groups when compared to the placebo group, OR of 3.42 Edema was greater in the risperidone and olanzapine groups when compared to the placebo group, OR of 1.99 Urinary tract infections (UTIs) and urinary incontinence were more common among the drug-treated group when compared to the placebo group, OR of 1.51 CVAEs were more common in the drug-treated group when compared to the placebo group, OR of 2.13 CVAEs were significantly higher in the risperidone group when compared to the placebo group, OR of 3.43
Katz et al. [24]	Somnolence was 18% in the risperidone group when compared to the 8% in the placebo group EPS was 12% in the risperidone group when compared to 6% in the placebo group CVAEs was 1.6% in the risperidone group when compared to 0.8% in the placebo group Deaths within 30 days of the last dose was 3.1% in the risperidone group when compared to 1.8% in the placebo group, but this was not statistically significant There was no association between all-cause mortality and the severity of behavioral symptoms at baseline
Maher et al. [26]	Cardiovascular effects were more common among the olanzapine and the risperidone groups when compared to placebo group, OR of 2.30 and 2.10 respectively Cerebrovascular accident was more common among individuals treated with risperidone when compared to placebo-treated individuals, pooled OR of 3.12 Increased appetite and weight gain were more common among individuals treated with olanzapine and risperidone when compared to placebo, pooled OR of 4.70 and 3.40, respectively, and the number needed to harm (NNH) was 25 Olanzapine showed significantly greater anticholinergic effects when compared to placebo, OR of 3.30 and NNH of 6 Olanzapine, quetiapine, and risperidone were associated with sedation and fatigue when compared to placebo with an OR of 4.60, 5.20, and 2.30, respectively Olanzapine and risperidone were associated with an increase in extrapyramidal symptoms when compared to placebo, OR 15.20 and 3.00, NNH of 10 and 20, respectively Olanzapine, quetiapine, and risperidone were associated with an increase in urinary tract symptoms, OR of 9.5, 2.4, and 1.6, respectively, and the NNH ranged from 16 to 36 when compared to placebo Six head-to-head trials showed that olanzapine use resulted in more neurological symptoms such as confusion, dizziness, headaches, etc. when compared to risperidone, OR of 1.54
Ma et al. [28]	EPS was 15.2% in the drug-treated group when compared to 8.6% in the placebo group, OR of 1.74 and the risk for EPS was higher in the olanzapine and risperidone groups Somnolence was 17.0% when compared to 7.2% in the placebo group, OR of 2.95 and the risk for somnolence was greater in the aripiprazole, olanzapine, quetiapine, and risperidone groups CVAEs were 2.1% in the drug-treated group when compared to 0.9% in the placebo group, OR of 2.50.

Table 2. (Continued)

Study	Outcomes
	Gait abnormality was 6.9% in the drug-treated group when compared to the 1.7% in the placebo group, the risk for gait abnormality greater in the olanzapine and risperidone groups Deaths within 30 days of drug discontinuation was 3.6% in the drug-treated group when compared to 2.3% in the placebo group, OR of 1.5, the subgroup meta-analyses did not identify any greater risk of death among the aripiprazole, olanzapine, quetiapine, or risperidone groups Edema was 9.3% in the drug-treated group when compare to 5.2% in the placebo group, OR of 1.8 Urinary tract infection was 14.9% in the drug-treated group when compared to 10.9% in the placebo group, OR of 1.35 Falls were 15.2% in the drug treated group when compared to 18.8% in the placebo group
Wang et al. [30]	Drop outs due to adverse events were greater in the atypical antipsychotic group when compared to the placebo group, RR of 2.24 Adverse effects were greater in the atypical antipsychotic group when compared to the placebo group, RR of 1.17
Tan et al. [31•]	Somnolence was greater in the atypical antipsychotic group when compared to the placebo group, OR of 3.7 Somnolence was greater in aripiprazole group (OR, 3.51), olanzapine group (OR, 3.61), and quetiapine group (OR, 5.88) when compared to the placebo group Abnormal gait was more frequent in atypical antipsychotic group when compared to the placebo group, OR of 1.84, with rates being highest in the olanzapine group when compared to the placebo group, OR of 3.84 Edema was more common in quetiapine group when compared to the placebo group, OR of 1.51 UTIS were more common in the atypical antipsychotic group when compared to placebo group, OR of 1.91, with risk highest in the olanzapine (6.93) and risperidone (2.28) groups Strokes more common in the drug-treated group when compared to placebo group, OR of 2.62, with the risk highest in the risperidone group, OR of 4.53 Deaths were more common in the atypical antipsychotic group when compared to placebo group, OR of 1.06, there was no increased risk of death noted with any individual drug
Hulshof et al. [33]	Pooled risk difference for death was 0.1% for the conventional antipsychotic group when compared to the placebo group, RR of 1.07 Pooled risk difference for death was 0.4% in the haloperidol group when compared to the placebo group, RR of 1.25, which was not statistically significant Point estimates of adverse effects were higher in the dementia trials (0.5%) when compared to delirium-prevention trials (–0.4%)

investigated the properties of the more commonly used SSRIs (fluoxetine and sertraline) among individuals with dementia. The investigators found that on the Cornell Scale for Depression in Dementia (CSDD) and on the psychiatrist's global rating at 12 weeks, the results favored the treatment group when compared to the placebo group. The number of individuals who suffered at least

Table 3. Discontinuation of antipsychotics

Study	Details of the study	Outcomes
Declercq et al. [27•]	Dementia 9 trials 7 trials in nursing homes 1 trial in an outpatient setting 1 trial in both nursing home and outpatient setting	There were no overall differences between the groups on the primary outcomes In one trial, the time to relapse was shorter in the discontinuation group when compared to the continuation group, $P = 0.04$ In one trial, the discontinuation of the medication led to an increase in the NPI-core score of ≥30% in the discontinuation group when compared to the continuation group, HR of 1.94 In one trial, individuals with milder behavioral symptoms at baseline were less agitated in the discontinuation group when compared to the continuation group, $P = 0.018$ In two trials, individuals with more severe baseline symptoms had a worsening of symptoms when they were withdrawn from the antipsychotics, $P = 0.009$
Pan et al. [29]	Dementia 9 trials	There were no statistically significant differences between the groups on the behavioral severity score change from baseline, SMD of 0.19 There were a higher proportion of individuals whose behavioral symptoms worsened in the drug discontinuation group when compared to the drug continuation group, RR of 1.78 The drug discontinuation group had higher rates of early study termination when compared to the drug continuation group, RR of 1.11 The drug discontinuation group had lower mortality during follow-up when compared to the drug continuation group, RR of 0.83

one adverse event at 6 to 12 weeks favored the placebo group when compared to the active treatment group. The results also favored the placebo group when compared to the active treatment group on individuals experiencing at least one nervous system adverse event, experiencing at least one gastrointestinal system adverse event, and on subjects experiencing dry mouth.

In the second meta-analysis by Thompson et al. [35], the investigators included data from five studies that were completed among individuals with AD. They found that antidepressants were superior to placebo for both the treatment response and the remission of depression among individuals with AD. Additionally, the numbers needed to treat (NNT) was 5 for both outcomes. The antidepressants were well tolerated in this population with no significant differences noted between both treatment groups for a change in cognition, overall dropouts, or dropout due to adverse events (AEs).

In the third study, Seitz et al. included data from nine trials that used antidepressants for the management of agitation and psychosis among

individuals with dementia [36]. The investigators found that there was a significant reduction in the Cohen Mansfield Agitation Inventory (CMAI) total score for the SSRI (citalopram and sertraline) group when compared to the placebo group. The two studies that compared SSRIs (fluoxetine and sertraline) to haloperidol did not find any significant difference in the change in CMAI total scores between the two groups. Two studies found that there was no significant difference in the change in CMAI score for trazodone group when compared to the haloperidol group. Two studies that reported on the number of individuals who were assessed to be "much improved" or "very much improved" per the Clinical Global Impression (CGI) scale for trazodone versus haloperidol, found no statistically significant differences between the two groups. Data from four studies found that the proportion of individuals with trial withdrawal due to adverse events was not significantly different between the SSRI and placebo groups. Additionally, the proportion of individuals with trial withdrawal due to adverse events showed no difference between the fluoxetine or haloperidol groups or between the citalopram and the perphenazine groups. Furthermore, the proportion of individuals with trial withdrawal due to any cause was no different between the trazodone and haloperidol groups (Table 4).

Mood stabilizers

There were two meta-analyses that evaluated the use of mood stabilizers among individuals with dementia [37, 38]. In the first meta-analysis by Lonergan et al. [37], the investigators used data from three studies to evaluate the use of valproate preparations for treating agitation in dementia. Two of the studies could not be combined in the meta-analyses and the third study showed no benefit for the use of valproate to treat agitation among individuals with dementia. Furthermore, none of the studies showed any benefit in the treatment of aggression among individuals with dementia. The data from all three studies indicated that adverse effects were more common in the valproate-treated group when compared to placebo group, especially sedation and urinary tract infections.

In the second meta-analysis, Xiao et al [38] included data from five studies (three—valproate/divalproex, one—carbamazepine, and one—lithium study) that evaluated the use of mood stabilizers among individuals with AD. The investigators found that data from two studies indicated that when compared to mood stabilizers (valproate/divalproex and carbamazepine) plus conventional therapies versus conventional therapies alone (three pairs of comparison), behavioral symptoms as assessed by Neuropsychiatric Inventory (NPI) total scores were worse in the mood stabilizer group when compared to the conventional therapies group. Data from two studies (valproate/divalproex) indicated that mood stabilizers plus conventional drugs were not superior to conventional drugs alone in improving behavioral symptoms as assessed by the NPI/Brief Psychiatric Rating Scale (BPRS) agitation subscales. However, the data from all the five studies indicated that mood stabilizers plus conventional drugs might prevent a decline in cognition as measured by the Mini Mental State Examination (MMSE) scores, although this effect was small. Data from three studies (two—valproate/divalproex and one—carbamazepine) showed that on the Physical Self Maintenance Scale (PSMS) there were no significant effects of

Table 4. Antidepressants among individuals with dementia

Study	Details of the study	Outcomes	Adverse effects
Bains et al. [34]	Dementia 7 included studies Four studies were included in the meta-analyses	Of these four studies, two investigated the properties of TCAs that are not commonly used in this population, Only two studies investigated the properties of the more commonly used SSRIs On the Cornell Scale for Depression in Dementia (CSDD) and on the psychiatrist's global rating, the results favored the treatment group when compared to placebo at 12 weeks, WMD of −6.70 and OR of 7.33, respectively	The number of individuals suffering at least one adverse event at 6 to 12 weeks favored the placebo group when compared to active treatment group, OR of 1.42 The results favored the placebo group when compared to the active treatment group on individuals experiencing at least one nervous system adverse event OR of 9.36, experiencing at least one gastrointestinal system adverse event OR of 2.84 and individuals experiencing dry mouth OR of 1.68
Thompson et al. [35]	AD 5 studies	Antidepressants were superior to placebo for both treatment response OR of 2.32 and remission of depression OR of 2.75 The numbers needed to treat for response to antidepressant treatment and for remission of depression were both 5	There were no significant differences between both treatment groups for change in cognition WMD of −0.71, overall dropouts OR of 0.70, and dropout due to AEs OR of 1.41
Seitz et al. [36]	Dementia 9 studies 5 studies compared SSRIs to placebo 2 studies were combined in a meta-analysis	There was a significant reduction in the CMAI total score for the SSRI (citalopram and sertraline) group when compared to the placebo group, MD of −0.89 and $P < 0.00001$ Two studies that compared SSRIs to haloperidol did not find any significant difference in the change in CMAI total scores between the two groups, MD of 4.66 and $P = 0.27$ Two studies found no significant difference in the change in the CMAI score for trazodone when compared to haloperidol, MD of 3.28 and $P = 0.33$ Two studies reported on numbers of individuals who were assessed to be much or very much improved per the CGI for trazodone when compared to haloperidol found no statistically significant difference between the two groups, RR of 1.25 and $P = 1.00$	There were no significant differences in the rates of trial withdrawals due to any cause between the SSRI and placebo groups, RR of 0.91 and $P = 0.56$ There were no significant differences in the risk of withdrawal due to adverse events between the fluoxetine and haloperidol groups, RR of 0.13 and $P = 0.22$ There were no significant differences in the risk of trial withdrawals due to any cause between the citalopram and the perphenazine groups, RR of 0.89 and $P = 0.81$ There were no significant differences in the risk of trial withdrawal due to any cause between the trazodone and haloperidol groups, RR of 0.79 and $P = 0.45$

Table 5. Mood stabilizers among individuals with dementia

Study	Details of the study	Outcomes	Adverse effects
Lonergan and Luxenberg [37]	Dementia 3 studies	Because of methodological problems, 2 studies could not be included in the meta-analysis The third study showed no significant difference in the response of agitation, between the valproate and control groups, $P = 0.08$ No study demonstrated overall improvement of aggression in the valproate group when compared to the placebo group, $P > 0.05$	Overall the number of adverse events were more frequent in the active treatment group when compared to the control groups, OR of 3.22 and $P = 0.0001$ Meta-analysis of three pooled studies showed an overall increase in adverse effects among the valproate group when compared to the control group with sedation, OR of 2.64 and $P = 0.002$ and UTI, OR of 3.02 and $P = 0.04$ being significantly greater in the active treatment group
Xiao et al. [38]	AD 5 RCTs	Two RCTs that compared mood stabilizers (valproate/divalproex and carbamazepine) plus conventional therapies versus conventional therapies (3 pairs of comparison) indicated that mood stabilizers significantly worsened NPI total scores among the mood stabilizer group, WMD of 3.71 and $P = 0.04$ Meta-analysis of two RCTs (valproate/divalproex) indicated that mood stabilizers plus conventional drugs were not superior to conventional drugs alone in improving NPI/BPRS agitation subscale scores, SMD of 0.30 and $P = 0.53$ The meta-analysis of all the five RCTs (3 valproate/divalproex, 1 carbamazepine and 1 lithium) indicated that mood stabilizers plus conventional drugs might prevent a decline in MMSE scores, WMD of –0.89 and $P = 0.03$ The meta-analysis of three studies (2 valproate/divalproex, 1 carbamazepine) showed that on the Physical Self Maintenance Scale (PSMS) there were no significant effects of mood stabilizers on the daily functional ability as indicated by the PSMS change scores, WMD of 0.35 and $P = 0.24$	No analysis of adverse effects noted in the paper

mood stabilizers on the daily functional ability as indicated by the PSMS change scores. The authors of this study did not comment on the adverse effect profile of these drugs when used among individuals with AD (Table 5).

Melatonin

The use of melatonin in individuals with dementia has been evaluated in two meta-analyses [39, 40].

In the first meta-analysis by Jansen et al. [39], the investigators found that data from five studies indicated that the use of melatonin did not appear to improve cognition among individuals with dementia, irrespective of the dose of the medication (2.5, 3, or 10 mg a day), the duration of treatment (4 or 7 weeks), or the type of test used to assess cognition, i.e., the Mini Mental State Examination (MMSE) or the Alzheimer's Disease Cooperative Study (ADAS)-Cog. Surprisingly, melatonin improved behavioral symptoms when compared to placebo at 2.5 or 3 mg a day and in 4 to 7 weeks based on either the neuropsychiatric interview (NPI) or the ADAS-non-cognitive scale. Melatonin appeared to be well tolerated with no significant difference between melatonin and placebo groups in the adverse effect profile.

In the second study by Xu et al., the investigators included seven trials that evaluated the use of melatonin for sleep disorders and cognition among individuals with dementia [40]. The investigators found that melatonin improved sleep efficacy (SE) and total sleep time (TST) among individuals with dementia. The sleep parameters appeared to be slightly better when the duration of treatment was 4 weeks when compared to any duration. However, the use of melatonin did not appear to improve cognition among individuals with dementia irrespective of the duration of treatment or the type of test used to assess cognition, i.e., the MMSE or the ADAS-cog. Melatonin appeared to be well tolerated in these trials with no significant adverse effects being reported or there being no significant difference between the active treatment and placebo groups in terms of adverse effects (Table 6).

For sleep disturbance

We found one meta-analysis that evaluated pharmacotherapeutic agents for sleep disturbance among individuals with AD [41]. The investigators included data from four RCTs for the three drugs: melatonin (two yielded data suitable for meta-analysis), trazodone (one study), and ramelteon (one study) in this meta-analysis. The melatonin and trazodone studies were for individuals with moderate-to-severe AD whereas the ramelteon study included individuals with mild-to-moderate AD. The investigators found that melatonin, either immediate- or slow-release, did not improve any of the major sleep outcomes in individuals with AD. The total nocturnal sleep time and the ratio of daytime sleep to night-time sleep were no different in the melatonin group when compared to the placebo group. No serious adverse effects of melatonin were reported in the included studies.

The trazodone study indicated that trazodone 50 mg administered at night for 2 weeks significantly improved total nocturnal sleep time and sleep efficiency. There was no effect noted for trazodone on the amount of time spent awake after sleep onset, the number of nocturnal awakenings, the amount of time spent asleep during the day, or the number of daytime naps. Additionally,

Table 6. Melatonin among individuals with dementia

Study	Details of the study	Outcomes	Adverse effects
Jansen et al. [39]	Dementia 5 studies	Data from 3 studies showed a non-significant effect for changing cognition (MMSE) in the melatonin group when compared to the placebo group, WMD of 0.29, $P = 0.53$ Data from 2 trials indicated that there was no significant difference between the melatonin and placebo groups on cognition as measured by Alzheimer's Disease Cooperative Study (ADAS)-cognitive scores, WMD of –2.64, $P = 0.12$ Data from 2 trials indicated that melatonin improved behavioral symptoms that were rated on the ADAS-non-cognitive scale and the NPI, WMD of –3.48, $P < 0.00001$	Two studies that investigated adverse events found a decrease in the mean seriousness of adverse events in the melatonin group when compared to the placebo group, WMD of –0.10, $P = 0.01$ All other estimates of adverse effects between the melatonin and placebo groups were non-significant
Xu et al. [40]	Dementia 7 studies	Data from 4 trials indicated that melatonin marginally improved sleep efficacy (SE), MD of 1.78, $P = 0.07$ when involving all treatment duration After melatonin administration for more than 4 weeks, the SE showed a statistically significant improvement by 2.23%, $P = 0.02$ For individuals with AD the SE was increased significantly by 1.86%, $P = 0.02$ when involving all treatment duration Among individuals with AD there was a significant improvement of SE by 2.0%, $P = 0.01$ after more than 4 weeks of treatment Data from 6 trials indicated that melatonin prolonged total sleep time (TST) by 24.36 min, $P = 0.02$ in individuals with dementia when involving all treatment duration A follow-up of over 4 weeks indicated that melatonin prolonged TST by 28.78 min, $P = 0.02$ Among individuals with AD melatonin prolonged TST by 23.98 min, $P = 0.12$ when involving all treatment duration and by 29.69 min, $P = 0.07$ when	Data from 3 trials showed that melatonin use was not associated with any significant adverse events (AEs) One study reported that spontaneously reported AEs were no different between the melatonin and placebo groups One study reported that drowsiness and irritability were the most commonly reported AEs but headache, hyperactivity, sweating, and trembling hands were reported more commonly in the melatonin group than in the placebo group but were not statistically significant, $P > 0.05$

Table 6. (Continued)

Study	Details of the study	Outcomes	Adverse effects
		individuals were treated over a period of more than 4 weeks Data from 5 studies indicated that in individuals with dementia melatonin improved MMSE scores by 0.06, $P = 0.85$ when involving all treatment duration but this result was not statistically significant Over a period of greater than 4 weeks there was no significant improvement in MMSE scores, MD of 0.04, $P = 0.90$ Data from three trials involving individuals with AD who used melatonin for more than 4 weeks did not significantly change the MMSE scores, MD of 0.08, $P = 0.81$ Data from 2 trials that assessed cognition using the ADAS-cog and included individuals who were treated with melatonin for 4 to 8 weeks did not show any significant improvements in the cognitive scores, MD of −1.73, $P = 0.11$	

there were no significant differences between the trazodone and placebo groups on cognition or ADLs. Adverse events were not significantly different between the trazodone and placebo groups and were rated as being mild.

In the ramelteon study, there were no significant differences between the ramelteon and placebo groups for the primary outcome of night-time total sleep time at week 1 or between the groups at 1 week in the percentage of participants whose night-time sleep time increased by 30 min or more, in time awake after sleep onset, in sleep efficiency, or in the number of daytime naps. The daytime total sleep time was higher in the ramelteon group at 1 week but not at the later time points. The ramelteon group also had a significantly higher ratio of daytime to night-time sleep at weeks 1, 4, and 8/early termination. No other sleep outcomes differed significantly between groups at week 8. The investigators found lower Neuropsychiatric Inventory (NPI) disinhibition score at week 8/early termination in the ramelteon group when compared to the placebo group. They also found that adverse effects were similar in the placebo and ramelteon treatment groups (Table 7).

Specifically for BPSD

We found one meta-analysis that specifically evaluated the use of antipsychotics, antidepressants, and mood stabilizers for BPSD [30]. The investigators

Table 7. Medications for sleep disturbances among individuals with dementia

Study	Details of the study	Outcomes	Adverse effects
McCleery et al. [41]	AD 4 RCTs for three drugs: melatonin (two yielded data suitable for meta-analysis), trazodone (one study), and ramelteon (one study) Melatonin and trazodone studies were for individuals with moderate-to-severe AD Ramelteon study was for individuals with mild-to-moderate AD	Melatonin, either immediate- or slow-release did not improve any major sleep outcomes in individuals with AD Total nocturnal sleep time, MD of 10.68 min and the ratio of daytime sleep to night-time sleep, MD of –0.13 Trazodone 50 mg administered at night for 2 weeks significantly improved total nocturnal sleep time, MD of 42.46 min and sleep efficiency, MD of 8.53 Trazodone had no effect on the amount of time spent awake after sleep onset, MD of –20.41, the number of nocturnal awakenings, MD of –3.71, the amount of time spent asleep during the day, MD of 5.12 min or the number of daytime naps, MD of 0.84 There were no significant differences between the groups on cognition or ADLs In the ramelteon study there were no significant difference between groups for the primary outcome of night-time total sleep time at week 1, MD of 18.2 min, or between groups at 1 week in the percentage of participants whose night-time sleep time increased by 30 min or more, in time awake after sleep onset, in sleep efficiency or in the number of daytime naps. Daytime total sleep time was higher in the ramelteon group at one week, MD of 43.1, $P = 0.010$, but not at later time points The ramelteon group also had a significantly higher ratio of daytime to night-time sleep at	No serious adverse effects of melatonin were reported in the included studies Adverse events were not significantly different between the trazodone and placebo groups and were rated as being mild Adverse effects were similar in the placebo and ramelteon treatment Groups, 27.9 versus 29.0%

Table 7. (Continued)

Study	Details of the study	Outcomes	Adverse effects
		weeks 1, 4, and 8/early termination, $P = 0.014$, $P = 0.019$, $P = 0.029$, respectively No other sleep outcomes differed significantly between groups at week 8 Lower Neuropsychiatric Inventory (NPI) disinhibition score at week 8/early termination in the ramelteon group, MD of –0.9, $P = 0.039$ when compared to placebo	

included data from nine studies including six studies of atypical antipsychotics, two for antidepressants, and one for mood stabilizers. The investigators found that the atypical antipsychotics produced significant improvements on the NPI total score when compared to placebo. In subgroup analyses, the olanzapine significantly improved behaviors among individuals with AD when compared to placebo. Additionally, among the aripiprazole subgroup, there was significant improvement on NPI scale when compared to placebo. The investigators did not find significant differences in the number of dropouts caused by any reason between the antipsychotics treatment group and placebo treatment group. However, the dropout rates due to adverse events were higher in the atypical antipsychotic-treated group when compared to the placebo group.

The only two RCTs using antidepressants that were included in this meta-analysis compared sertraline to placebo among individuals with AD. Neither of the two trials found any significant difference in the NPI total scores between the sertraline and placebo groups over time. There were no significant differences in the number of dropouts caused by any reason between the sertraline and placebo treatment groups. The investigators were unable to estimate the dropout rates due to adverse events in this study.

The investigators were only able to include one RCT of valproate versus placebo in this meta-analysis. They found no significant differences in the change of NPI total scores between the valproate and placebo groups, but it appeared that treatment with valproate might worsen the NPI total score when compared to treatment with placebo. Unfortunately, no data on adverse effects is available for the valproate study (Table 8).

Discussion

This systematic review identified 24 meta-analyses that evaluated the use of antipsychotics, antidepressants, anticonvulsants, melatonin, and benzodiazepines among individuals with dementia. Most of these meta-analyses (16 out of

Table 8. Medications specifically for BPSD

Study	Details of the study	Outcomes	Adverse effects
Wang et al. [30]	AD Atypical antipsychotics = 6	Significant improvements on the NPI total score among individuals treated with atypical antipsychotics when compared to placebo, SMD of –0.21. In the subgroup analyses, the olanzapine significantly improved behaviors among individuals with AD, SMD of –0.18 Among the aripiprazole subgroup, there was significant improvement on NPI scale, SMD of –0.20	There were no significant differences in the number of dropouts caused by any reason between the antipsychotic treatment group and the placebo treatment group, OR of 0.94 The dropout rates due to adverse events were higher in the atypical antipsychotic-treated group when compared to the placebo group, RR of 2.24
	Antidepressants = 2	Only two RCTs on sertraline were included in the study The two trials found no significant differences in the NPI total scores between the sertraline and placebo groups over time, SMD of 0.01	There were no significant differences in the number of dropouts caused by any reason between the antidepressant treatment group and the placebo treatment group, OR of 1.01 The dropout rates due to adverse events were not estimable in this study
	Mood stabilizers = 1	Only one eligible RCT of valproate was included in the study There were no significant differences on the changes of NPI total scores between the valproate and placebo groups, $P = 0.075$, but it appeared that treatment with valproate might worsen the NPI total score when compared to placebo	No data provided in the study

24, 64%) evaluated the use of antipsychotics among individuals with dementia. One of the 16 meta-analyses also evaluated the use of antipsychotics, antidepressants, and mood stabilizers among individuals with BPSD [30]. The rest of the eight meta-analyses included three studies on antidepressants, two studies on mood stabilizers, two studies on melatonin, and one study on medications for sleep disturbances in dementia.

Available data indicates that among atypical agents, risperidone, olanzapine, and aripiprazole appear to show modest efficacy for the treatment of psychosis, aggression, and agitation when used in individuals with dementia. Quetiapine appears to have limited efficacy in treating these types of symptoms. More severe symptoms appear to be particularly responsive to treatment with atypical antipsychotics. Weaker effects are

noted for less severe dementia and among individuals receiving outpatient treatment. Typical antipsychotics have modest efficacy when used among individuals with dementia with no superiority noted for any medication in this drug-class. Antipsychotic use among individuals with dementia appears to cause greater number of adverse effects when compared to placebo including CVAEs and deaths. The risk of CVAEs appeared to be most significant among the risperidone-treated group. The risk of death did not appear to be associated with any particular drug but became significant when the data were pooled together from the different studies. The risk of death did not appear to be associated with the severity of dementia, the severity of behavioral symptoms, by the sample selection, or by the diagnosis. There was no evidence to suggest a difference in the rates of mortality between typical and atypical antipsychotics when used in individuals with dementia. Sedation, abnormal gait, and EPS appeared to be more common among individuals treated with risperidone and olanzapine. The discontinuation of antipsychotics appeared to worsen BPSD among individuals with greater baseline behavioral symptoms. Data from one meta-analysis indicated that mortality rates were lower among the drug discontinuation group when compared to the drug continuation group.

Antidepressants especially the SSRIs appear to be beneficial in treating the symptoms of depression among individuals with dementia. They also appeared to improve symptoms of agitation among these individuals. Trazodone appeared to improve multiple sleep parameters among individuals with dementia and was also found to be not significantly different from haloperidol in the management of BPSD. Antidepressants including trazodone appeared to be well tolerated by individuals with dementia. Mood stabilizers especially valproate preparations do not appear to be beneficial when used among individuals with dementia. Additionally, they appear to cause significant adverse effects in these individuals.

Melatonin appeared to improve multiple sleep parameters among individuals with dementia and in one study melatonin also improved behavioral symptoms when compared to placebo. Melatonin appeared to be well tolerated among individuals with dementia. Ramelteon was not reviewed in this paper but was evaluated in one meta-analysis on pharmacotherapy for sleep disturbances among individuals with dementia along with melatonin and trazodone. Ramelteon appeared to improve daytime total sleep time when compared to placebo. It also appeared to improve some behavioral symptoms among individuals with dementia and was well tolerated. There is no data from meta-analyses on the use of benzodiazepines among individuals with dementia, but data from a recent systematic review indicated limited efficacy for this class of medication when used among individuals with dementia [42].

One weakness of this review is the use of data from meta-analyses published only in English language or with an official English language translation. In addition, there was significant heterogeneity among the various meta-analyses based on the inclusion and exclusion criteria, the medications used, the dosage ranges of medications used, the rating scales used, and the duration of included studies. Furthermore, we did not use statistical methods to correct for the heterogeneity in the

included studies. The strength of this review includes a comprehensive search of five large databases, adherence to the PRISMA guidelines for systematic reviews, and compilation of data from 24 meta-analyses.

Non-pharmacological treatments appeared to show benefit in the management of BPSD [9, 43•, 44]. Multiple different studies recommend these interventions as first line strategy for the management of BPSD [45, 46]. Current data also indicates efficacy for different classes of medications for the treatment of BPSD [47]. Acetylcholinesterase inhibitors (AChEIs) may improve symptoms of depression, dysphoria, apathy, and anxiety among individuals with dementia. Memantine may improve behavioral symptoms when compared to placebo among individuals with dementia [48]. Other medications that have shown potential for the treatment of BPSD include dextromethorphan/quinidine, cannabinoids, scyllo-inositol, brexpiprazole, and prazosin [49]. Although previously thought to be beneficial for treating apathy among individuals with dementia, a recent systematic review indicated that the data for using stimulants, analgesics, and oxytocin for treating apathy among individuals with dementia is still inconclusive [50]. Based on available efficacy data for these agents, it would be prudent to conclude that there is insufficient evidence at this time for recommending their routine use among individuals with BPSD.

Based on the data from this review, it would be appropriate to conclude that among individuals with dementia, antipsychotics should be reserved for treating psychosis, aggression, and agitation that are severe and are not responsive to non-pharmacological management strategies. Among the antipsychotic medications, risperidone, olanzapine, and aripiprazole would be the preferred agents for use among individuals with dementia. Current data does not allow for conclusions to be made regarding the dosages for these medications and the duration of their use. However, these medications should be used in strict adherence with the recent American Psychiatric Association (APA) guideline regarding their use to optimize outcomes and minimize medico-legal risks [51•]. Antidepressants should be used to treat symptoms of depression among individuals with dementia. They may also improve behavioral symptoms among these individuals. Melatonin and trazodone can be used to improve sleep issues among individuals with dementia and may also help with behavioral symptoms. Mood stabilizers do not appear to have any role among individuals with dementia given their lack of efficacy and significant adverse effect profile.

Conclusions

Available data indicates that antipsychotic medications have modest efficacy when used among individuals with dementia. Antipsychotics appear to be particularly effective for more severe behavioral symptoms. When using antipsychotics among individual with dementia, strict adherence to the recent APA guidelines should be maintained. Antidepressants appear to improve symptoms of depression among individuals with dementia and may also improve behavioral symptoms

among these individuals. Melatonin and trazodone appear to improve sleep parameters among individuals with dementia and may also improve behavioral symptoms. These medications should be used among individuals with dementia in conjunction with non-pharmacological management techniques to optimize outcomes.

Compliance with ethical standards

Conflict of interest
Rajesh R. Tampi declares that he has no conflict of interest. Deena J. Tampi declares that she has no conflict of interest. Silpa Balachandran declares that she has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors

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