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Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses

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Abstract

Background: The purpose of this review is to evaluate the data on the use of antipsychotics in individuals with dementia from meta-analyses.

Methods: We performed a literature search of PubMed, MEDLINE, EMBASE, PsycINFO and Cochrane collaboration databases through 30 November, 2015 using the following keywords: 'antipsychotics', 'dementia' and 'meta-analysis'. The search was not restricted by the age of the patients or the language of the study. However, in the final analysis we only included studies involving patients that were published in English language journals or had official English translations. In addition, we reviewed the bibliographic databases of published articles for additional studies.

Results: This systematic review of the literature identified a total of 16 meta-analyses that evaluated the use of antipsychotics in individuals with dementia. Overall, 12 meta-analyses evaluated the efficacy of antipsychotics among individuals with dementia. Of these, eight also assessed adverse effects. A further two studies evaluated the adverse effects of antipsychotics (i.e. death). A total of two meta-analyses evaluated the discontinuation of antipsychotics in individuals with dementia. Overall, three meta-analyses were conducted in individuals with Alzheimer's disease (AD) whereas one focused on individuals with Lewy Body Dementia (LBD). The rest of the 12 meta-analyses included individuals with dementia.

Conclusions: Antipsychotics have demonstrated modest efficacy in treating psychosis, aggression and agitation in individuals with dementia. Their use in individuals with dementia is often limited by their adverse effect profile. The use of antipsychotics should be reserved for severe symptoms that have failed to respond adequately to nonpharmacological management strategies.

Keywords: antipsychotics, benefits, dementia, meta-analysis, risks, therapy

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Introduction

Antipsychotic medications are often used to treat behavioral and psychological symptoms of dementia (BPSD) [Zuidema *et al.* 2015]. Evidence indicates that the prescription rates for antipsychotics among individuals with dementia vary between 20% and 50% [Feng *et al.* 2009; Wetzels *et al.* 2011]. In addition, individuals with dementia who live in skilled nursing facilities have significantly greater rates of prescription of antipsychotic medications when compared with those individuals living in the community [Maguire, 2013]. Available data also indicate antipsychotics are often used in individuals with dementia for sustained periods (⩾6 months) with limited monitoring of their effects [Wetzels *et al.* 2011; Barnes *et al.* 2012; Gustafsson *et al.* 2013; Chen *et al.* 2010; Gellad *et al.* 2012].

Available evidence indicates that risperidone, olanzapine and aripiprazole exhibit modest benefits in the management of aggression and psychosis over a 6–12-week period in individuals with Alzheimer's disease (AD) [Ballard *et al.* 2009].

However, similar benefits have not been observed for quetiapine. In addition, there is limited evidence for the use of these medications in individuals with non-AD type dementia [Ballard *et al.* 2008]. Furthermore, the benefit of using antipsychotics as a longer-term treatment in individuals with dementia is unclear.

The use of antipsychotics in the management of psychotic symptoms and aggression in individuals with dementia must be balanced against their serious adverse effects profile [Ballard *et al.* 2009]. Antipsychotic use increases the risk for death, cerebrovascular adverse events (CVAEs), Parkinsonism, sedation, gait disturbance, cognitive decline and pneumonia [Ballard *et al.* 2009; Chiu *et al.* 2015; Mittal *et al.* 2011]. Given the significant risk for mortality when antipsychotics are used in individuals with dementia, the US Food and Drug Administration (FDA), the European Medicines Agency and the UK Medicines and Healthcare Products Regulatory Agency have issued warnings regarding their use in individuals with dementia [Mittal *et al.* 2011]. Data also indicate that the risk for mortality remains elevated for at least 2 years, and the actual number of deaths due to antipsychotics increases with their longer duration of use. The US FDA has not yet approved any medication for treating agitation associated with dementia and AD and in the European Union and Australia only risperidone is indicated for the short-term management of persisting and severe aggression in individuals with AD who have failed nonpharmacological trials [Maher *et al.* 2011]. Despite these warnings, the off-label use of antipsychotics for treating individuals with dementia appears to have grown over the past two decades.

Numerous reviews have evaluated the use of antipsychotics in individuals with dementia [Gallagher and Herrmann, 2015; Madhusoodanan and Ting, 2014; Gareri *et al.* 2014]. However, none of these reviews have systematically studied the data on the use of antipsychotics in individuals with dementia exclusively from meta-analyses. Systematic reviews and meta-analyses of well-designed and completed randomized controlled trials (RCTs) can provide the highest levels of evidence to support therapeutic interventions [McNamara and Scales, 2011; Sauerland and Seiler, 2005]. In order to fill this void in the literature, we decided to conduct a systematic review of meta-analyses that evaluated the use of antipsychotics in individuals with dementia. Our goal was to assess the highest level of evidence on the use of antipsychotics in individuals with dementia so that these data can be used to improve the care of these vulnerable individuals.

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 [Shamseer *et al.* 2015]. The purpose of this review is to evaluate the data on the use of antipsychotics in individuals with dementia from meta-analyses. We performed a literature search of PubMed, MEDLINE, EMBASE, PsycINFO and Cochrane collaboration databases through 30 November, 2015 using the following keywords: 'antipsychotics', 'dementia' and 'meta-analysis'. The search was not restricted by the age of the patients or the language of the study. However, in the final analysis we only included studies involving patients that were published in English language journals or had official English translations. In addition, we reviewed the bibliographic databases of published articles for additional studies.

The review of all the abstracts and full-text articles from the citations obtained *via* the search of the databases was carried out by three of the authors (RRT, DJT and SC). 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. See Figure 1.

Results

This systematic review of the literature identified a total of 16 meta-analyses that evaluated the use of antipsychotics in individuals with dementia [Schneider *et al.* 1990, 2005, 2006; Kirchner *et al.* 2001; Ballard and Waite, 2006; Yury and Fisher, 2007; Katz *et al.* 2007; Cheung and Stapelberg, 2011; Maher *et al.* 2011; Declercq *et al.* 2013; Ma *et al.* 2014; Pan *et al.* 2014; Wang *et al.* 2015; Tan *et al.* 2015; Stinton *et al.* 2015; Hulshof *et al.* 2015].

Among the 16 meta-analyses, 12 evaluated the efficacy of antipsychotics among individuals with dementia [Schneider *et al.* 1990; Kirchner *et al.* 2001; Ballard and Waite, 2006; Schneider *et al.* 2006; Yury and Fisher, 2007; Katz *et al.* 2007; Cheung and Stapelberg, 2011; Maher *et al.* 2011;

Ma *et al.* 2014; Wang *et al.* 2015; Tan *et al.* 2015; Stinton *et al.* 2015]. A total of 8 of the 12 stud*ies also assessed adverse effects [Kirchner *et al.* 2001; Ballard and Waite, 2006; Schneider *et al.* 2006; Katz *et al.* 2007; Maher *et al.* 2011; Ma *et al.* 2014; Wang *et al.* 2015; Tan *et al.* 2015]. There were two studies that evaluated the adverse effects of antipsychotics (i.e. death) [Schneider *et al.* 2005; Hulshof *et al.* 2015]. A total of two studies focused on the discontinuation of antipsychotics among individuals with dementia [Declercq *et al.* 2013; Pan *et al.* 2014]. There were three meta-analyses that were conducted in individuals with AD [Ballard and Waite, 2006; Katz *et al.* 2007; Wang *et al.* 2015] whereas one focused on individuals with Lewy body dementia (LBD) [Stinton *et al.* 2015]. LBD includes individuals with dementia with Lewy bodies (DLB) and Parkinson's disease dementia. The rest of the 12 meta-analyses included individuals with dementia [Schneider *et al.* 1990, 2005, 2006; Kirchner *et al.* 2001; Yury and Fisher, 2007; Cheung and Stapelberg, 2011; Maher *et al.* 2011; Declercq *et al.* 2013; Ma *et al.* 2014; Pan *et al.* 2014; Tan *et al.* 2015; Hulshof *et al.* 2015]. A total of seven of the meta-analyses were completed prior to 2010 [Schneider *et al.* 1990, 2005, 2006; Kirchner *et al.* 2001; Ballard and Waite, 2006; Yury and Fisher, 2007; Katz *et al.* 2007] when compared with nine studies after 2010 [Cheung and Stapelberg, 2011; Maher *et al.* 2011; Declercq *et al.* 2013; Ma *et al.* 2014; Pan *et al.* 2014; Wang *et al.* 2015; Tan *et al.* 2015; Stinton *et al.* 2015; Hulshof *et al.* 2015].

In the next section we describe the data on efficacy, adverse effects and the evidence for discontinuation of antipsychotics in individuals with dementia.

Data on efficacy

This section contains data from 12 meta-analyses that evaluated the efficacy of antipsychotics in individuals with dementia [Schneider *et al.* 1990, 2006; Kirchner *et al.* 2001; Ballard and Waite, 2006; Yury and Fisher, 2007; Katz *et al.* 2007; Cheung and Stapelberg, 2011; Ma *et al.* 2014; Wang *et al.* 2015; Tan *et al.* 2015; Stinton *et al.* 2015]. The meta-analyses have been arranged in a chronological order with the oldest study first and the latest study at the end.

In the earliest meta-analysis that was identified in this review, Schneider and colleagues evaluated the use of typical antipsychotic medications in individuals with dementia [Schneider *et al.* 1990]. The investigators found that these medications were more effective than placebo in treating agitation in dementia with a modest effect size (0.18). They found that when thioridazine and haloperidol were compared with the other typical antipsychotics there was no significant difference noted between these two drugs and the other medications.

In a meta-analysis that evaluated the use of thioridazine in individuals with dementia, the investigators found that, when compared with placebo, thioridazine reduced symptoms of anxiety in these individuals [Kirchner *et al.* 2001]. However, there were no significant effects noted on clinical global change in thioridazine-treated individuals when compared with placebo. Thioridazine was found to be superior to diazepam for anxiety symptoms. Both medications did not improve global clinical evaluation scales in individuals with dementia. Thioridazine was found to be inferior to chlormethiazole in managing behavioral symptoms. Thioridazine was no better than etoperidone, loxapine or zuclopenthixol when used in individuals with dementia.

In the meta-analysis by Ballard and Waite, the investigators found that among individuals with dementia, the use of risperidone and olanzapine improved aggression when compared with placebo [Ballard and Waite, 2006]. In addition, they found that the use of risperidone also improved psychotic symptoms among these individuals. Schneider and colleagues, in their meta-analysis evaluating the use of atypical antipsychotics for dementia, found efficacy for aripiprazole and risperidone but not for olanzapine when used in these individuals [Schneider *et al.* 2006]. They also noted smaller effects for less-severe dementia, outpatients and individuals with psychotic symptoms. In the meta-analysis by Yuri and Fisher, the investigators included data from 13 studies that compared risperidone, olanzapine, and quetiapine with either placebo or with each other [Yury and Fisher, 2007]. The investigators found the overall mean effect size from the seven placebo-controlled studies for primary measures to be 0.45 for atypical antipsychotics when compared with 0.32 for placebo in individuals with dementia. For all measures of behavioral problems, the mean effect size was 0.43 for the atypical antipsychotic group when compared with 0.26 for the placebo group.

In a meta-analysis, Katz and colleagues compared data from four large placebo-controlled clinical trials of risperidone in individuals with psychosis of AD or dementia [Katz *et al.* 2007]. The investigators found that that risperidone when compared with placebo improved scores on the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), psychosis subscale, (effect size 0.87 *versus* 0.57) with an estimated effect size between groups at endpoint of 0.15. On the Clinical Global Impression (CGI) scale the estimated effect size at endpoint was 0.17 between the risperidone and placebo-treated groups. Secondary analyses indicated that individuals with more severe symptoms showed better response to treatment with risperidone when compared with placebo (effect size 1.14 *versus* 0.61) with an estimated effect size difference at endpoint of 0.29. Cheung and Stapleberg conducted a meta-analysis on the efficacy of quetiapine for BPSD [Cheung and Stapelberg, 2011]. Based on the data from five studies, the investigators found a mean difference of −3.05 and −0.31 respectively on the Neuropsychiatric Inventory (NPI) total score and the CGI of Change scale (CGI-C) score when comparing quetiapine with placebo-treated individuals.

Maher and colleagues in their meta-analysis used data from 18 RCTs that evaluated the use of atypical antipsychotic medications in individuals with dementia [Maher *et al.* 2011]. They examined three types of outcomes: improvement in psychosis (delusions and hallucinations, principally), improvement in agitation (including physical aggression, verbal aggression, excitability, oppositional behaviors, and excessive motor activity) and a total global score that included cumulative psychiatric symptoms of delusions, hallucinations, suspiciousness, dysphoria, anxiety, motor agitation, aggression, hostility, euphoria, disinhibition, irritability, apathy and other behavioral disturbances. The investigators found that for aripiprazole, olanzapine and risperidone, the effect size for treating these symptoms was small (0.12–0.20), but statistically significant. The effect size for quetiapine was 0.11, which was not statistically significant. The mean change in the NPI total score in individuals treated with an antipsychotic medication was a 35% improvement compared with baseline, while the difference in the pooled NPI total score between treatment and placebo was 3.41 points. The investigators also found that aripiprazole (10 mg a day) or risperidone (2 mg a day) may be more effective than lower doses in treating the behavioral symptoms. For the treatment of psychosis, the effect sizes were 0.20 for risperidone, 0.20 for aripiprazole, 0.05 for olanzapine and −0.03 for quetiapine. Aripiprazole, olanzapine and risperidone were all associated with statistically significant improvements in agitation with effect sizes between 0.19 and 0.31 whereas the effect size for quetiapine was 0.05. The three trials that compared risperidone with olanzapine or risperidone with quetiapine did not find any significant difference between these drugs for treating behavioral symptoms. A total of five trials that compared an atypical antipsychotic medication with haloperidol for the total global outcome also did not consistently identify any statistically significant difference between these drugs.

In a meta-analysis by Ma and colleagues the investigators studied the efficacy of atypical antipsychotic medications for BPSD from 16 RCTs [Ma *et al.* 2014]. They found that atypical antipsychotics showed efficacy on the Brief Psychiatric Rating Scale (BPRS), weighted mean difference (WMD, −1.58), the Cohen–Mansfield Agitation Inventory (CMAI, −1.84), NPI (−2.81), CGI-C (−0.32) and the Clinical Global Impression of Severity (CGI-S, −0.19) when compared with individuals receiving placebo.

In a meta-analysis that evaluated the efficacy of pharmacological treatments for neuropsychiatric symptoms (NPSs) among individuals with AD, Wang and colleagues found that available data from six studies indicate that atypical antipsychotics improve NPI total score [standardized mean difference (SMD) −0.21] when compared with placebo [Wang *et al.* 2015]. In the subgroup analyses, the investigators found that olanzapine improved behavioral symptoms in individuals with AD (SMD −0.18) whereas aripiprazole produced improvements on the NPI scale (SMD −0.20) when compared with placebo. Tan and colleagues in their meta-analysis of 23 studies of atypical antipsychotics in individuals with dementia found that the WMD in change scores for the NPI total score was only significant for aripiprazole (−4.4) when compared with placebo [Tan *et al.* 2015]. They also found that WMD in change scores for the BEHAVE-AD was only significant for risperidone (−1.48).

In a meta-analysis that evaluated all pharmacological treatment strategies for individuals with LBD the investigators could not conduct a

meta-analysis of antipsychotic medications as there was an inadequate number of eligible studies [Stinton *et al.* 2015]. However, the investigators found a secondary analysis of a RCT that used olanzapine in individuals with AD who were retrospectively identified as meeting the LBD criteria [Cummings *et al.* 2002]. Among individuals with LBD ($N = 29$), those individuals treated with 5 mg a day of olanzapine ($N = 10$) showed greater reductions in scores on the NPI subscales for delusions (−3.8 points) and hallucinations (−5.9 points) when compared with individuals receiving placebo ($N = 10$). The investigators did not find significant differences between the olanzapine 10 mg and the 15 mg groups and the placebo groups on psychiatric symptoms. The investigators also found a randomized placebo-controlled trial of quetiapine among individuals with LBD dementia and AD with Parkinsonian features [Kurlan *et al.* 2007]. They found no difference on measures of psychiatric symptoms between the quetiapine and the placebo-treated groups in this study.

A summary of the 12 meta-analyses that evaluated the efficacy of antipsychotic medications in individuals with dementia indicates that 10 of these studies (83%) evaluated atypical antipsychotic medications and only 2 meta-analyses evaluated typical antipsychotics. The two meta-analyses that studied the use of typical antipsychotics found that these medications have modest efficacy when used in individuals with dementia. There was no superiority noted for any particular medication in this drug-class. Atypical antipsychotic medications (risperidone, olanzapine and aripiprazole) showed modest efficacy when used in individuals with dementia including AD. Quetiapine was found to have limited efficacy when used in individuals with dementia. Psychosis, aggression, agitation and more severe symptoms appear to be particularly responsive to the atypical antipsychotics. Smaller effects were noted for less severe dementia and individuals receiving outpatient treatment. There was no meta-analysis identified on the use of antipsychotic medications among individuals with LBD. However, one RCT found that olanzapine at 5 mg a day improved delusions and hallucinations in these individuals. See Table 1.

Data on adverse effects

Overall 10 of the 16 meta-analyses commented on adverse effects when antipsychotic medications were used in individuals with dementia [Kirchner *et al.* 2001; Schneider *et al.* 2005, 2006; Ballard and Waite, 2006; Katz *et al.* 2007; Maher *et al.* 2011; Ma *et al.* 2014; Wang *et al.* 2015; Tan *et al.* 2015; Hulshof *et al.* 2015]. This includes eight studies that also assessed efficacy of these medications in individuals with dementia including AD [Kirchner *et al.* 2001; Ballard and Waite, 2006; Schneider *et al.* 2006; Katz *et al.* 2007; Maher *et al.* 2011; Ma *et al.* 2014; Wang *et al.* 2015; Tan *et al.* 2015]. There were two studies that exclusively commented on the adverse effects (i.e. death) when these medications are used in individuals with dementia [Schneider *et al.* 2005; Hulshof *et al.* 2015]. The meta-analyses have been arranged in a chronological order with the oldest study first and the latest study at the end.

In the meta-analysis by Kirchner and colleagues, the investigators noted that adverse events were not reported in a systematic manner in any of the trials [Kirchner *et al.* 2001]. However, no deaths were reported in any of the studies. The studies also provided limited or no information regarding EKG changes in the participants.

The meta-analysis by Schneider and colleagues evaluated the risk of death with atypical antipsychotics when used in individuals with dementia. The investigators found that more deaths occurred among individuals who were randomized to the drugs when compared with placebo (118 [3.5%] *versus* 40 [2.3%]) [Schneider *et al.* 2005]. The odds ratio (OR) by meta-analysis was 1.54 and the risk difference (RD) of 0.01. There was no evidence noted for differential risks based on individual drugs, severity of dementia, sample selection or by the diagnosis.

The meta-analysis by Ballard and Waite indicates that risperidone-treated individuals have greater odds of dropping out of the study due to adverse effects especially at the 2 mg a day dose when compared with placebo [Ballard and Waite, 2006]. In addition, the odds of developing somnolence, urinary tract infection (UTI), falls, extrapyramidal symptoms (EPSs), pain, peripheral edema, fever, gait abnormality, urinary incontinence and asthenia were greater in the risperidone-treated individuals when compared with placebo. Adverse effects were greater in the risperidone 2 mg dosing when compared with 1 mg dosing. Overall, five trials found that CVAEs were more common in the risperidone group (all doses pooled) when compared with placebo (OR 3.64). Among the olanzapine studies, dropouts due to

adverse effects were greater in the drug-treated group when compared with placebo. Abnormal gait, somnolence, fever and urinary incontinence were greater in the olanzapine-treated individuals when compared with placebo-treated individuals. Aripiprazole-treated individuals had greater risk of somnolence when compared with placebo-treated individuals. Quetiapine worsened cognition when compared with placebo.

In their second meta-analysis, Schneider and colleagues evaluated the risk of adverse events when atypical antipsychotic medications are used in individuals with dementia [Schneider *et al.* 2006]. The investigators found that somnolence was higher among drug-treated individuals (OR 2.84) when compared with placebo. The risk for somnolence was greater for olanzapine-treated individuals when compared with aripiprazole (RD 0.16 *versus* 0.06). There was increased risk for EPSs (OR 1.51) for the drug-treated individuals when compared with placebo. The highest risk for EPSs was noted for risperidone (OR 1.8 and RD 0.06). Abnormal gait (OR 3.42) was noted in the active drug group (risperidone and olanzapine) when compared with placebo. There was increased risk for edema (OR 1.99) among the drug-treated group (risperidone and olanzapine) when compared with placebo. UTIs and urinary incontinence were more common among the drug-treated group (OR 1.51) when compared with placebo. CVAEs were more common in the drug treated group (OR 2.13) when compared with placebo. This risk was significantly higher for risperidone (OR 3.43) when compared with placebo. The risk of death was evaluated in the previous meta-analysis [Schneider *et al.* 2005].

In the meta-analysis by Katz and colleagues, the investigators found that somnolence (18% *versus* 8%) and EPSs (12% *versus* 6%) were more common in the risperidone group when compared with the placebo group [Katz *et al.* 2007]. They also noted that there were more CVAEs in the risperidone group (1.6% *versus* 0.8%) when compared with the placebo group although this difference was not statistically significant. The investigators found that there were 16 deaths (3.1%) in the risperidone group, including deaths occurring within 30 days of the last dose of study drug, compared with 7 deaths (1.8%) in the placebo group. This difference was deemed not to be statistically significant. There was no association noted between all-cause mortality and the severity of behavioral problems at baseline for both groups.

In the meta-analysis by Maher and colleagues the investigators found that the use of olanzapine and risperidone were associated with cardiovascular effects (OR 2.30 and 2.10 respectively) [Maher *et al.* 2011]. Cerebrovascular accident was more common among individuals treated with risperidone (OR 3.12). Increased appetite and weight gain were more common among individuals treated with olanzapine and risperidone (OR 4.70 and 3.40 respectively) with a number needed to harm (NNH) of 25. Olanzapine showed significantly greater central and peripheral anticholinergic effects (OR 3.30) and NNH of 6 when compared with placebo. Olanzapine, quetiapine and risperidone were associated with sedation and fatigue (OR 4.60, 5.20 and 2.30 respectively). Olanzapine and risperidone were associated with an increase in EPSs (OR 15.20 and 3.00) and NNH of 10 and 20, respectively. Olanzapine, quetiapine and risperidone, were associated with an increase in urinary tract symptoms (OR 9.5, 2.4 and 1.6, respectively) with NNH ranging from 16 to 36. The data from six head-to-head trials showed that individuals taking olanzapine had greater odds of having a neurological symptom such as confusion, dizziness, and headaches when compared with those taking risperidone (OR 1.54).

The meta-analysis by Ma and colleagues indicated that EPSs were greater among the drug-treated individuals with dementia when compared with placebo-treated individuals (15.2% *versus* 8.6%) with an OR 1.74 [Ma *et al.* 2014]. The risk for EPSs was higher for individuals receiving olanzapine and risperidone. A total of 17.0% of individuals in the drug-treated group experienced somnolence when compared with 7.2% of the placebo-treated individuals with an OR 2.95. Individuals receiving aripiprazole, olanzapine, quetiapine and risperidone were at higher risk for somnolence when compared with those individuals receiving placebo. The individuals in the drug-treated group were more likely to experience CVAEs when compared with placebo-treated individuals (2.1% *versus* 0.9%) with an OR 2.50. A total of 6.9% of individuals in the drug-treated group experienced gait abnormality when compared with 1.7% of the placebo-treated individuals with an OR 3.35. Individuals who were treated with olanzapine and risperidone were at higher risk for gait abnormalities when compared with placebo treated individuals. The investigators found that 3.6% of drug-treated individuals died during the trials or within 30 days of discontinuation of

the drug when compared with 2.3% individuals in the placebo group for an OR 1.5. Common causes of death were pneumonia, stroke and cardiac arrests. Subgroup meta-analyses did not identify greater risk of death for individuals receiving aripiprazole, olanzapine, quetiapine or risperidone when compared with placebo. Individuals receiving active drugs were at higher risk of developing edema (9.3% *versus* 5.2%, OR 1.8) and UTI (14.9% *versus* 10.9%, OR 1.35). However, falls (15.2% *versus* 18.8%, OR 0.89) and insomnia (5.4% *versus* 5.4%, OR 0.94) were no different between the two groups.

The meta-analysis by Wang and colleagues indicated that in this study there was no significant difference in the number of dropouts caused by any reason between the groups treated with atypical antipsychotics and placebo, risk ratio (RR) of 0.94 [Wang *et al.* 2015]. However, the number of individuals who dropped out of the study due to adverse events was greater in the atypical antipsychotic group when compared with the placebo group (RR 2.24). In addition, individuals in the atypical antipsychotic group experienced greater number of adverse events than placebo-treated individuals (RR 1.17).

In the meta-analysis by Tan and colleagues, the investigators found that somnolence was greater in the group treated with atypical antipsychotics when compared with placebo-treated individuals (OR 3.7) [Tan *et al.* 2015]. Somnolence was greater among individuals treated with aripiprazole (OR 3.51), olanzapine (OR 3.61) and quetiapine (OR 5.88). However, injury/accidental injury and falls were no different between the drug-treated and placebo-treated groups (OR 0.89). Abnormal gait was more frequent in the group treated with atypical antipsychotics when compared with placebo (OR 1.84). The highest risk was in the olanzapine-treated group (OR 3.84). Edema was more common in the individuals treated with quetiapine (OR 1.51) when compared with placebo-treated individuals. UTIs were more common in the atypical antipsychotic-treated individuals when compared with placebo-treated individuals (OR of 1.91). The risks were highest in the olanzapine (6.93) and risperidone-treated (2.28) groups. Strokes were more common in the drug-treated group when compared with the placebo-treated group (OR 2.62). The risk was highest in the risperidone treated group (OR 4.53). The overall OR by meta-analysis for death in individuals treated with antipsychotics when compared with placebo was 1.06 with no increased risk of death noted with any individual drug.

In the meta-analysis by Hulshof and colleagues, the investigators included data from 17 trials that evaluated the use of conventional antipsychotics among individuals with dementia and delirium [Hulshof *et al.* 2015]. They found that the pooled RD for death among individuals treated with conventional antipsychotics when compared with placebo was 0.1% with a RR of 1.07. When the data were analyzed from the 11 trials that evaluated haloperidol the RD was 0.4% and the RR was 1.25. These findings were not statistically significant. On sensitivity analyses the investigators found that the point estimate for risk was higher in the dementia trials (0.5%) and lower in delirium-prevention trials (−0.4%). The risks were also lower in trials with low risk because of baseline differences (0.0%), inadequate blinding (0.0%), and dropout (−0.6%). This pattern also occurred for the haloperidol trials.

A summary of these 10 meta-analyses indicate that antipsychotic use in individuals with dementia results in a greater number of adverse effects when compared with individuals treated with placebo, including the risk of CVAEs and deaths. The risk of CVAEs was most prominent in the risperidone-treated group. The risk of death was not associated with any particular drug but was appreciated when the antipsychotic drugs were considered together as a group. The risk of death was not associated with the severity of dementia or behavioral symptoms, by the sample selection or by the diagnosis. Sedation, abnormal gait and EPSs appear to be most prominent with the use of risperidone and olanzapine. See Table 2.

Withdrawal of antipsychotics

There were two meta-analyses that evaluated the discontinuation of antipsychotics in individuals with dementia [Declercq *et al.* 2013; Pan *et al.* 2014].

In the first meta-analysis by Declercq and colleagues, the investigators included data from nine trials. There were seven trials conducted in nursing homes while one trial was conducted in an outpatient setting and one trial in both settings [Declercq *et al.* 2013]. The investigators used success of withdrawal (i.e. participants remaining in study off antipsychotics) and the NPSs as primary efficacy

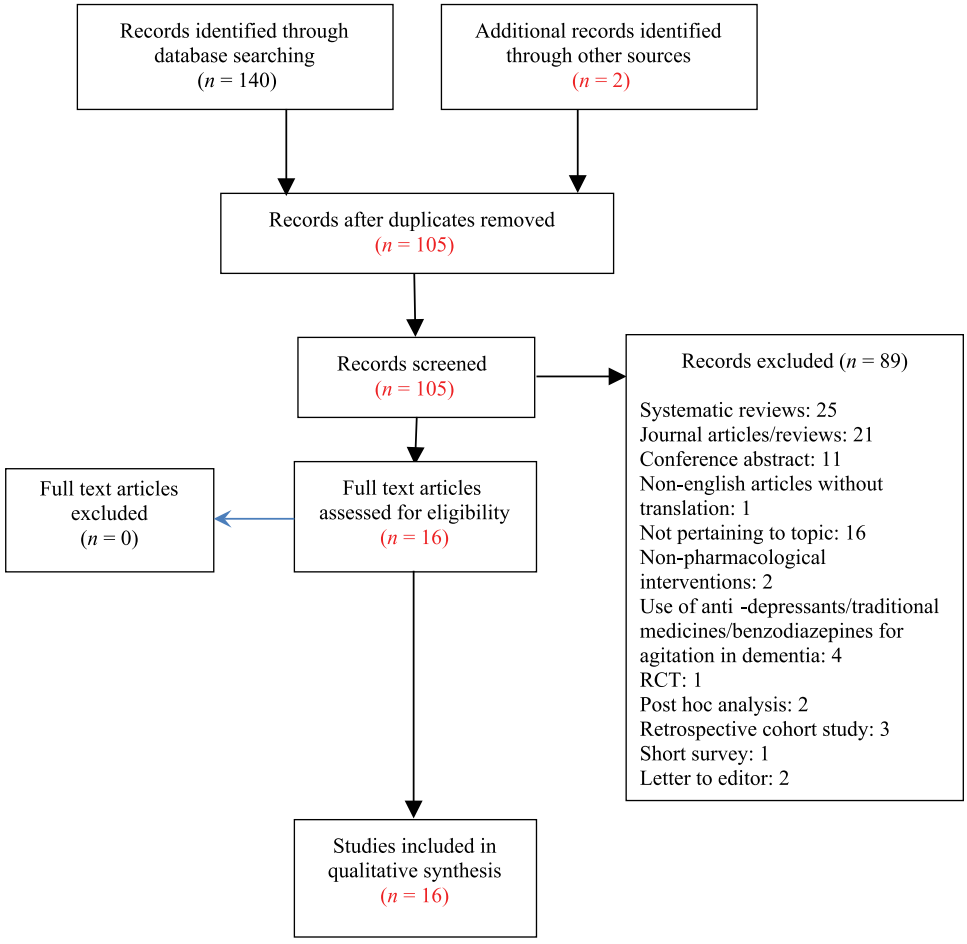

Figure 1. PRISMA flow diagram.
PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

measures from these studies. Overall, eight of nine studies found no overall difference between the groups on the primary outcomes. In one study of individuals with psychosis and agitation that responded to haloperidol, the time to relapse was shorter in the discontinuation group when compared with the continuation group ($p = 0.04$). In one trial that included individuals with dementia and psychosis or agitation who had responded well to risperidone for 4–8 months, discontinuation of the medication led to an increase in the NPI-core score $\geqslant$ 30% in the discontinuation group when compared with the continuation group Hazard Ratio (HR of 1.94). Pooled NPI-score (two studies) indicated that there was no significant difference between individuals who discontinued the drug *versus* those continuing on antipsychotics at 3 months [mean difference (MD) −1.49]. In one study, those individuals with milder behavioral symptoms at baseline were significantly less agitated at 3 months in the discontinuation group when compared with the continuation group ($p = 0.018$). In both studies, there was evidence for significant worsening of behavioral symptoms in individuals with more severe baseline symptoms who were withdrawn from the antipsychotics when compared with those who continued on the medications ($p = 0.009$).

In a meta-analysis of published randomized controlled studies that compared the effects of antipsychotic discontinuation *versus* continuation in individuals with dementia, Pan and colleagues included data from a total of nine studies [Pan *et al.* 2014]. The investigators found that there was no statistically significant difference between the group that discontinued the antipsychotic medication when compared with the group that continued on the antipsychotic medication on behavioral severity score change from baseline

Table 1. Efficacy of antipsychotics in individuals with dementia.

Study	Objectives	Details of the study	Comparators	Outcomes
[Schneider *et al*. 1990]	To study the efficacy of typical antipsychotics in individuals with dementia	7 RCTs	Typical antipsychotics *versus* placebo. One typical antipsychotic *versus* another typical antipsychotic	Modest effect size (0.18) for treating agitation. Thioridazine and haloperidol were no different from the other medications
[Kirchner *et al*. 2001]	To study efficacy of thioridazine in individuals with dementia	8 RCTs	Thioridazine *versus* placebo. Thioridazine *versus* no treatment. Thioridazine *versus* alternative pharmacological intervention. Thioridazine *versus* behavioral intervention	Thioridazine superior to diazepam for anxiety symptoms. Thioridazine had no efficacy on global clinical evaluation scales. Thioridazine was inferior to chlormethiazole for behavioral symptoms. Thioridazine was no better than etoperidone, loxapine or zuclopenthixol for behavioral symptoms
[Ballard *et al*. 2006]	To study efficacy of atypical antipsychotics for the treatment of aggression, agitation and psychosis in individuals with AD	10 RCTs	Atypical antipsychotics *versus* placebo. One atypical antipsychotic medication *versus* other atypical antipsychotic medication	Risperidone and olanzapine improved aggression when compared with placebo. Risperidone improved psychotic symptoms in these individuals
[Schneider *et al*. 2006]	To study efficacy of atypical antipsychotics in individuals with dementia	15 RCTs	Atypical antipsychotics *versus* placebo. One atypical antipsychotic medication *versus* other atypical antipsychotic medication(s)	Efficacy noted for aripiprazole and risperidone but not for olanzapine. Smaller effects noted for less severe dementia, outpatients and individuals with psychotic symptoms
[Yury and Fisher, 2007]	To study effectiveness of atypical antipsychotics for behavioral problems in individuals with dementia	7 RCTs	Atypical antipsychotics *versus* placebo	Overall mean effect size from the 7 placebo-controlled studies for primary measures was 0.45 for atypical antipsychotics and 0.32 for placebo. For all measures of behavioral problems, the mean effect size was 0.43 for the atypical antipsychotic group when compared with 0.26 for the placebo group
[Katz *et al*. 2007]	To study efficacy of risperidone for psychosis of AD and mixed dementia	4 RCTs	Risperidone *versus* placebo	Risperidone improved scores on the (BEHAVE-AD) Psychosis subscale compared with placebo (effect size 0.87 *versus* 0.57) with an estimated effect size between groups at endpoint of 0.15. On the CGI scale the estimated effect size at endpoint was 0.17 between the risperidone and placebo treated groups Individuals with more severe symptoms showed better response to risperidone when compared with placebo (effect size 1.14 *versus* 0.61) with an estimated effect size difference at endpoint of 0.29

(Continued)

Table 1. (Continued)

Study	Objectives	Details of the study	Comparators	Outcomes
[Cheug and Stapleberg, 2011]	To study efficacy of quetiapine for BPSD	5 RCTs	Quetiapine *versus* placebo	Mean difference of –3.05 and –0.31 respectively was noted on the NPI total score and the CGI-C score when quetiapine group was compared with placebo group
[Maher *et al*. 2011]	To study the efficacy and safety of atypical antipsychotic medications for use in conditions lacking approval for labeling and marketing by the US Food and Drug Administration	18 RCTs in individuals with dementia	Atypical antipsychotics *versus* placebo	For aripiprazole, olanzapine and risperidone the effect size for treating behavioral symptoms ranged from 0.12–0.20 and for quetiapine it was 0.11. For the treatment of psychosis, the effect sizes were 0.20 for risperidone, 0.20 for aripiprazole, 0.05 for olanzapine and –0.03 for quetiapine. For the treatment of agitation, aripiprazole, olanzapine and risperidone had effect sizes between 0.19 and 0.31 whereas the effect size for quetiapine was 0.05
[Ma *et al*. 2014]	To study the efficacy of atypical antipsychotics for BPSD	16 RCTs	Atypical antipsychotics *versus* placebo	Atypical antipsychotics showed efficacy on the BPRS (WMD), [–1.58], CMAI (–1.84), NPI (–2.81), CGI-C (–0.32) and the CGI-S (–0.19) when compared with placebo
[Wang *et al*. 2015]	To study the efficacy of pharmacological treatments for neuropsychiatric symptoms of AD	6 RCTs	Atypical antipsychotics *versus* placebo	Atypical antipsychotics improve NPI total score [(SMD) –0.21] when compared with placebo. Olanzapine improved behavioral symptoms in AD patients (SMD –0.18) when compared with placebo. Aripiprazole produced improvements on the NPI scale (SMD –0.20) when compared with placebo
[Tan *et al*. 2015]	To study the efficacy of atypical antipsychotics in individuals with dementia	23 RCTs	Atypical antipsychotics *versus* placebo	The WMD in change scores for the NPI total score was only significant for aripiprazole (–4.4) when compared with placebo. The WMD change scores for the BEHAVE-AD was only significant for risperidone (–1.48)
[Stinton *et al*. 2015]	To study the efficacy of pharmacological treatment strategies for individuals with LBD	No meta-analysis conducted for antipsychotics but 1 RCT for olanzapine and 1 RCT for quetiapine was included in the manuscript	Antipsychotics *versus* placebo antipsychotics *versus* any treatment	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) compared with placebo. Quetiapine was no better than placebo for psychiatric symptoms

AD, Alzheimer's disease; BPRS, Brief Psychiatric Rating Scale; BPSD, behavioral and psychological symptoms of dementia; CGI-C, Clinical Global Impression of Change; CGI-S, Clinical Global Impression of Severity; CMAI, Cohen-Mansfield Agitation Inventory; LBD, Lewy Body Dementia; NPI, Neuropsychiatric Inventory; RCT, randomized controlled trials; SMD, standardized mean difference; WMD, weighted mean difference.

Table 2. Adverse effects from antipsychotics.

Study	Outcomes
[Kirchner *et al*. 2001]	No deaths were reported in any of the studies
[Schneider *et al*. 2005]	118 (3.5%) deaths in drug treated group *versus* 40 deaths (2.3%) in placebo groups, OR 1.54 and RD 0.01. No differential risk for individual drugs, severity of dementia, sample selection or by the diagnosis
[Ballard *et al*. 2006]	Somnolence, UTI, falls, EPSs, pain, peripheral edema, fever, gait abnormality, urinary incontinence and asthenia greater in the risperidone group *versus* placebo group Adverse effects and dropouts greater in the risperidone 2 mg dosing *versus* 1 mg dosing CVAEs more in the risperidone group *versus* placebo group, OR 3.64 Dropouts due to adverse effects greater in the olanzapine group *versus* placebo group. Abnormal gait, somnolence, fever and urinary incontinence greater in the olanzapine group *versus* placebo group. Somnolence greater in the aripiprazole group compared with placebo group. Quetiapine worsened cognition compared with placebo
[Schneider *et al*. 2006]	Somnolence greater in the drug treated group *versus* placebo group, OR 2.84. Somnolence greater for olanzapine group *versus* aripiprazole group when compared with placebo group, RD 0.16 *versus* 0.06. Risk for EPSs greater in the drug treated group *versus* placebo group, OR 1.51. Highest risk for EPSs in the risperidone group *versus* placebo group, OR 1.8 and RD 0.06. Abnormal gait more often in the risperidone and olanzapine groups *versus* placebo group, OR 3.42. Edema greater in the risperidone and olanzapine groups *versus* placebo group, OR 1.99. UTIs and urinary incontinence more common among the drug treated group *versus* placebo group, OR 1.51. CVAEs more common in the drug treated group *versus* placebo group, OR 2.13. CVAEs significantly higher in the risperidone group *versus* placebo group, OR 3.43.
[Katz *et al*. 2007]	Somnolence (18% *versus* 8%) risperidone *versus* placebo group. EPSs (12% *versus* 6%) risperidone *versus* placebo group. CVAEs (1.6% *versus* 0.8%) risperidone *versus* placebo group. Deaths within 30 days of last dose (3.1% *versus* 1.8%) risperidone *versus* placebo group, not statistically significant. No association between all-cause mortality and the severity of behavioral problems at baseline.
[Maher *et al*. 2011]	Cardiovascular effects were more common among users of olanzapine and risperidone, OR 2.30 and 2.10. Cerebrovascular accident was more common among individuals treated with risperidone, pooled OR 3.12. Increased appetite and weight gain were more common among individuals treated with olanzapine and risperidone, pooled OR 4.70 and 3.40 and NNH of 25. Olanzapine showed significantly anticholinergic effects, OR 3.30 and NNH of 6. Olanzapine, quetiapine, and risperidone were associated with sedation and fatigue with an OR 4.60, 5.20 and 2.30. Olanzapine and risperidone were associated with an increase in extrapyramidal symptoms, OR 15.20 and 3.00, NNH of 10 and 20. Olanzapine, quetiapine and risperidone were associated with an increase in urinary tract symptoms, OR 9.5, 2.4 and 1.6 respectively and NNH ranging from 16 to 36. 6 head-to-head trials showed that olanzapine use resulted in more neurological symptom such as confusion, dizziness, headaches etc. when compared with risperidone, OR 1.54
[Ma *et al*. 2014]	EPSs (15.2% *versus* 8.6%) drug *versus* placebo group, OR 1.74 with risk for EPSs higher in olanzapine and risperidone groups. Somnolence (17.0% *versus* 7.2%) drug *versus* placebo group, OR 2.95 with risk for somnolence greater in the aripiprazole, olanzapine, quetiapine and risperidone groups. CVAEs (2.1% *versus* 0.9%) drug *versus* placebo group, OR 2.50. Gait abnormality (6.9% *versus* 1.7%) drug *versus* placebo group, risk for gait abnormality greater in the olanzapine and risperidone groups. Deaths within 30 days of drug discontinuation (3.6% *versus* 2.3%) drug *versus* placebo group, OR 1.5, subgroup meta-analyses did not identify greater risk of death in aripiprazole, olanzapine, quetiapine or risperidone groups. Edema (9.3% *versus* 5.2%, OR 1.8) drug *versus* placebo group Urinary tract infection (14.9% *versus* 10.9%, OR 1.35), drug *versus* placebo group. Falls (15.2% *versus* 18.8%, OR 0.89) drug *versus* placebo group

(Continued)

Table 2. (Continued)

Study	Outcomes
[Wang *et al*. 2015]	Dropout due to adverse events greater in the atypical antipsychotic group compared with placebo group, RR 2.24. Adverse effects greater in the atypical antipsychotic group compared with placebo group, RR 1.17
[Tan *et al*. 2015]	Somnolence greater in the atypical antipsychotic group compared with placebo group, OR 3.7. Somnolence greater in aripiprazole (OR, 3.51), olanzapine (OR, 3.61) and quetiapine (OR, 5.88) groups when compared with placebo groups. Abnormal gait more frequent in atypical antipsychotic group compared with placebo group, OR 1.84, highest in the olanzapine group, OR 3.84. Edema more common in quetiapine group compared with placebo group, OR 1.51. UTI more common in the atypical antipsychotic group compared with placebo group, OR of 1.91, risk highest in the olanzapine (6.93) and risperidone (2.28) groups. Strokes more common in the drug-treated group compared with placebo group, OR 2.62, risk highest in risperidone group, OR 4.53. Deaths more in the atypical antipsychotic group compared with placebo group, OR 1.06, no increased risk of death noted with any individual drug.
[Hulshof *et al*. 2015]	Pooled risk difference for death (0.1%), conventional antipsychotic group *versus* placebo group, RR 1.07. Pooled risk difference for death (0.4%), haloperidol group *versus* placebo group, RR 1.25, not statistically significant. Point estimate higher in the dementia trials (0.5%) *versus* delirium-prevention trials (–0.4%)

CVAEs, cerebrovascular adverse events; EPS, extrapyramidal symptoms; NNH, number needed to harm; OR, odds ratio; RD, risk difference; RR, risk ratio; UTI, urinary tract infection.

Table 3. Withdrawal of antipsychotics.

Name of the study	Outcomes
[Declercq *et al*. 2013]	No overall difference between the groups on the primary outcomes. In one trial, the time to relapse was shorter in the discontinuation group when compared with the continuation group, $p = 0.04$. In one trial, discontinuation of the medication led to an increase in the NPI-core score $\geqslant$ 30% in the discontinuation group, HR 1.94. In one trial, individuals with milder behavioral symptoms at baseline were less agitated in the discontinuation 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*. 2014]	No statistically significant difference between the groups on the behavioral severity score change from baseline, SMD of 0.19. There was a higher proportion of individuals whose behavioral symptoms worsened in the drug discontinuation group when compared with the drug continuation group, RR 1.78 The drug discontinuation group had higher rates of early study termination when compared with the drug continuation group, RR 1.11. The drug discontinuation group had lower mortality during follow up when compared with the drug continuation group, RR 0.83

HR, Hazard Ratio; NPI, Neuropsychiatric Inventory; RR, risk ratio; SMD, standardized mean difference.

[standardized mean difference (SMD), 0.19]. However, the discontinuation group had a higher proportion of individuals whose behavioral symptoms worsened, (RR 1.78) and this outcome was statistically significant. In addition, the discontinuation group had higher rates of early study termination (RR 1.11) when compared with the drug continuation group. The discontinuation group had lower mortality during follow up when compared with the continuation group (RR 0.83). The last two outcomes were not statistically significant.

A summary of these two meta-analyses indicate that discontinuation of antipsychotic medication may not necessarily worsen behavioral symptoms

in all individuals with dementia. However, individuals with greater baseline behavioral symptoms may have a worsening of symptoms when the antipsychotic medication is discontinued. Mortality rates were noted to be lower in the discontinuation group from one meta-analysis. See Table 3.

Discussion

This systematic review indicates that there are a fair number of meta-analyses that have evaluated the use of antipsychotics in individuals with dementia. The majority (12 of 16, 75%) of the meta-analyses evaluated the efficacy of these medications in individuals with dementia. Of these 12 studies, 8 also assessed adverse effects of these medications. There were two additional meta-analyses that assessed adverse effects (deaths) with the use of these medications in individuals with dementia. There were two meta-analyses that evaluated the discontinuation of the antipsychotic medications in these individuals.

Efficacy data indicate that 83% (10 of 12) of the meta-analyses evaluated atypical antipsychotic medications in individuals with dementia. Risperidone, olanzapine and aripiprazole show modest efficacy in treating psychosis, aggression and agitation when used in individuals with dementia including AD. Quetiapine was found to have limited efficacy in treating these types of symptoms in individuals with dementia. More severe symptoms appear to be particularly responsive to the atypical antipsychotics. Smaller effects were noted for less severe dementia and individuals receiving outpatient treatment. The two meta-analyses that assessed the use of typical antipsychotics found that these medications have modest efficacy when used in individuals with dementia with no superiority noted for any particular medication in this drug-class. We did not identify any meta-analysis that studied the use of antipsychotic medications among individuals with LBD or vascular dementia (VD).

Data from 10 meta-analyses indicate that the use of antipsychotics among individuals with dementia results in greater number of adverse effects when compared with placebo-treated individuals including CVAEs and deaths. The risk of CVAEs was most prominent among the risperidone-treated group. The risk of death was not associated with any particular drug but became significant when the data from the different studies were pooled together. The risk of death was not associated with the severity of dementia, the severity of behavioral symptoms, by the sample selection or by the diagnosis. Sedation, abnormal gait and EPSs appear to be most prominent with the use of risperidone and olanzapine.

Data from two meta-analyses indicate that discontinuation of antipsychotic medication results in worsening of symptoms among individuals with greater baseline behavioral symptoms. Data from one meta-analysis indicate that mortality rates are lower in the drug-discontinuation group when compared with the group that continued on the drug.

This review has several weaknesses. We only used data from meta-analyses published in the English language or with an official English language translation. Additionally, there was significant heterogeneity between the various meta-analyses based on inclusion and exclusion criteria, the medications and dosages used, the rating scales used and the duration of included studies. We did not use any statistical method to correct for this heterogeneity. Furthermore, there were no meta-analyses that evaluated the use of antipsychotics in individuals with less common types of dementia including LBD and VD.

The strengths of this review include a comprehensive search of five large databases and adherence to the PRISMA guidelines for systematic reviews. In addition, this review is the first attempt to collate data from all the published meta-analyses on the use of antipsychotics in individuals with dementia.

This systematic review did not find any meta-analysis that evaluated the difference in rates of mortality between first and second generation antipsychotics (FGAs and SGAs) when used in older adults. However, one systematic review and meta-synthesis that included data from 20 studies found that among older adults the use of FGAs increased the risk for stroke, ventricular arrhythmia, myocardial infarction and hip fracture when compared with SGAs [Jackson *et al.* 2014]. Antipsychotic-induced stroke accounted for 6.7% of this difference, hip fracture for 6.5%, myocardial infarction for 3.5%, and ventricular arrhythmia for 0.9%. When combined, these medical events explained about one-sixth (17%) of the mortality differences between FGAs and SGAs but the investigators opine that this difference could be as large as 42%. These data are comparable to the data obtained by Kales and colleagues and Maust and colleagues in their database review

of US Department of Veterans Affairs that included individuals with dementia [Kales *et al.* 2012; Maust *et al.* 2015]. The investigators found that the use of haloperidol (NNH, 26) resulted in the highest mortality rates when compared with risperidone (NNH, 27), olanzapine (NNH, 40) and quetiapine (NNH, 50) when used in older individuals with dementia.

The data on worse outcomes including severe adverse effects among individuals with dementia who are prescribed antipsychotics should not be entirely attributed to medication effects. A recent study that evaluated the use of typical and atypical antipsychotics on the time to nursing home admission and the time to death in a group of individuals with mild-to-moderate probable AD found that after adjustment for psychiatric symptoms the association between time to admission to a nursing home or to death were no longer significant [Lopez *et al.* 2013]. Psychosis was strongly associated with nursing home admission and time to death.

Multiple high quality studies have indicated that nonpharmacological treatments show benefit when used in individuals with BPSD [Livingston *et al.* 2005; Livingston et al. 2014; Cooper *et al.* 2012; Brodaty and Arasaratnam, 2012]. These interventions are recommended as first-line management strategies for individuals with BPSD [Kales *et al.* 2014; Kales, 2015]. Available data also indicate some efficacy for other classes of medications for the treatment of certain types of behavioral symptoms in dementia [Panza *et al.* 2015]. Acetylcholinesterase inhibitors may be beneficial for treating depression, dysphoria, apathy and anxiety in individuals with dementia. Memantine has shown modest efficacy in improving behavioral symptoms among individuals with dementia when compared with placebo [Maidment *et al.* 2008]. Sertraline and citalopram have been shown to reduce agitation among individuals with dementia when compared with placebo [Seitz *et al.* 2011]. Other medications that have shown potential in the treatment of behavioral symptoms in dementia include dextromethorphan/quinidine, cannabinoids, scyllo-inositol, brexpiprazole and prazosin [Antonsdottir *et al.* 2015]. However, none of these agents appear to have sufficient evidence in treating agitation in individuals with dementia and to be recommended for routine clinical practice.

A recent American Psychiatric Association (APA) practice guideline on the use of antipsychotics to treat agitation or psychosis in individuals with dementia recommends that before nonemergency treatment with an antipsychotic is initiated in individuals with dementia, the potential risks and benefits from these medications must be assessed by the clinician and discussed with the patient, their family and or the surrogate decision maker [Reus *et al.* 2016]. The APA guideline recommends that if the risks and benefits assessment favors the use of an antipsychotic for behavioral/psychological symptoms in individuals with dementia, the treatment should be initiated at a low dose and to be titrated up to the minimum effective dose as tolerated. The guideline also recommends that if the individual with dementia experiences a clinically significant adverse effect due to the antipsychotic medication, the potential risks and benefits of the antipsychotic medication should be reviewed by the clinician to determine if tapering and discontinuing of the medication is indicated. In addition, the APA guideline recommends that in individuals with dementia and agitation or psychosis if there is no clinically significant response after a 4-week trial of an adequate dose of an antipsychotic then the medication should be tapered and discontinued. It is also recommended that among individuals who show a positive response to treatment, the decision to possibly taper the antipsychotic medication should be discussed with the patient, the patient's family and or the surrogate decision maker. Among the individuals who show an adequate response to treatment with an antipsychotic, an attempt to taper and withdraw the medication should be made within 4 months of initiation of treatment unless the individual experiences a recurrence of symptoms with previous attempts at tapering the antipsychotic medication. Additionally, while the antipsychotic medication is being tapered, assessment of symptoms should occur at least every month during the taper and for at least 4 months after the medication is discontinued to identify signs of recurrence and if there is a recurrence of symptoms, the reevaluation of the benefits and risks of antipsychotic treatment. The APA also recommends that in the absence of delirium, if nonemergency antipsychotic medication treatment is indicated then haloperidol should not be used as a first-line agent. Furthermore, the APA recommended that in individuals with dementia and agitation or psychosis a long-acting injectable antipsychotic medication should not be utilized unless it is otherwise indicated for a co-occurring chronic psychotic illness.

Based on the available data from this review it would be prudent to state that antipsychotics should be used with caution in individuals with dementia given their significant adverse effect profile and modest efficacy data. These medications should be reserved for treating psychosis, aggression and agitation that are severe and are unresponsive to nonpharmacological strategies. Among the atypical antipsychotics, risperidone, olanzapine and aripiprazole appear to have stronger data when compared with quetiapine for treating the above mentioned symptoms. The data on the dosages of these medications to be used and the duration of treatment are still unclear from these meta-analyses. However, the recent APA guideline identifies 4 months of effective treatment after which a possible taper of the medication should be evaluated. There are no meta-analyses of newer atypical antipsychotics such as ziprasidone, paliperidone, iloperidone, asenapine, lurasidone in individuals with dementia. Among typical antipsychotic medications the data did not indicate superiority for any particular medication.

Conclusion

Available data indicate that antipsychotic medications have modest efficacy when used in individuals with dementia. These medications are associated with significant adverse effects including CVAEs and death when used in this population. Among the atypical drugs, risperidone, olanzapine and aripiprazole appear to have stronger data in treating psychosis, aggression and agitation when compared with quetiapine. There are no controlled data on the use of the newer atypical antipsychotic medications in individuals with dementia. Typical antipsychotics also have modest efficacy when used in individuals with dementia with no superiority noted for any particular drug. These medications should be used in individuals with dementia only when nonpharmacological management has failed to provide benefit. Antipsychotics appear to be particularly effective for more severe symptoms. Controlled data for the use of these medications in individuals with LBD and VD are currently unavailable.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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