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REVIEW

Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review

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ABSTRACT

Background: Medications are frequently prescribed for neuropsychiatric symptoms (NPS) associated with dementia, although information on the efficacy and safety of medications for NPS specifically in long-term care (LTC) settings is limited. The objective of this study was to provide a current review of the efficacy and safety of pharmacological treatments for NPS in LTC.

Methods: We searched MEDLINE, EMBASE, PsychINFO, and the Cochrane Library for randomized controlled trials comparing medications with either placebo or other interventions in LTC. Study quality was described using the Cochrane collaboration risk of bias tool. The efficacy of medications was evaluated using NPS symptom rating scales. Safety was evaluated through rates of trial withdrawals, trial withdrawals due to adverse events, and mortality.

Results: A total of 29 studies met inclusion criteria. The most common medications evaluated in studies were atypical antipsychotics (N = 15), typical antipsychotics (N = 7), anticonvulsants (N = 4), and cholinesterase inhibitors (N = 3). Statistically significant improvements in NPS were noted in some studies evaluating risperidone, olanzapine, and single studies of aripiprazole, carbamazepine, estrogen, cyproterone, propranolol, and prazosin. Study quality was difficult to rate in many cases due to incomplete reporting of details. Some studies reported higher rates of trial withdrawals, adverse events, and mortality associated with medications.

Conclusions: We conclude that there is limited evidence to support the use of some atypical antipsychotics and other medications for NPS in LTC populations. However, the generally modest efficacy and risks of adverse events highlight the need for the development of safe and effective pharmacological and non-pharmacological interventions for this population.

Key words: dementia, Alzheimer, long-term care, pharmacological, medications

Introduction

Neuropsychiatric symptoms (NPS) associated with dementia are common in long-term care (LTC) settings with approximately 80% of individuals with dementia in LTC exhibiting NPS at any time (Zuidema *et al.*, 2007; Seitz *et al.*, 2010). Guidelines (Canadian Coalition for Seniors' Mental Health, 2006; Herrmann *et al.*, 2007) and previous reviews (Sink *et al.*, 2005) have emphasized the importance of comprehensive assessment to rule out pain (Cohen-Mansfield and Mintzer, 2005; Sink *et al.*, 2005), delirium (Sink *et al.*, 2005), and environmental or interpersonal factors (Sink *et al.*, 2005) which may precipitate behaviors. Non-pharmacological interventions are usually recommended as first-line treatments for NPS. Unfortunately, knowledge of psychosocial interventions in LTC is low (Cohen-Mansfield and Jensen, 2008), access to services for these

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interventions is limited (Conn, 1992; Burns *et al.*, 1993; Meeks, 1996; Reichman *et al.*, 1998; Seitz *et al.*, 2011), their effectiveness may be modest (Seitz *et al.*, 2012), and patients may not cooperate with these interventions (Cohen-Mansfield *et al.*, 2012). Therefore, there remains a potential role for medications in managing NPS in LTC.

Psychotropic medications are frequently prescribed in LTC (Gruber-Baldini *et al.*, 2004; Pitkala *et al.*, 2004; Selbaek *et al.*, 2007). The estimated prevalence of the use of these medications among LTC residents with dementia is 25%–40% for antipsychotics (Pitkala *et al.*, 2004; Rochon *et al.*, 2007; Selbaek *et al.*, 2008; Nijk *et al.*, 2009; Larrayadieu *et al.*, 2011; Snowdon *et al.*, 2011), 25%–30% for antidepressants (Pitkala *et al.*, 2004; Nijk *et al.*, 2009; Snowdon *et al.*, 2011), cognitive enhancers in 25%–30% (Seitz *et al.*, 2009), and benzodiazepines in 15%–30% (Pitkala *et al.*, 2004; Selbaek *et al.*, 2008; Nijk *et al.*, 2009; Snowdon *et al.*, 2011). Systematic reviews and meta-analyses have indicated that some typical antipsychotics (Schneider *et al.*, 1990; Lanctot *et al.*, 1998), atypical antipsychotics (Ballard and Waite, 2006; Schneider *et al.*, 2006b), and antidepressants (Seitz *et al.*, 2011) may have benefits in treating certain NPS, although the magnitude of benefit may be limited and potentially outweighed by adverse events. Atypical antipsychotics, the most extensively studied and utilized medications for NPS, are also associated with serious adverse events such as death (Schneider *et al.*, 2005; Wang *et al.*, 2005; Gill *et al.*, 2007) or stroke (Herrmann *et al.*, 2004, Gill *et al.*, 2005), as well as falls (Hien Le *et al.*, 2005), sedation (Schneider *et al.*, 2006a), and cognitive decline (Schneider *et al.*, 2006a; Vigen *et al.*, 2011). Although there has been a decline in the use of antipsychotics with dementia recently, these medications continue to be used frequently (Kales *et al.*, 2011). The safety of other medications used to treat NPS in LTC has also been questioned (Huybrechts *et al.*, 2011).

Although there are previous reviews on the use of psychotropic medications for the management of NPS (Schneider *et al.*, 1990; 2006a; Borson and Raskind, 1997; Lanctot *et al.*, 1998; Sutor *et al.*, 2001; Kindermann *et al.*, 2002; Snowden *et al.*, 2003; Alexopoulos *et al.*, 2005; Bharani and Snowden, 2005; Sink *et al.*, 2005; Ballard and Howard, 2006; Kozman *et al.*, 2006; Herrmann and Lanctot, 2007; Konavalov *et al.*, 2007; Saddichha and Pandey, 2008; Ballard *et al.*, 2009a; 2009b; Conn and Seitz, 2010; Gauthier *et al.*, 2010), few have focused exclusively on studies conducted in LTC settings (Snowden *et al.*, 2003; Bharani and Snowden, 2005). Residents of LTC facilities with dementia may be particularly susceptible to adverse events associated with psychotropics when compared with community or hospital-based populations. Controlled trials and observational studies of older adults with dementia have indicated that LTC residents have more advanced age, more severe cognitive impairment, higher rates of comorbidity (Schneider *et al.*, 2006a; Gill *et al.*, 2007; Rochon, 2008), and receive lower quality of routine and preventative care (Fahey *et al.*, 2003) than outpatient or hospital populations. In addition, higher rates of mortality have been observed for LTC residents with dementia newly started on antipsychotics when compared with community-dwelling populations (Gill *et al.*, 2007; Rochon *et al.*, 2008). For these reasons, LTC residents may be particularly susceptible to mortality and other adverse events associated with psychotropic use which may have been underestimated in previous reviews which included both LTC and other populations within the same review. Also, some reviews have included both randomized and non-randomized studies (Bharani and Snowden, 2005). Importantly, only a few previous reviews have assessed the quality of studies (Schneider *et al.*, 2006a). Therefore, the objectives of this study were to provide a systematic review of randomized controlled trials (RCTs) for pharmacological treatments of NPS conducted specifically in LTC settings and evaluate the efficacy, and safety of treatments as well as the quality of studies.

Methods

Search strategy

Standard guidelines for conducting systematic reviews were used to guide the review process (Moher *et al.*, 2009). We searched the electronic databases Medline, EMBASE, and PsychINFO (January 1980–February 2011), and the Cochrane Library using free text and medical subject headings to identify relevant articles (see Box 1, available as supplementary material attached to the electronic version of this paper at www.journals.cambridge.org/jid_IPG). Google Scholar was also searched for additional articles using key words and citation lists. Hand-searches of reference lists of retrieved articles, previous reviews, and guidelines (Canadian Coalition for Seniors' Mental Health, 2006) were used to supplement the electronic database search.

Study selection

The titles and abstracts of citations from electronic databases were independently reviewed by two study authors. Full-text articles were then reviewed

for inclusion criteria. Randomized, parallel-group, controlled trials comparing any pharmacological intervention to placebo, another medication, or non-pharmacological interventions were included. We only included studies where NPS was the primary study outcome. We included studies reporting overall levels of NPS using composite measures of NPS on commonly utilized rating scales (e.g. Neuropsychiatric Inventory) or on specific measures of agitation, psychosis, or aggression. Studies that only evaluated depression or apathy in LTC residents with dementia were excluded. We excluded uncontrolled pre–post studies and crossover designs given the high-placebo response rate observed in some studies (Schneider *et al.*, 2006a). Study populations had to be exclusively from LTC or where LTC residents formed the majority (>50%) of participants. All English-language publications that provided sufficient detail for data extraction were included. Full-text articles were reviewed for inclusion criteria by two study authors with discrepancies resolved through discussion.

Data extraction

We extracted the following information from studies: dose of medication, number of participants, gender distribution, number and location of LTC facilities, dementia severity, method for diagnosing dementia, and study duration. We categorized studies according to pharmacological class. Baseline severity of NPS and change in NPS as reported on NPS rating scales (e.g. Cohen-Mansfield Agitation Inventory) were recorded. For dichotomous outcomes (e.g. number of individuals with a treatment response), the number of individuals with the outcome was recorded. For studies that did not report a primary outcome, we selected the change in NPS symptom rating scale total score as measured at study endpoint as the primary measure of efficacy. Safety and tolerability outcomes included: rates of trial withdrawals due to any cause, trial withdrawals due to adverse events, and mortality. All data were extracted in duplicate by two study authors using a standard data extraction form and discrepancies were resolved through further discussion.

Study quality

The Cochrane collaboration risk of bias assessment tool was utilized to describe the potential risk of bias associated with various aspects of study design (Higgins and Green, 2008). This tool evaluates the following properties of studies: method of random sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias including sponsorship bias (i.e. whether the funding source could have led to a potential financial conflict of interest). Each item was rated as being potentially at low risk of bias ("Yes"), high risk of bias ("No"), or unclear. All items were rated in duplicate by two authors.

Data synthesis

Information on study characteristics, assessment of study quality, and efficacy and safety outcomes was summarized in tables. We summarized the effects of pharmacological interventions by medication class. The studies that reported on both antipsychotics and another active comparator were described in the non-antipsychotic category (e.g. studies comparing antipsychotics and cholinesterase inhibitors were described under the cholinesterase inhibitor section).

Results

Study selection

The flow of studies through the review process is summarized in Figure 1. A total of 8,342 citations were identified through searches of electronic databases and 315 full-text articles were retrieved and reviewed. From these articles, 29 studies were identified that met our inclusion criteria.

Characteristics of included studies

The 29 studies meeting inclusion criteria encompassed 19 studies of antipsychotics (Barnes *et al.*, 1982; Cantillon *et al.*, 1996; De Deyn *et al.*, 1999; 2004; Katz *et al.*, 1999; Street *et al.*, 2000; Gaber *et al.*, 2001; Brodaty *et al.*, 2003; Fontaine *et al.*, 2003; Ballard *et al.*, 2005; Mintzer *et al.*, 2006; 2007; Tariot *et al.*, 2006; Verhey *et al.*, 2006; Holmes *et al.*, 2007; Huertas *et al.*, 2007; Zhong *et al.*, 2007; Streim *et al.*, 2008; Rappaport *et al.*, 2009) (15 studies of atypical antipsychotics (De Deyn *et al.*, 1999; 2004; Katz *et al.*, 1999; Street *et al.*, 2000; Brodaty *et al.*, 2003; Fontaine *et al.*, 2003; Ballard *et al.*, 2005; Mintzer *et al.*, 2006; 2007; Tariot *et al.*, 2006; Verhey *et al.*, 2006; Holmes *et al.*, 2007; Zhong *et al.*, 2007; Streim *et al.*, 2008; Rappaport *et al.*, 2009) and seven of typical antipsychotics (Barnes *et al.*, 1982; Cantillon *et al.*, 1996; De Deyn *et al.*, 1999; Gaber *et al.*, 2001; Tariot *et al.*, 2006; Verhey *et al.*, 2006; Huertas *et al.*, 2007)), three studies of cholinesterase inhibitors (Tariot *et al.*, 2001; Ballard *et al.*, 2005; Holmes *et al.*, 2007), four studies of anticonvulsants (Tariot *et al.*, 1998; 2005; Porsteinsson *et al.*, 2001; Sommer *et al.*, 2009), one study of antidepressants

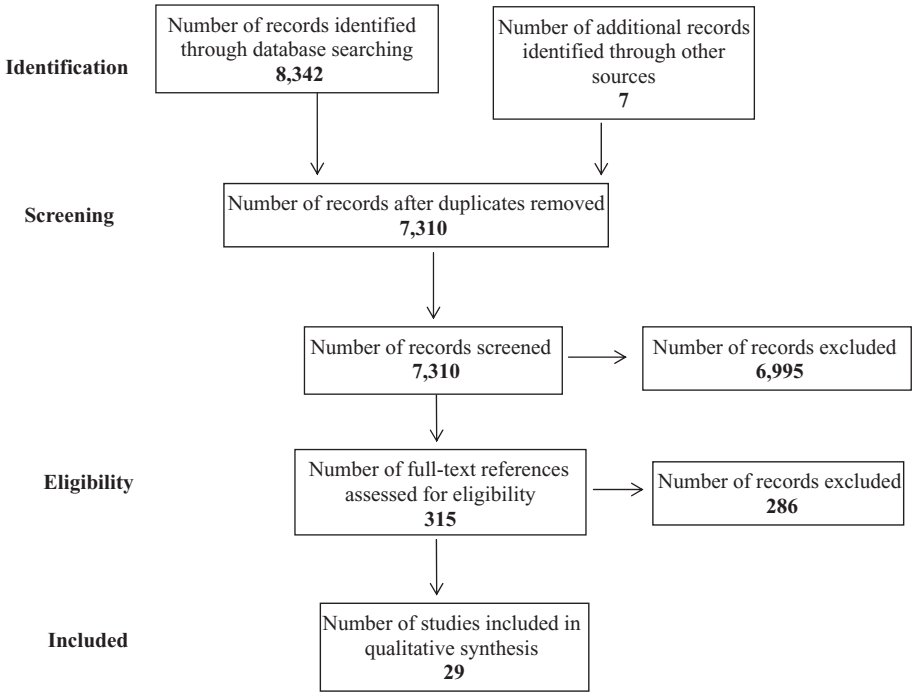

Figure 1. Flow of studies through the review process.

(Gaber *et al.*, 2001), and seven studies evaluating medications from other classes (Cantillon *et al.*, 1996; Kyomen *et al.*, 1999; Hall *et al.*, 2005; Peskind *et al.*, 2005; Huertas *et al.*, 2007; Gehrman *et al.*, 2009; Wang *et al.*, 2009) (Table 1). Of these studies, 20 were placebo-controlled (Barnes *et al.*, 1982; Tariot *et al.*, 1998; 2001; 2005; De Deyn *et al.*, 1999; 2004; Katz *et al.*, 1999; Kyomen *et al.*, 1999; Street *et al.*, 2000; Porsteinsson *et al.*, 2001; Brodaty *et al.*, 2003; Ballard *et al.*, 2005; Hall *et al.*, 2005; Peskind *et al.*, 2005; Mintzer *et al.*, 2006; 2007; Tariot *et al.*, 2006; Zhong *et al.*, 2007; Streim *et al.*, 2008; Gehrman *et al.*, 2009; Rappaport *et al.*, 2009; Sommer *et al.*, 2009; Wang *et al.*, 2009), and 11 compared two medications within the same trial (Barnes *et al.*, 1982; Cantillon *et al.*, 1996; De Deyn *et al.*, 1999; Gaber *et al.*, 2001; Fontaine *et al.*, 2003; Ballard *et al.*, 2005; Tariot *et al.*, 2006; Verhey *et al.*, 2006; Holmes *et al.*, 2007; Huertas *et al.*, 2007). All of the studies used oral formulations of medications except for one trial that utilized intramuscular aripiprazole (Rappaport *et al.*, 2009) and one study of transdermal estrogen (Hall *et al.*, 2005). A total of 4,954 individuals were included with a median study sample size of 76 (range = 14–625 participants per trial). The median age of participants in studies was 83 years and 71% were women in studies reporting the gender distribution. Most study participants had moderate to severe dementia with average Mini-Mental State Examination (MMSE) scores of between 5 and 14. The median trial duration was 56 days (range = 1–90 days). A variety of outcome measures were reported in studies including composite measures of NPS (Barnes *et al.*, 1982; Cantillon *et al.*, 1996; Tariot *et al.*, 1998; 2001; 2005; 2006; De Deyn *et al.*, 1999; 2004; Katz *et al.*, 1999; Street *et al.*, 2000; Porsteinsson *et al.*, 2001; Fontaine *et al.*, 2003; Peskind *et al.*, 2005; Gehrman *et al.*, 2009; Sommer *et al.*, 2009; Wang *et al.*, 2009), agitation (Gaber *et al.*, 2001; Ballard *et al.*, 2005; Verhey *et al.*, 2006; Holmes *et al.*, 2007; Zhong *et al.*, 2007; Rappaport *et al.*, 2009,), aggression (Kyomen *et al.*, 1999; Brodaty *et al.*, 2003; Hall *et al.*, 2005; Huertas *et al.*, 2007), or psychosis (Mintzer *et al.*, 2006; 2007; Streim *et al.*, 2008).

Efficacy of interventions on neuropsychiatric symptoms of dementia

The efficacy of pharmacological interventions for NPS is summarized in Table 1.

Antipsychotics

The 15 studies of atypical antipsychotics involved risperidone (N = 6), olanzapine (N = 4), quetiapine (N = 3), and aripiprazole (N = 3). Statistically significant results on change in NPS scores compared with placebo were noted in two studies of risperidone (Katz *et al.*, 1999; Brodaty *et al.*, 2003), two studies of olanzapine (Street *et al.*, 2000; De Deyn *et al.*, 2004), and one study of aripiprazole (Mintzer *et al.*, 2007). One study comparing risperidone and olanzapine found no

Table 1. Included studies of pharmacological interventions for long-term care residents with dementia

	INTERVENTION	NUMBER	AGE, MEAN (SD)	FEMALE GENDER, N (%)	SETTING AND DURATION	DEMENTIA DIAGNOSIS, AVERAGE MMSE SCORES	OUTCOME MEASURE	CHANGE IN NPS	PERCENTAGE OF TRIAL WITHDRAWALS/ WITHDRAWAL DUE TO ADVERSE EVENTS/ MORTALITY	COMMENT
Antipsychotics										
Barnes *et al.* (1982)	Loxapine 10.5 mg/day	19	83	–	LTC in the USA	DSM-III	BPRS total	–	43.3/–/–	All groups significantly different from baseline but no difference between groups.
	Thioridazine 62.5 mg/day	17	–	–	8 weeks	–		–	–/–/–	
	Placebo	17	–	–		–		–	–/–/–	
De Deyn *et al.* (1999)	Risperidone 0.5–4 mg/day (mean = 1.1 mg/day)	115	81	65 (56.5)	51 LTC, 8 countries	DSM-IV, 6.3–8.6	BEHAVE-AD total	−5.2	40.9/–/–	Individuals completing 12 weeks of risperidone were improved compared with placebo.
	Haloperidol 0.54 mg/day (mean = 1.2 mg/day)	115	82	62 (53.9)	12 weeks			−6.6	30/–/–	
	Placebo	114	81	67 (58.8)				−4.2	35.1/–/–	
Katz *et al.* (1999)	Risperidone 0.5 mg/day	149	83.2 (7.9)	108 (72.5)	LTC hospital in the USA	DSM-IV, 6.3–7.7	BEHAVE-AD total	−4.8	21.5/8.1/4.8	
	Risperidone 1.0 mg/day	148	83.1 (7.2)	98 (66.2)				−6.5*	30.4/16.2/8.8*	
	Risperidone 2.0 mg/day	165	82.0 (78)	108 (65.5)	12 weeks			−6.4*	41.8*/24.2*/3.6	
	Placebo	163	82.6 (7.7)	110 (67.5)				−4.2	27/12.3/3.1	
Street *et al.* (2000)	Olanzapine 5 mg	56	82.9 (6.5)	33 (58.9)	28 LTC in the USA	NINCDS–ADRDA, 6.4–7.3	NPI	−7.6*	19.6/10.7/0	NPI core consisting of agitation/ aggression, delusions, and hallucinations.
	Olanzapine 10 mg	50	83.6 (6.5)	33 (66.0)				−6.1*	28.0/8.0/0	
	Olanzapine 15 mg	53	83.0 (6.7)	31 (58.5)	6 weeks			−4.9	34.0/17.0*/0	
	Placebo	47	81.4 (6.7)	29 (61.7)				−3.7	23.4/4.3/0	

Table 1. Continued

	INTERVENTION	NUMBER	AGE, MEAN (SD)	FEMALE GENDER, N (%)	SETTING AND DURATION	DEMENTIA DIAGNOSIS, AVERAGE MMSE SCORES	OUTCOME MEASURE	CHANGE IN NPS	PERCENTAGE OF TRIAL WITHDRAWALS/ WITHDRAWAL DUE TO ADVERSE EVENTS/ MORTALITY	COMMENT
Brodaty *et al.* (2003)	Risperidone 0.5–2 mg/day (mean = 0.95 mg/day)	153	83.2 (0.5)	109 (71)	14 LTC sites in Australia and New Zealand	DSM-IV, AD, vascular, mixed	CMAI–total aggression	−7.5*	26.9/13.2/3.6	BEHAVE-AD score also improved with risperidone.
	Placebo	156	82.7 (0.6)	113 (72)		5.1–5.8		−3.1	32.9/8.2/2.4	
Fontaine *et al.* (2003)	Olanzapine 2.5–10 mg (mean 6.6 mg/day)	20	83.3 (5.7)	12 (60)	LTC in the USA	DSM-IV, dementia	NPI	−15	20/20/0	Both groups improved, no difference between groups.
	Risperidone 0.5–2 mg (mean 1.5 mg/day)	19	83.0 (9.4)	14 (74)	12 weeks	7.2–9.3		−23.6	32.9/8.2/2.4	
De Deyn *et al.* (2004)	Olanzapine 1 mg/day	128	76.6 (10.4)	489 (75)	LTC or continuing-care hospitals in Europe, Australia, Israel, Lebanon, South Africa 10 weeks	NINCDS–ADRDA, DSM-IV-TR, AD 13.7 (5.1)	NPI–NH total	−14.8		
	Olanzapine 2.5 mg/day	134	–	–				−15.7		
	Olanzapine 5 mg/day	123	–	–				−16.3		
	Olanzapine 7.5 mg/day	128	–	–				−17.7*		
	Placebo							−13.7		
Mintzer *et al.* (2006)	Risperidone 0.5–1.5 mg daily (mean = 1.0 mg/day)	202	83.4 (7.0)	152 (75.2)	44 LTC 8 weeks	AD 13.1–13.2	BEHAVE-AD Psychosis	−2.9	25.5/10.6/0.8	
	Placebo	214	83.3 (7.43)	163 (76.2)				−2.3	24.8/10.1/0	
Tariot *et al.* (2006)	Quetiapine 100 mg/day	91	81.9 (6.9)	66 (73)	47 LTC in the USA 10 weeks	DSM-IV, NINCDS–ADRDA, AD, vascular, alcohol 12.4–13.2	BPRS total	−9.1	31.9/11.0/0	
	Haloperidol 2.5 mg/day	94	83.5 (6.1)	63 (67)				−7.1	41.5/18.1/1.1	
	Placebo	99	83.9 (6.7)	79 (80)				−6.7	36.4/13.1/0	

Verhey *et al.* (2006)	Olanzapine 2.5–7.5 mg/day (mean = 4.7 mg)	30	82.4 (5.5)	17 (56.7)	4 LTC and 2 outpatient sites in the Netherlands 5 weeks	DSM-IV, dementia 10.0–10.9	CMAI total Score	−10.1	15.5/–/–	Both groups improved, no difference between groups.
	Haloperidol 1–3 mg/day (mean = 1.7 mg/day)	28	83.3 (8.1)	16 (57.1)				−16.6	–/–/–	
Mintzer *et al.* (2007)	Aripiprazole 2 mg/day	118	83.0	81	81 LTC residential-assisted living facilities in the USA, Australia, Canada, South Africa, and Argentina 10 weeks	DSM-IV, AD 12.4	NPI–NH Psychosis	–	34.7/7.6/3.4	
	Aripiprazole 5 mg/day	122	82.4	76				–	40.2/18/2.5	
	Aripiprazole 10 mg/day	126	82.3	76				−6.9	45.2/24.6*/6.3	
	Placebo	121	82.2	82				−5.1	46.3/13.2/2.5	
Zhong *et al.* (2007)	Quetiapine 200 mg/day	117	83.5 (8.0)	92 (78.6)	53 LTC and assisted living in the USA 10 weeks	DSM-IV, NINCDS-ADRDA, possible or probable AD, vascular 4.8–5.6	PANSS-EC	−4.9	34.7/8.1/7.3	
	Quetiapine 100 mg/day	124	83.0 (7.2)	90 (72.6)				−5.7	36.8/14.5/5.1	
	Placebo	92	83.2 (7.2)	65 (70.7)				−3.9	34.8/9.8/3.3	
Streim *et al.* (2008)	Aripiprazole 2–15 mg/day (mean = 9 mg/day)	131	83.0	74 (56.5)	NH or residential assisted-living facilities in the USA 10 weeks	DSM-IV, AD 13.9 (8.6)	NPI–NH Psychosis	−4.5	30.4*/12.8/2.4	CMAI and NPI total score decreased significantly in treatment compared with placebo.
	Placebo	125	83.0	78 (62.4)		13.3 (8.9)		−4.6	49.0/8.4/2.3	
Rappaport (2009)	Aripiprazole 2.5–5 mg IM	12	80.2 (5.4)	8 (67)	16 LTC in the USA	DSM-IV, AD, vascular, mixed	PANSS-EC	−4	0/0/0	

Table 1. Continued

	INTERVENTION	NUMBER	AGE, MEAN (SD)	FEMALE GENDER, N (%)	SETTING AND DURATION	DEMENTIA DIAGNOSIS, AVERAGE MMSE SCORES	OUTCOME MEASURE	CHANGE IN NPS	PERCENTAGE OF TRIAL WITHDRAWALS/ WITHDRAWAL DUE TO ADVERSE EVENTS/ MORTALITY	COMMENT
Rappaport *et al.* (2009)	Aripiprazole 5–10 mg IM	78	80.0 (10.3)	50 (64)	24 hours			−7	0/1.3/0	
	Aripiprazole 10–15 mg IM	13	79.9 (6.0)	9 (69)				−8	7.7/0/7.7	
	Placebo	26	79.5 (7.8)	16 (62)				−5	3.8/0/0	
Cholinesterase inhibitor										
Tariot *et al.* (2001)	Donepezil 10 mg	103	85.4	85 (83)	27 LTC in the USA	NINDS-ADRDA	NPI–NH	−2.3	18/11/3	
	Placebo	105	85.9	86 (82)	24 weeks	14.4		−4.9	26/18/6.6	
Ballard *et al.* (2005)	Rivastigmine 6–12 mg/day,	31	84.3 (7.8)	23 (74)	LTC in the UK	AD, dementia SIB:	CMAI	−5.1	41.9*/16.1/6.5	All treatments showed
	Quetiapine 50–100 mg	31	84.2 (8.6)	27 (87)	6 weeks	58.8–69.0		−4.0	32.2*/6.5/6.5	reduction in agitation score
	Placebo	31	83.0 (6.8)	24 (77)				−6.2	3.2/0/0	after 6 weeks with no difference between groups.
Holmes *et al.* (2007)	Rivastigmine 3–6 mg/day	15	87.0 (6.5)	12 (80)	LTC in the UK	NINCDS–ADRDA, probable AD 6.3–9.0	CMAI	−1.9	–/–/–	Risperidone more effective than rivastigmine.
	Risperidone 0.5–1 mg/day	12	85.3 (5.0)	8 (67)				−24.8*	–/–/–	
Anticonvulsant										
Tariot *et al.* (1998)	Carbamazepine 300 mg/day	27	87.1 (6.2)	23 (85)	4 LTC in USA	NINCDS-ADRDA, AD, vascular, mixed 3.9–8.3	BPRS total	−7.7*	14.8/3.7/0	
	Placebo	24	84.8 (6.5)	18 (75)	6 weeks			−0.9	0/0/0	

	Porsteinsson *et al.* (2001)	Divalproex sodium 375 mg/day	28	85.3 (8.1)	17 (61)	7 LTC in the USA	DSM-IV, NINCDS–ADRDA, AD, vascular, mixed 6.7–7.0	BPRS total	−6.9	6.7/6.7/0	No significant difference reported on CMAI.
		Placebo	28	84.7 (6.0)	22 (79)	6 weeks			−5.9	12.5/12.5/0	
	Tariot *et al.* (2005)	Divalproex sodium 800 mg/day	75	84.2 (6.6)	48 (63)	LTC in the USA	NINCDS–ADRDA, probable AD 10.5–10.8	BPRS total	−4.2	14.7/6.6/1.3	
		Placebo	78	83.9 (5.9)	57 (73)	6 weeks			−5.1	17.9/6.4/0	
	Sommer *et al.* (2009)	Oxcarbazepine 300–900 mg/day	52	83	35 (67.3)	35 LTC in Norway	ICD-10, AD, vascular 5.4–6.2	NPI–NH	–	28.8*/21.1/0	Change in score not reported but difference not statistically significant.
		Placebo	51	84	38 (74.5)	8 weeks			–	9.8/7.9/0	
Antidepressant											
	Gaber *et al.* (2001)	Sertraline 25–50 mg/day	13	81.5 (6.7)	–	Institutionalized in Italy	DSM-IV, dementia	CMAI	−13	–/–/–	No significant differences from baseline to 10 weeks in either group.
		Haloperidol 1–2 mg/day	10	–	–	10 weeks	– –		−10	–/–/–	
Other											
	Cantillon *et al.* (1996)	Buspirone 5 mg TID	12	78.8 (5.1)	8 (66.7)	LTC in USA	NINCDS-ADRDA, probable AD 2.5–2.6	BPRS total	−6.7	–/–/–	
		Haloperidol 0.5 mg TID	14	79.6 (4.9)	9 (64.3)	10 weeks				–/–/–	
	Kyomen *et al.* (1999)	Estrogen 0.625–2.5 mg	8	81.0 (3.7)	7 (87.5)	LTC in USA	DSM-III-R, dementia 4.1–5.5	OAS	+4.7*	0/0/0	
		Placebo	6	87.8 (8.27)	5 (83.3)	4 weeks			+2.1	16.7/0/0	
	Hall *et al.* (2005)	Estrogen transdermal patch, 50–100 mcg/day	13	78.1 (6.2)	0 (0)	LTC and psych inpatient ward, Australia	DSM-IV, dementia 2.6–5.4	RAGE	∼2.5	–/–/0	Results reported as “no significant difference” on RAGE.
		Placebo	14	78.8 (9.6)	0 (0)	8 weeks			∼1	–/–/0	

Table 1. Continued

	INTERVENTION	NUMBER	AGE, MEAN (SD)	FEMALE GENDER, N (%)	SETTING AND DURATION	DEMENTIA DIAGNOSIS, AVERAGE MMSE SCORES	OUTCOME MEASURE	CHANGE IN NPS	PERCENTAGE OF TRIAL WITHDRAWALS/ WITHDRAWAL DUE TO ADVERSE EVENTS/ MORTALITY	COMMENT
Peskind *et al.* (2005)	Propranolol 30–120 mg/day	17	86 (8)	14 (82.4)	1 NH in the USA	NINCDS–ADRDA, probable AD 7. 2–7.8	NPI	−8.0*	35.3*/0/0	
	Placebo	14	84 (8)	11 (78.6)	6 weeks			−0.4	78.6/14.3/0	
Huertas *et al.* (2007)	Cyproterone 100 mg/day	14	79.9 (7.3)	7 (50)	LTC and outpatient in Spain 90 days	DSM-III-R, NINCDS–ADRDA, AD 6.8–6.9	SOAS		21.4/21.4/0	Outcome was number of individuals with SOAS response.
	Haloperidol 2 mg/day	13	81.6 (6.9)	12 (92.3)					0/0/0	
Gehrman *et al.* (2009)	Melatonin 10 mg	24	82.9 (7.0)	16 (68.3)	NH in the USA 10 days	NINCDS–ADRDA, AD 5.8	CMAI total	–	0/0/	Difference not statistically significant. No difference noted on the ABRS scale.
	Placebo	17	–	–				–	0/0/0	
Wang *et al.* (2009)	Prazosin 1–6 mg daily	11	83.2 (11.5)	4 (36.4)	1 NH in the USA 8 weeks	NINCDS–ADRDA, probable or possible AD 9.3–12.0	NPI	−19*	41.6/–/0	Prazosin also more effective on BPRS.
	Placebo	11	78.1 (10.8)	5 (45.5)				−2	50/–/0	

*$p < 0.05$ when compared with placebo or other comparator medication in the study; – = not reported.
ACES = Agitation–Calmness Evaluation Scale; AD = Alzheimer's disease; BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; CMAI = Cohen-Mansfield Agitation Inventory; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Disease; NH = nursing home; MMSE = Mini-Mental State Examination; NINCDS–ADRDA = National Institutes of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; NPI = Neuropsychiatric Inventory; OAS = Overt Aggression Scale; PANSS-EC = Positive and Negative Syndrome Scale – Excited Component; RAGE = Rating Scale for Aggressive Behavior in the Elderly; SIB = Severe Impairment Battery; SOAS = Staff Observation Aggression Scale.

statistically significant difference between the two groups (Fontaine *et al.*, 2003). Olanzapine and haloperidol were both associated with reductions in agitation and NPS with no significant differences between groups (Verhey *et al.*, 2006). Risperidone was associated with greater reductions in agitation when compared with rivastigmine in one study (Holmes *et al.*, 2007). One study also found no significant differences when either quetiapine or rivastigmine was compared with placebo (Ballard *et al.*, 2005). A trial of quetiapine, haloperidol, and placebo found no difference between either of the two active treatment groups and placebo in measures of NPS (Tariot *et al.*, 2006). A single trial compared the typical antipsychotics loxapine, thioridazine, and placebo and found no benefit for either medication over placebo (Barnes *et al.*, 1982).

Eight studies reported change in NPS using dichotomized outcomes. Risperidone was associated with overall clinical improvement in NPS when compared with placebo in two studies (Brodaty *et al.*, 2003; Mintzer *et al.*, 2006) and significant reduction in NPS in a second study (Katz *et al.*, 1999). However, a third study did not find any difference in response rates for risperidone compared with either haloperidol or placebo (De Deyn *et al.*, 1999). Olanzapine at doses of 5 and 10 mg daily were more likely to produce significant reductions in NPS when compared with placebo, although the 15 mg dose was not better than placebo (Street *et al.*, 2000). Aripiprazole was associated with a greater response rate than placebo in one study (Streim *et al.*, 2008), while a second study did not find any difference in response (Mintzer *et al.*, 2007). Quetiapine at 200 mg daily was found to be associated with a higher proportion of individuals with significant global improvement than placebo in one study, while 100 mg was not associated with significant benefit (Zhong *et al.*, 2007).

Cholinesterase inhibitors

One study of donepezil found no benefit for the medication when compared with placebo on measures of NPS (Tariot *et al.*, 2001). Two studies evaluated the cholinesterase inhibitor rivastigmine (Ballard *et al.*, 2005; Holmes *et al.*, 2007), with there being no benefit for rivastigmine when compared with placebo (Ballard *et al.*, 2005), or the atypical antipsychotics quetiapine (Ballard *et al.*, 2005) or risperidone (Holmes *et al.*, 2007).

Anticonvulsants

Of the four placebo-controlled studies involving anticonvulsants, one evaluated carbamazepine (Tariot *et al.*, 1998), two examined divalproex sodium (Porsteinsson *et al.*, 2001; Tariot *et al.*, 2005), and one study examined oxcarbazepine (Sommer *et al.*, 2009). Only carbamazepine was associated with a statistically significant reduction in NPS symptoms (Tariot *et al.*, 1998) while the other studies showed no benefit for other anticonvulsants compared with placebo (Porsteinsson *et al.*, 2001; Tariot *et al.*, 2005; Sommer *et al.*, 2009).

Antidepressants

A single small study compared sertraline with haloperidol on NPS and found that both groups had a non-significant reduction in NPS with no difference between groups (Gaber *et al.*, 2001).

Other medications

A study comparing buspirone and haloperidol found no significant difference between the two groups on symptoms of NPS (Cantillon *et al.*, 1996). Two placebo-controlled studies evaluated the effects of estrogen therapy on NPS, one with oral estrogen (Kyomen *et al.*, 1999) and a second with a transdermal estrogen patch (Hall *et al.*, 2005), with only the study in which estrogen was administered orally demonstrating benefit over placebo. A single trial of the androgen antagonist cyproterone acetate compared with haloperidol and found that cyproterone was associated with greater improvement in NPS (Huertas *et al.*, 2007). A placebo-controlled trial of the β-adrenergic antagonist propranolol demonstrated improvement in NPS symptoms scores and global improvement in NPS (Peskind *et al.*, 2005). One study of the α-1 adrenergic antagonist prazosin demonstrated benefits on NPS when compared with placebo (Wang *et al.*, 2009). A placebo-controlled study of melatonin did not demonstrate any benefit for NPS (Gehrman *et al.*, 2009).

Safety and tolerability

A total of 24 studies reported on trial withdrawals due to any cause (Tariot *et al.*, 1998; 2001; 2005; 2006; De Deyn *et al.*, 1999; 2004; Katz *et al.*, 1999; Kyomen *et al.*, 1999; Street *et al.*, 2000; Porsteinsson *et al.*, 2001; Brodaty *et al.*, 2003; Fontaine *et al.*, 2003; Ballard *et al.*, 2005; Peskind *et al.*, 2005; Mintzer *et al.*, 2006; 2007; Huertas *et al.*, 2007; Streim *et al.*, 2008; Gehrman *et al.*, 2009; Rappaport *et al.*, 2009; Sommer *et al.*, 2009; Wang *et al.*, 2009), 21 studies reported on trial withdrawals due to adverse events (Tariot *et al.*, 1998; 2001; 2005; 2006; Katz *et al.*, 1999; Kyomen *et al.*, 1999; Street *et al.*, 2000; Porsteinsson *et al.*, 2001; Brodaty *et al.*, 2003; Fontaine *et al.*, 2003; De Deyn *et al.*, 2004; Ballard *et al.*, 2005; Peskind *et al.*, 2005; Mintzer *et al.*, 2006; 2007; Huertas *et al.*, 2007; Zhong *et al.*, 2007; Streim *et al.*, 2008; Gehrman *et al.*, 2009; Rappaport *et al.*, 2009; Sommer *et al.*, 2009), and 23 studies reported

mortality rates (Tariot *et al.*, 1998; 2001; 2005; 2006; Katz *et al.*, 1999; Kyomen *et al.*, 1999; Street *et al.*, 2000; Porsteinsson *et al.*, 2001; Brodaty *et al.*, 2003; Fontaine *et al.*, 2003; De Deyn *et al.*, 2004; Ballard *et al.*, 2005; Hall *et al.*, 2005; Peskind *et al.*, 2005; Mintzer *et al.*, 2006; 2007; Huertas *et al.*, 2007; Zhong *et al.*, 2007; Streim *et al.*, 2008; Gehrman *et al.*, 2009; Rappaport *et al.*, 2009; Sommer *et al.*, 2009; Wang *et al.*, 2009) (Table 1). Trial withdrawals due to any cause or adverse events were common in many studies. One risperidone trial found that the 2 mg dose was associated with higher rates of overall trial withdrawals and trial withdrawals due to adverse events compared with placebo, while mortality was higher with 1 mg daily when compared with placebo (Katz *et al.*, 1999). Olanzapine at 15 mg daily was associated with higher rates of withdrawal due to adverse events although lower doses were not significantly different from placebo (Street *et al.*, 2000). Only the 10 mg dose of aripiprazole was associated with an increased risk of adverse events when compared with placebo in one study (Mintzer *et al.*, 2007), while a second of aripiprazole found that overall rates of trial withdrawal were higher with aripiprazole (Streim *et al.*, 2008). Both quetiapine and rivastigmine were associated with higher rates of withdrawal than placebo in one study (Ballard *et al.*, 2005) as was oxcarbazepine when compared with placebo (Sommer *et al.*, 2009). One study of propranolol found lower rates of trial withdrawals associated with drug treatment when compared with placebo (Peskind *et al.*, 2005).

Quality of studies

In general, most studies were rated as being at low or unclear risk of bias due to various aspects related to study design (Table 2). Only one study was rated as being at low risk of bias on all the risk of bias items (Ballard *et al.*, 2005). For the assessment of potential risk of bias associated with the study sponsor, 14 studies were funded by pharmaceutical companies, including 12 studies sponsored by the manufacturers of atypical antipsychotics (De Deyn *et al.*, 1999; 2004; Katz *et al.*, 1999; Street *et al.*, 2000; Brodaty *et al.*, 2003; Fontaine *et al.*, 2003; Mintzer *et al.*, 2006; 2007; Tariot *et al.*, 2006; Zhong *et al.*, 2007; Streim *et al.*, 2008; Rappaport *et al.*, 2009), one study of typical antipsychotics (Barnes *et al.*, 1982), and one study of cholinesterase inhibitors (Tariot *et al.*, 2001).

Discussion

Our review identified a number of RCTs evaluating a variety of medications for the management of NPS in LTC settings. Overall, the most frequently studied class of medications was atypical antipsychotics. There is some evidence to support the efficacy of the atypical antipsychotics risperidone, olanzapine, and aripiprazole when compared with placebo on change in NPS symptom scores. There were additional single small positive studies with carbamazepine, estrogen, cyproterone acetate, propranolol, and prazosin. The effects of medications tended to be clinically modest and only a few studies reported on the rates of clinically significant outcomes such as symptom remission. Some medications may be effective in reducing overall levels of NPS and specific NPS including agitation and aggression. The risk of bias for these studies varied, although many studies had some potentially important methodological limitations. Trial withdrawals, adverse events, and mortality were relatively common outcomes in many studies. Importantly, there were no studies comparing pharmacological agents to non-pharmacological approaches and a limited number of studies directly comparing different pharmacological agents.

The findings of our review of pharmacological treatments for NPS in LTC are consistent with previous broader reviews of antipsychotics and other medications for the treatment of NPS (Schneider *et al.*, 1990; 2006a; Borson and Raskind, 1997; Lanctot *et al.*, 1998; Sutor *et al.*, 2001; Kindermann *et al.*, 2002; Snowden *et al.*, 2003; Alexopoulos *et al.*, 2005; Sink *et al.*, 2005; Ballard and Howard, 2006; Kozman *et al.*, 2006; Herrmann and Lanctot, 2007; Konavalov *et al.*, 2007; Saddichha and Pandey, 2008; Ballard *et al.*, 2009a; 2009b; Conn and Seitz, 2010). The atypical antipsychotics (in particular risperidone, olanzapine, and aripiprazole) appear to have the most extensive evidence in favor of their use for NPS, although even this evidence is limited to a relatively small number of studies. There was only one study that directly compared two atypical antipsychotics with no statistically significant difference in NPS outcomes when comparing risperidone with olanzapine (Fontaine *et al.*, 2003). Results from a large RCT comparing olanzapine, risperidone, quetiapine, and placebo for outpatients with Alzheimer's disease found that the primary outcome of time to discontinuation of treatment due to any cause did not differ between any of the three active treatment groups compared with placebo. However, time to discontinuation due to lack of efficacy favored both risperidone and olanzapine in this study (Schneider *et al.*, 2006b). While most studies evaluated the effects of atypical antipsychotics on overall change in NPS, they appear to be most effective in reducing particular symptoms such as hostility, anger,

Table 2. Risk of bias assessment for pharmacological treatment of neuropsychiatric symptoms of dementia

	SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING	INCOMPLETE OUTCOME DATA	SELECTIVE OUTCOME REPORTING	OTHER – FUNDING SOURCE
Antipsychotic						
Barnes *et al.* (1982)	Unclear	Unclear	Unclear	Yes	Yes	No
De Deyn *et al.* (1999)	Yes	Yes	Unclear	Yes	Yes	No
Katz *et al.* (1999)	Yes	Unclear	Yes	Unclear	Yes	No
Street *et al.* (2000)	Unclear	Unclear	Unclear	Yes	Yes	No
Brodaty *et al.* (2003)	Yes	Unclear	Yes	Yes	Yes	No
Fontaine *et al.* (2003)	Unclear	Unclear	Unclear	No	Yes	No
De Deyn *et al.* (2004)	Unclear	Unclear	Unclear	Yes	Yes	No
Mintzer *et al.* (2006)	Unclear	Yes	Unclear	Unclear	Yes	No
Tariot *et al.* (2006)	Unclear	Unclear	Unclear	Yes	Yes	No
Verhey *et al.* (2006)	Unclear	Unclear	Unclear	Yes	Yes	Yes
Mintzer *et al.* (2007)	Unclear	Unclear	Unclear	Yes	Yes	No
Zhong *et al.* (2007)	Yes	Unclear	Unclear	Yes	Yes	No
Streim *et al.* (2008)	Unclear	Unclear	Unclear	Yes	Yes	No
Rappaport *et al.* (2009)	Unclear	Unclear	Unclear	Yes	No	No
Cholinesterase inhibitors						
Tariot *et al.* (2001)	Yes	Unclear	Yes	Yes	Yes	No
Ballard *et al.* (2005)	Yes	Yes	Yes	Yes	Yes	Yes
Holmes *et al.* (2007)	Unclear	Unclear	Yes	Yes	Yes	Yes
Anticonvulsant						
Tariot *et al.* (1998)	Unclear	Unclear	Yes	Yes	Yes	Yes
Porsteinsson *et al.* (2001)	Unclear	Unclear	Yes	Yes	Yes	Yes
Tariot *et al.* (2005)	Yes	Yes	Unclear	Yes	Yes	Yes
Sommer *et al.* (2009)	Unclear	Unclear	Unclear	Yes	Yes	Yes
Antidepressant						
Gaber *et al.* (2001)	Unclear	Unclear	Yes	Unclear	Yes	Yes
Other						
Cantillon *et al.* (1996)	Unclear	Unclear	Yes	Yes	Yes	Unclear
Kyomen *et al.* (1999)	Unclear	Yes	Unclear	Yes	Yes	Yes
Hall *et al.* (2005)	Unclear	Unclear	Unclear	Yes	Yes	Yes
Peskind *et al.* (2005)	Yes	Unclear	Yes	Yes	Yes	Yes
Huertas *et al.* (2007)	Unclear	Unclear	Unclear	Yes	Yes	Yes
Gehrman *et al.* (2009)	Unclear	Unclear	Yes	Unclear	Yes	Yes
Wang *et al.* (2009)	Yes	Unclear	Yes	Yes	Yes	Yes

and psychosis (Sultzer *et al.*, 2008). Although statistically significant results were observed in several studies in our review, clinically significant outcomes such as response rates or global clinical impression of change were only reported in a few studies.

Although there were few statistically significant differences noted on most safety outcomes, this is likely due to the limited power of many studies to detect adverse events associated with therapies. Existing meta-analyses and observational studies have however demonstrated major safety concerns with the use of atypical antipsychotics and other medications for NPS. Meta-analyses have demonstrated that atypical antipsychotics are associated with an increased risk of death (Schneider *et al.*, 2005) with an odds ratio of 1.54, and an absolute risk difference of approximately 1% from studies conducted in LTC and other settings. Observational studies have also found an increased risk of mortality (Gill *et al.*, 2007). Similarly, an increased risk of major cerebrovascular events associated with antipsychotics use has been observed in meta-analyses of RCTs (Herrmann and Lanctot, 2005), with a relative risk of 2.7 and an absolute risk difference of approximately 1%. Other less serious, but more common side effects associated with atypical antipsychotics include increased rates of somnolence (Schneider *et al.*, 2006a), falls (Hien Le *et al.*, 2005), and fall-related injuries including hip fractures (Jalbert *et al.*, 2010), which must also be monitored during therapy. There is also an increasing appreciation of the effects of atypical antipsychotics on cognitive and

functional decline in older adults with dementia (Vigen *et al.*, 2011).

There were relatively few studies that examined medications other than atypical antipsychotics. Some typical antipsychotics may also be effective for NPS (Schneider *et al.*, 1990; Lanctot *et al.*, 1998), although these medications are no more effective than atypical antipsychotics and are associated with higher rates of adverse events (De Deyn *et al.*, 1999; Verhey *et al.*, 2006; Tariot *et al.*, 2006). The risk of death (Wang *et al.*, 2005; Gill *et al.*, 2007) and stroke (Herrmann *et al.*, 2004; Gill *et al.*, 2005) associated with typical antipsychotics is similar to or greater than the risk observed with atypical antipsychotics. There was only a single small study of antidepressants for NPS conducted in LTC, although there is growing interest in the use of antidepressants for this indication (Seitz *et al.*, 2011). Recent RCTs of the antidepressant citalopram and escitalopram have indicated that these medications may be as effective as the antipsychotics risperidone (Pollock *et al.*, 2007) or perphenazine (Pollock *et al.*, 2002) and more effective than placebo (Pollock *et al.*, 2002) in hospitalized inpatient populations. Importantly, the rates of adverse events with antidepressants may be less than that observed with antipsychotics (Pollock *et al.*, 2007; Barak *et al.*, 2011). However, serotonergic antidepressants have been associated with serious adverse events in older adults including falls (Vestergaard *et al.*, 2006), fractures (Takkouche *et al.*, 2007), bleeding (Andrade *et al.*, 2010), and hyponatremia (Fabian *et al.*, 2004). Some observational studies have also reported that antidepressants may be associated with an increased risk of death (Huybrechts *et al.*, 2011) and stroke (Trifiro *et al.*, 2010; Wu *et al.*, 2011), although not all studies have confirmed these associations (Kales *et al.*, 2007). The anticonvulsant carbamazepine demonstrated benefit in terms of reduction of agitation in a single small study conducted in LTC (Tariot *et al.*, 1998) as well as two other small trials conducted outside of LTC (Cooney *et al.*, 1996; Olin *et al.*, 2001). Other medications reporting benefit were represented by single small studies and these agents may be considered for some individuals who do not tolerate or fail to respond to other treatments, although further research is needed to establish their efficacy and safety. Divalproex sodium was not effective at reducing NPS in studies included in our review (Porsteinsson *et al.*, 2001; Tariot *et al.*, 2005) and other studies have demonstrated that valproic acid may accelerate cognitive decline (Tariot *et al.*, 2011) and, as such, these medications should be avoided in patients with NPS. Studies of cholinesterase inhibitors for the treatment of NPS did not find that these medications were effective in reducing NPS among patients with significant symptoms (Tariot *et al.*, 2001; Ballard *et al.*, 2005; Holmes *et al.*, 2007), which has also been observed in trials conducted in community-based populations (Howard *et al.*, 2007).

Although most of the trials in our review were between 6 and 12 weeks in length, in clinical practice antipsychotics are often prescribed for prolonged periods of time in LTC (Ballard *et al.*, 2004; Ruths *et al.*, 2004; Gill *et al.*, 2007). The risk of adverse events associated with antipsychotics are greatest after initiating treatment (Gill *et al.*, 2007), although chronic therapy is also associated with risks (Ballard *et al.*, 2008). A placebo-controlled trial comparing continuation of antipsychotic therapy to placebo for LTC residents with NPS found that a decreased risk of mortality was associated with cessation of antipsychotics when compared with continued use (Ballard *et al.*, 2009c). Discontinuation of antipsychotic therapy did not result in worsening of NPS for most individuals (Ballard *et al.*, 2008). Additional RCTs have demonstrated that antipsychotics can be discontinued in the majority of individuals receiving chronic antipsychotic therapy without worsening of behavior (Cohen-Mansfield *et al.*, 1999; van Reekum *et al.*, 2002; Ballard *et al.*, 2004; Ruths *et al.*, 2004; 2008). Predictors of successful discontinuation of therapy include lower baseline severity of NPS (Ballard *et al.*, 2004; 2008) and lower dosages of antipsychotics to achieve symptom control (van Reekum *et al.*, 2002; Ruths *et al.*, 2008).

There are some limitations to our review. One limitation relates to the method by which NPS were assessed, that being by retrospective questionnaire ratings of NPS as reported by nursing staff or other caregivers. Direct observations of behaviors would be considered the "gold standard" method for measuring NPS although studies have demonstrated that directly observed levels of agitation and questionnaire reported agitation are only moderately correlated (Cohen-Mansfield and Libin, 2004). However, direct measures of NPS are too labor intensive to be used as outcome measures in large clinical studies and questionnaire reports of behavior are more feasible to use in this setting. We only focused on published English-language studies and there are additional unpublished studies that have been identified (Schneider *et al.*, 2006a), which may have introduced a publication bias in favor of studies showing benefits with medications (Turner *et al.*, 2008). Many of the studies in our review were sponsored by pharmaceutical companies and studies that are sponsored by pharmaceutical companies are more likely to report outcomes in

favor of the company's product than studies funded by other sources (Lexchin *et al.*, 2003). Finally, due to the range of medications, outcome measures, and clinical populations, we did not undertake meta-analysis to quantitatively summarize the effects of medications.

Particular strengths of our review should be highlighted. First, we restricted our review to randomized controlled clinical trials to evaluate only the highest level of evidence. We also included only those studies conducted in LTC settings and so the results observed should be generalizable to other LTC populations. Our review also assessed the quality of included studies to identify potential sources of bias which may influence the internal validity of the primary studies. Finally, we undertook a detailed examination of the efficacy and safety of medications to allow clinicians to better appreciate and communicate the potential benefits and risks of various treatments.

Conclusions

The best supported evidence for management of NPS in LTC is for some atypical antipsychotics in particular risperidone, olanzapine, and aripiprazole. There are relatively few studies of other medications which have sufficient evidence base to support their use. However, the known risks of adverse events associated with antipsychotics and other psychotropic medications in LTC highlight the need for safe and effective alternatives to antipsychotics and existing pharmacological treatments. Non-pharmacological interventions should continue to be used as initial treatments for NPS where these are available, also taking into consideration patient and caregivers priorities. Further research into the comparative effectiveness of pharmacological treatments and non-pharmacological treatments is required to further understand the relative risks and benefits of treatments for NPS in LTC.

Conflict of interest

Dr. Herrmann has received grants or research funds from Sonexa, Sonafi, Aventis, and Lundbeck, honoraria from Pfizer and Lundbeck, and served as a consultant for Lundbeck.

Description of authors' roles

All authors made substantial contributions to the conception and design of the study and analysis and interpretation of data. Dr. Seitz and Ms. Brisbin and Ms. Rines contributed to the acquisition of studies and data extraction. All authors contributed to drafting the paper and revising it critically for intellectual content. All authors approved of the final version of the manuscript.

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