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Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia (Review)

Van Leeuwen E, Petrovic M, van Driel ML, De Sutter AIM, Vander Stichele R, Declercq T, Christiaens T

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Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia

Ellen Van Leeuwen[1,2], Mirko Petrovic[3], Mieke L van Driel[2,4], An IM De Sutter[2], Robert Vander Stichele[1], Tom Declercq[2], Thierry Christiaens[1]

[1]Clinical Pharmacology Unit of the Department of Pharmacology, Ghent University, Ghent, Belgium. [2]Department of Family Medicine and Primary Health Care, Ghent University, Ghent, Belgium. [3]Department of Geriatrics, Ghent University Hospital, Ghent, Belgium. [4]Primary Care Clinical Unit, Faculty of Medicine, The University of Queensland, Brisbane, Australia

Contact address: Ellen Van Leeuwen, Clinical Pharmacology Unit of the Department of Pharmacology, Ghent University, Ghent, 9000, Belgium. ellen.vanleeuwen@ugent.be.

A B S T R A C T

Background

Antipsychotic agents are often used to treat neuropsychiatric symptoms (NPS) in people with dementia although there is uncertainty about the effectiveness of their long-term use for this indication and concern that they may cause harm, including higher mortality. When behavioural strategies have failed and treatment with antipsychotic drugs is instituted, regular attempts to withdraw them have been recommended in guidelines. Physicians, nurses and families of older people with dementia may be reluctant to stop antipsychotics, fearing deterioration of NPS.

This is an update of a Cochrane Review published in 2013.

Objectives

To evaluate whether withdrawal of antipsychotic agents is successful in older people with dementia and NPS in primary care or nursing home settings, to list the different strategies for withdrawal of antipsychotic agents in older participants with dementia and NPS, and to measure the effects of withdrawal of antipsychotic agents on participants' behaviour and assess safety.

Search methods

We searched the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (ALOIS), the *Cochrane Library*, MEDLINE, Embase, PsycINFO, CINAHL, LILACS, clinical trials registries and grey literature sources up to 11 January 2018.

Selection criteria

We included all randomised, controlled trials comparing an antipsychotic withdrawal strategy to continuation of antipsychotics in people with dementia who had been treated with an antipsychotic drug for at least three months.

Data collection and analysis

We used standard methodological procedures according to the *Cochrane Handbook for Systematic Reviews of Interventions.* We rated the quality of evidence for each outcome using the GRADE approach.

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Main results

We included 10 studies involving 632 participants. One new trial (19 participants) was added for this update.

One trial was conducted in a community setting, eight in nursing homes and one in both settings. Different types of antipsychotics at varying doses were discontinued in the studies. Both abrupt and gradual withdrawal schedules were used. Reported data were predominantly from studies at low or unclear risk of bias.

We included nine trials with 575 randomised participants that used a proxy outcome for overall success of antipsychotic withdrawal. Pooling data was not possible due to heterogeneity of outcome measures used. Based on assessment of seven studies, discontinuation may make little or no difference to whether or not participants complete the study (low-quality evidence).

Two trials included only participants with psychosis, agitation or aggression who had responded to antipsychotic treatment. In these two trials, stopping antipsychotics was associated with a higher risk of leaving the study early due to symptomatic relapse or a shorter time to symptomatic relapse.

We found low-quality evidence that discontinuation may make little or no difference to overall NPS, measured using various scales (7 trials, 519 participants). There was some evidence from subgroup analyses in two trials that discontinuation may reduce agitation for participants with less severe NPS at baseline, but may be associated with a worsening of NPS in participants with more severe NPS at baseline.

None of the studies assessed withdrawal symptoms. Adverse effects of antipsychotics (such as falls) were not systematically assessed. Low-quality evidence showed that discontinuation may have little or no effect on adverse events (5 trials, 381 participants), quality of life (2 trials, 119 participants), or cognitive function (5 trials, 365 participants).

There were insufficient data to determine whether discontinuation of antipsychotics has any effect on mortality (very low-quality evidence).

Authors' conclusions

There is low-quality evidence that antipsychotics may be successfully discontinued in older people with dementia and NPS who have been taking antipsychotics for at least three months, and that discontinuation may have little or no important effect on behavioural and psychological symptoms. This is consistent with the observation that most behavioural complications of dementia are intermittent and often do not persist for longer than three months. Discontinuation may have little or no effect on overall cognitive function. Discontinuation may make no difference to adverse events and quality of life. Based on the trials in this review, we are uncertain whether discontinuation of antipsychotics leads to a decrease in mortality.

People with psychosis, aggression or agitation who responded well to long-term antipsychotic drug use, or those with more severe NPS at baseline, may benefit behaviourally from continuation of antipsychotics. Discontinuation may reduce agitation for people with mild NPS at baseline. However, these conclusions are based on few studies or small subgroups and further evidence of benefits and harms associated with withdrawal of antipsychotic is required in people with dementia and mild and severe NPS.

The overall conclusions of the review have not changed since 2013 and the number of available trials remains low.

PLAIN LANGUAGE SUMMARY

Stopping or continuing long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia

Review question

We investigated the effects of stopping antipsychotic drugs in older people with dementia who had been taking them for three months or longer.

Background

People with dementia may have symptoms and behavioural problems that can be distressing and difficult for carers to manage. Such symptoms (often described as neuropsychiatric symptoms, or NPS) include anxiety, apathy, depression, psychosis (hallucinations and delusions), wandering, repeating words or sounds, shouting, and behaving in agitated or aggressive ways, or both.

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Antipsychotic drugs are often prescribed with the aim of controlling these symptoms and behaviours, although most current guidance suggests these drugs should only be used for short periods of time for the most challenging behaviours. This is largely because these drugs are thought to have risks of side effects (including some that are serious), and because many behavioural problems improve without treatment. However, many people with dementia continue to take antipsychotic drugs over long periods of time.

This review investigated whether it is feasible for older people with dementia and NPS to stop antipsychotic drugs which they have been taking for at least three months. This is an update of a Cochrane Review published in 2013.

Methods

We searched up to 11 January 2018 for any study that randomly allocated some people with dementia who were taking antipsychotic drugs to continue this treatment and others to stop taking antipsychotic drugs. Study participants were followed up over a period of time to see what happened.

Results

We included 10 studies with a total of 632 participants in our review. We added one new study with 19 participants for this update. Most participants lived in nursing homes. The studies varied considerably with regard to the people they included, the methods they used and the outcomes they measured.

Because the studies were so diverse, it was not possible to combine all the data numerically. We found low-quality evidence that older people with dementia may be able to stop long-term antipsychotics without their behavioural problems getting worse. However, in some people who had psychosis, agitation or aggression and who had improved significantly when they first started antipsychotic treatment, we found that stopping the drugs may increase the risk of the behavioural problems getting worse again. On the other hand, agitation decreased after stopping the drugs in some participants whose NPS at the beginning of the studies was relatively mild.

We did not find enough evidence to know whether stopping antipsychotics has beneficial effects on quality of life, thinking and remembering, or the ability to carry out daily tasks, nor if the risk of harmful events - such as falls - is reduced. We are uncertain whether stopping antipsychotics leads to people living longer.

Quality of the evidence

Overall, evidence was low- or very low-quality. This means we have limited or little confidence in the results, and that it is possible that other similar research could find something different. The main reasons for this assessment were that there were few studies that included few people, and a risk that results were not fully reported. All included studies had problems recruiting enough participants, making it more difficult for them to detect effects of stopping antipsychotics.

Conclusions

Limited evidence suggests that stopping long-term antipsychotic drug use in older people with dementia and NPS may be done without making their behaviour worse. There may be benefits especially for those with milder NPS. There may be people with more severe symptoms who benefit from continuing treatment, but more research in people with both milder and more severe NPS is needed to be sure about this. The overall conclusions have not changed since the last version of this review and the number of included trials is still low.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Discontinuation compared to continuation of antipsychotic medication for behavioural and psychological symptoms in older participants with dementia

Patient or population: older people with dementia who had been taking an antipsychotic drug for at least 3 months
Setting: any setting
Intervention: discontinuation of long-term antipsychotic drug use
Comparison: continuation of long-term antipsychotic drug use

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk *Continuation antipsychotics*	**Corresponding risk** *Discontinuation antipsychotics*				
Success of withdrawal from antipsychotics Measured with a variety of outcomes related to failure to complete the study Follow-up: 1 to 8 months	In 7 studies there was no overall difference in the outcomes reported for success of withdrawal In two studies of participants with psychosis, aggression or agitation who had responded to antipsychotic treatment, discontinuation accelerated symptomatic relapse without affecting the number of participants experiencing a relapse in one study and was associated with a higher rate of symptomatic relapse in the other study In one small study a high proportion of the participants in the discontinuation group failed to complete the study			575 (9 RCTs)	⊕⊕○○ LOW[ab]	Our intended primary outcome, success of withdrawal defined as the ability to complete the study in the allocated study group, i.e. no failure due to worsening of NPS or relapse to antipsychotic drug use, was not reported in any study. We used the difference between groups in the number of non-completers of the study as a proxy for our primary outcome. However, data could not be pooled due to variability in outcome measures

Behavioural and psychological symptoms Assessed with various scales. Follow up: 1 to 8 months	In 2 pooled studies there was no difference in NPI scores between the continuation and discontinuation groups (see Data and analyses and Figure 1). In five non-pooled studies, there was no difference in the outcomes on scales measuring overall behaviour and psychological symptoms between groups	519 (7 RCTs)	⊕⊕◯◯ LOW◯^{b}◯^{c}	Data could only be pooled for 2 studies due to variability in outcome measures The two pooled studies performed subgroup analyses according to baseline NPI-score ($\leq$ 14 or > 14). In one study, some participants with milder symptoms at baseline were less agitated at three months in the discontinuation group. In both studies, discontinuation led to worsening of NPS in some participants with more severe baseline NPS
Adverse events Assessed with various scales. Follow-up: 1 to 8 months	In 5 studies, there was no evidence of a difference between groups in adverse events	381 (5 RCTs)	⊕⊕◯◯ LOW^{ab}	Data could not be pooled due to variability in outcome measures. Adverse events of antipsychotics were not systematically reported
Quality of life (QoL) Assessed with DCM or QoL-AD. Follow-up: 3 months to 25 weeks	In 2 studies, there was no evidence of an effect on quality of life	119 (2 RCTs)	⊕⊕◯◯ LOW^{bc}	Data could not be pooled due to variability in outcome measures There was no difference between discontinuation and continuation group in the overall cohort or in subgroups

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				with baseline NPI score above or below the median (14)
Cognitive function Assessed with various scales. Follow-up: 1 to 8 months	In 5 studies, there was no evidence of an impact on scales measuring overall cognitive function In one of these trials, discontinuation improved a measure of verbal fluency	365 (5 RCTs)	⊕⊕◯◯ LOW[bc]	Data could not be pooled due to variability in outcome measures
Use of physical restraint Follow-up: 1 month	In one study there was no effect on the use of physical restraint	36 (1 RCT)	⊕◯◯◯ VERY LOW[cd]	Conclusion made by the authors but not supported by data.
Mortality Assessed with various scales. Follow-up: 4 to 12 months	In two studies there was no evidence of an effect on mortality	275 (2 RCTs)	⊕◯◯◯ VERY LOW[cd]	Data could not be pooled due to clinical heterogeneity. In a long-term follow-up of 36 months after the 12 months randomised discontinuation trial (Devanand 2012), we were uncertain whether discontinuation decreased mortality

*The basis for the assumed risk (e.g. the median control group risk across the studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High-quality evidence: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-quality evidence: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-quality evidence: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low-quality evidence: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[a] Downgraded one level for indirectness.
[b] Downgraded one level for risk of bias.
[c] Downgraded one level for imprecision due to a small number of participants.
[d] Downgraded two level for risk of bias.

Figure 1. Forest plot of comparison: 1 Discontinuation versus continuation of long-term antipsychotic drug use: continuous data, analysis method: mean difference, outcome: 1.1 Behavioural assessment by using Neuropsychiatric Inventory (NPI) measuring neuropsychiatric symptoms (NPS) at 3 months (Ballard 2004 and Ballard DART-AD) (Analysis 1.1).
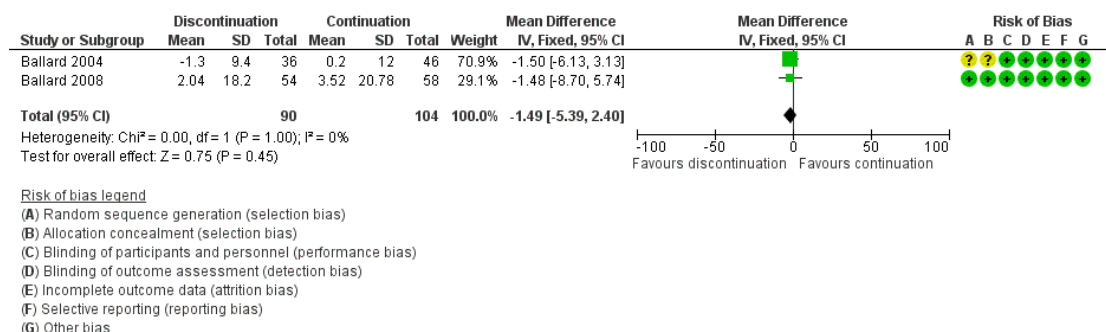
BACKGROUND

Description of the condition

According to the World Health Organization (WHO), the need for healthcare services for older people with dementia will increase significantly over coming years (Ferri 2005). Today, nearly 50 million people worldwide have dementia (Livingston 2017). By 2030, it is estimated that more than 75 million people will be living with dementia, and the number is expected to increase to more than 131 million by 2050, as populations age. (Prince 2016). The risk of dementia rises sharply with age, with an estimated 25% to 30% of people aged 85 years or over having some degree of cognitive decline (WHO 2015).

Although cognitive deficits are the clinical hallmark of dementia, non-cognitive symptoms are common and can dominate the disease presentation. These symptoms include a wide range of neuropsychiatric symptoms (NPS), such as agitation, aggression, psychosis (hallucinations and delusions), anxiety, apathy, depression, wandering, repetitive vocalisations, shouting and many other symptoms. These NPS have been observed in 60% to 98% of people with dementia, especially in later stages of the disease. The reported prevalence of each type of NPS varies considerably, from 3% to 54% for delusions, 1% to 39% for hallucinations, 8% to 74% for depressed mood, 7% to 69% for anxiety, 17% to 84% for apathy, 48% to 82% for aggression or agitation, and 11% to 44% for physical aggression (Zuidema 2007). Some NPS may be more likely than chance to occur together and different 'clusters'

have been described. Petrovic 2007 reports four behavioural syndromes: a cluster with predominantly psychotic symptoms (hallucinations, irritability, agitation and anxiety); a cluster with predominantly mood symptoms (disinhibition, elation and depressive symptoms); a cluster with predominantly psychomotor symptoms (aberrant motor behaviour) and a cluster with predominantly instinctual symptoms (appetite disturbance, sleep disturbance and apathy). Clusters may differ in prevalence, course over time, biological correlates, psychosocial determinants and treatment response. There is probably overlap between clusters. In general, NPS follow a fluctuating course and high placebo response rates have been reported.

NPS can lead to significant carer stress and cause considerable emotional discomfort. They are associated with higher mortality, higher use of physical restraints, increased length of hospitalisation, and often precipitate admission into a nursing home (Gilley 2000). Up to 30% of the costs of caring for people with dementia are directly attributed to the management of NPS (Herrmann 2006).

The treatment of NPS includes non-pharmacologic and pharmacologic therapies. Non-pharmacologic therapy is recommended as first-line treatment of NPS and pharmacologic therapy can be used when non-pharmacologic therapy fails (NICE 2016).

A wide variety of pharmacological agents are used in the management of neuropsychiatric symptoms but results of individual RCTs on the efficacy and safety of these agents conflict, and most trials investigating the efficacy of drug treatment are only short term (Ballard 2011).

Antipsychotics are often first-choice drugs for agitation in demen-

tia, however these drugs have low efficacy for managing agitation in dementia. Risperidone has the best evidence for improving agitation and psychotic symptoms, particularly when aggression was the target symptom, but only for 12 weeks. Haloperidol has effects on quelling aggression, although not on other symptoms of agitation. Olanzapine and quetiapine do not improve psychosis, aggression, or agitation, but aripiprazole may improve agitation (Livingston 2017).

Drugs for cognition, such as cholinesterase inhibitors, including donepezil and memantine, have not been shown to be useful for agitation when agitation is the target symptom. Rivastigmine appears to be beneficial in rate of decline of cognitive function and activities of daily living for people with mild to moderate Alzheimer's disease, although the effects were small and of uncertain clinical importance and have poor safety outcomes with increased risk of adverse events (Wang 2015).

Evidence for carbamazepine in managing behavioural and psychological symptoms of dementia, is very limited with an increased risk of adverse effects (NICE 2016)

A Cochrane Review reported that the selective serotonin reuptake inhibitors (SSRIs) sertraline and citalopram were associated with moderate reduction in symptoms of agitation when compared to placebo in two studies (Seitz 2011). Citalopram in higher doses than recommended, may have benefits, especially in individuals with milder Alzheimer's disease and milder agitation, but has some important adverse effects (Porsteinsson 2014). NICE guidelines did not recommend using SSRIs as treatment for NPS (NICE 2016).

The use of benzodiazepines in the treatment of NPS in older people with dementia is not evidence-based and should be discouraged because of the risk of dependence and falls (CADTH 2010).

A major concern about the use of antipsychotics to treat behavioural symptoms in people with dementia is increased risk of mortality and stroke (Schneider 2005; Schneider 2006). Product side effect and hazard warnings have been issued for atypical antipsychotics (FDA 2005), and for the older typical or first-generation antipsychotics in the treatment of psychotic symptoms in older people with dementia. In the UK, Banerjee 2009 concluded it was "time for action" in his report to the Minister of State and recommended using antipsychotics only "when they really need it" and that more attention should go to training and non-pharmacological interventions. The literature review by Banerjee 2009 of antipsychotic treatment in older people with dementia revealed that while improvement in behavioural disturbance was minimal after 6 to 12 weeks of treatment (estimated effect size 0.1 to 0.2), there was an increase in absolute mortality risk of approximately 1%.

Description of the intervention

Withdrawal from antipsychotic agents can be either abrupt (immediate cessation of the active drug) or tapered (gradual with-

drawal according to a predefined dosing schedule or following clinical response). In this review, we appraised RCTs investigating interventions aimed at assisting older people with dementia to withdraw from antipsychotics, either by stopping abruptly or by tapering.

How the intervention might work

Withdrawal of antipsychotic agents from older, often frail, people with dementia and NPS might improve cognitive function, quality of life (QoL) of people with dementia and their carers, and decrease mortality and adverse events (e.g. falls and extrapyramidal symptoms). However, drug withdrawal may also cause a recurrence or worsening of the original NPS with a negative impact on QoL, and may cause a temporary withdrawal syndrome.

Why it is important to do this review

Carers looking after people who are agitated and taking drugs that may be suppressing NPS are sometimes understandably reluctant to consider withdrawal of the drug. However, the episodic nature of such symptoms and the harms associated with antipsychotic use, are less well appreciated. Antipsychotic drugs remain in widespread use in this population. An update of our 2013 Cochrane Review (Declercq 2013) of the risks and benefits associated with antipsychotic withdrawal was therefore needed.

O B J E C T I V E S

To evaluate whether withdrawal of antipsychotic agents is feasible in older people with dementia and NPS in primary care or nursing home settings; to list the different strategies for withdrawal of antipsychotic agents in older people with dementia and NPS; and to measure the effects of the withdrawal of antipsychotic agents on peoples' behaviour and assess safety issues such as mortality, adverse effects or withdrawal symptoms.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials. Withdrawal trials that were not placebo-controlled were included only if the outcome assessors were blinded to treatment allocation. No language restrictions were applied.

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Types of participants

Older participants with dementia living in the community or in nursing homes and taking an antipsychotic drug.

Older participants were defined as 65 years or over without upper age limit.

Dementia was defined as an acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behaviour, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. We accepted studies for inclusion if the reports stated that participants had dementia or any subtype of dementia. If there was any doubt about this diagnosis, first authors of studies were asked to provide further information. All grades of dementia severity were included, regardless of the method of diagnosis. Participants with schizophrenia were excluded if this was reported in the trial.

Nursing homes are defined as institutions in which long-term care is provided by professional care workers for three or more unrelated, frail, older individuals.

Types of interventions

We included studies in which the intervention was withdrawal of antipsychotic drugs prescribed long-term for neuropsychiatric symptoms (NPS) in older participants with dementia.

Long-term antipsychotic drug use is defined as use of at least three months of any antipsychotic agent, either typical (first generation) or atypical (second generation) at a fixed dosage. Although there is no good definition of the subgroup of atypical antipsychotic drugs, we prefer this term to 'new' or 'second generation' antipsychotics. The antipsychotic agents are listed according to the Anatomical Therapeutic Chemical (ATC) classification. Names of drug classes and individual drugs are presented in Table 1 and Table 2, respectively; atypical antipsychotic agents are labelled with an asterisk. Antipsychotic agents should be used in a stable dose, and within the therapeutic range specified in the drug product information insert. Defined daily doses (per os), as mentioned in the ATC classification, are also listed in Table 2. Chlorpromazine is considered to be the reference drug. Baseline dosage regimen is classified as very low, low or high for each antipsychotic agent, according to the dosage table proposed by Ballard 2008 (e.g. for risperidone a dose of 0.5 mg once daily is very low, 0.5 mg twice daily is low and 1 mg twice daily is high; for haloperidol 0.75 mg once daily is very low, 0.75 mg twice daily is low and 1.5 mg twice daily is high; for the referent molecule chlorpromazine 12.5 mg once daily is very low, 12.5 mg twice daily is low and 25 mg twice daily is high).

Types of outcome measures

Primary outcomes

1. Success of withdrawal from antipsychotics over short-term (four weeks or less) and long-term (more than four weeks) follow-up. Success is defined as the ability to complete the study in the allocated study group, i.e. no dropout due to worsening of NPS, or no relapse to antipsychotic drug during the trial.
2. Behavioural and psychological symptoms (especially agitation, aggression and psychotic symptoms) measured with appropriate scales (e.g. Neuropsychiatric Inventory score (NPI), Neuropsychiatric Questionnaire score (NPI-Q)).
3. Presence or absence of withdrawal symptoms or withdrawal syndrome in the first four weeks.

    i) Withdrawal symptoms or withdrawal syndrome include autonomic and behavioural symptoms such as nausea, vomiting, anorexia, rhinorrhoea, diarrhoea, diaphoresis, myalgia, paraesthesia, anxiety, as well as movement disorders, such as withdrawal emergent parkinsonism, withdrawal dyskinesia and covert dyskinesia.

    ii) Agitation, insomnia and restlessness have also been reported during withdrawal, although it is possible these symptoms occur due to rebound phenomenon. It is impossible to discriminate between these aetiological phenomena.

    iii) A withdrawal neuroleptic malignant syndrome is a very rare but extremely severe condition that can complicate abrupt antipsychotic discontinuation.

4. Adverse events attributable to antipsychotics (e.g. falls, extrapyramidal symptoms, cardiovascular events and diabetes.

Secondary outcomes

1. Cognitive function (general or domain-specific, e.g. short-term memory, frontal executive function, language) measured with appropriate scales (e.g. Severe Impairment Battery (SIB) score, Standardised Mini-Mental State Examination (SMMSE), FAS verbal fluency test, Sheffield Test for Acquired Language Disorder (STALD receptive and STALD expressive skill).
2. Quality of life of participants, carers, family of participants or a combination of these, measured with appropriate scales (e.g. Dementia Care Mapping (DCM) and Quality of life-Alzheimer Disease (QoL-AD)).
3. Time, in days, until prescription of any psychotropic or any antipsychotic agent.
4. Use of physical restraint.
5. Mortality.
6. Other secondary outcomes reported in the primary papers (e.g. global functioning, sleep, clinical global impression) measured with appropriate scales.

Search methods for identification of studies

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Electronic searches

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Specialized Register to 10 January 2018. We performed an interim search on 3 March 2017. Searches for the previous version of this review were performed in February 2009, March 2011, June 2011, November 2011, August 2012, and November 2012 (Declercq 2013).

ALOIS is maintained by the Cochrane Dementia and Cognitive Improvement Group's Information Specialists and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. Studies are identified from:

1. MEDLINE, Embase, CINAHL, PsycINFO and LILACS;
2. trial registers: ISRCTN, UMIN (Japan's Trial Register), the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (which covers ClinicalTrials.gov, ISRCTN, the Chinese Clinical Trials Register, the German Clinical Trials Register, the Iranian Registry of Clinical Trials, and the Netherlands National Trials Register, among others);
3. the Cochrane Library's Central Register of Controlled Trials (CENTRAL); and
4. grey literature sources: ISI Web of Knowledge Conference Proceedings, Index to Theses, Australasian Digital Theses.

Aee About ALOIS for all sources searched.

Details of the search strategies used to retrieve reports of trials from healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section in editorial information about the Dementia and Cognitive Improvement Group. Additional searches were performed in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date and as comprehensive as possible. Search strategies are presented in Appendix 1, Appendix 2 and Appendix 3.

Appendix 4 lists abbreviations used in this review.

Searching other resources

We reviewed reference lists of included and excluded studies to identify any additional studies.

Data collection and analysis

Presentation of results and 'Summary of findings' tables

We included a 'Summary of findings' table, which included seven outcomes, prepared using GRADEpro GDT. We used the GRADE approach to assess evidence quality for all outcomes. Evidence was assessed as high-, moderate-, low-, or very low-quality, depending on the seriousness of concern about risk of bias, imprecision, inconsistency, indirectness, and publication bias. For each outcome in the 'Summary of findings' table we presented a summary of the available data, the magnitude of the effect size, and the quality of the evidence. We justified all decisions to downgrade the quality of evidence in the footnotes of the 'Summary of findings' table.

Selection of studies

For this update, two review authors (EVL, MP) independently screened study titles and abstracts retrieved from the search for their relevance. We removed obviously irrelevant reports and duplicated reports of the same study. We obtained full-text versions of potentially relevant reports. We examined these independently to assess compliance with the predefined eligibility criteria. Two review authors independently decided which trials met the inclusion criteria. Differences between authors were resolved by discussion and by consulting other review authors (MVD, TC). We entered all search results into RevMan 5 (Review Manager 2014). We listed excluded studies and reasons for exclusion in the Characteristics of excluded studies tables.

Data extraction and management

Three review authors (TD, MA, EVL) independently extracted data from included studies using a predefined data extraction form. Differences between authors were resolved by discussion and by consulting the review authors (MVD, TC). We extracted the following data:

- first author, publication year, journal;
- number, age and gender distribution of the participants included in the trial;
- withdrawal method (e.g. abruptly versus tapered withdrawal);
- baseline severity of NPS (e.g. NPI-score), agitation (e.g. Cohen-Mansfield Agitation Inventory (CMAI) scale or psychotic symptoms (hallucinations, delusions);
- baseline severity of dementia as determined by the MMSE score (e.g. mild: 19 to 16; moderate: 15 to 10; severe: 9 to untestable), or other appropriate scales;
- baseline dose of antipsychotic agent (very low, low, high) and type of antipsychotic agents (typical or atypical); and
- results (primary and secondary outcomes).

If a paper did not provide sufficient information about either study details or results, we contacted the study authors where possible.

Assessment of risk of bias in included studies

Three review authors (TD, EVL, MVD) independently assessed each included study using the Cochrane's tool for assessing risk of bias, described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion with co-authors (MP, TC). We assessed:

- random sequence generation;

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- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessors;
- incomplete outcome data;
- dropout/selective outcome reporting; and
- other potential sources of bias.

We judged each potential source of bias as high, low or unclear and provided a quote from the study report together with justification for our judgement in 'Risk of bias' tables. We summarised the risk of bias judgements across different studies for each of the domains listed. We reported the risk of bias using the 'Risk of bias' tool from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

In this update, we assessed bias related to blinding of participants and personnel separately from bias related to blinding of outcome assessment (Higgins 2016).

Measures of treatment effect

We entered data into RevMan 5 software for data analysis (Review Manager 2014). For continuous data, we calculated the mean difference (MD) if the same scale was used, or a standardised mean difference (SMD), which is the absolute mean difference divided by the pooled SD, if different scales were used to measure the same construct. We calculated a 95% confidence interval (CI) for each estimate. Dichotomous outcomes were reported as odds ratios (ORs). We pooled data reported as mean differences by using the inverse variance method as described in the *Cochrane Handbook for systematic Reviews of Interventions* (Higgins 2011).

Unit of analysis issues

Participants in randomised controlled trials (RCTs) was the unit of analysis.

Cross-over trials were included using the results from paired analyses, which adjust for within-individual comparisons (Elbourne 2002). The unit of analysis in Cohen-Mansfield 1999 was paired data for drug versus placebo at the end of intervention period 1 and intervention period 2. Different analysis for assessment of within-subject variable and between-subject variable were performed.

Dealing with missing data

We reported where data were missing from published reports. We contacted the original investigators to request missing data. If these data remained unavailable we analysed the available data. We used intention-to-treat (ITT) analyses where possible. Any statistical method used by the study authors (e.g. multiple imputation analysis, last observation carried forward) to deal with not-missing-at-random data was reported. If study authors reported outcomes for participants who completed the study, as well as carried forward or otherwise imputed data, we used the latter data for pooling.

Assessment of heterogeneity

We assessed heterogeneity in two ways. First, we explored the presence of heterogeneity at face value by comparing population groups, interventions or outcomes across studies. In the case of clear face value heterogeneity, we reported the outcomes of the studies narratively and did not pool the results. Meta-analysis was only performed when studies were sufficiently homogeneous in terms of participants, interventions, and outcomes. If there was no obvious clinical heterogeneity we used statistical tests such as the Cochran Chi² (Q) test and the I² statistic to determine the presence and level of statistical heterogeneity for each outcome. An I² value of 50% or higher was considered as significantly heterogeneous (Higgins 2011; Review Manager 2014).

Assessment of reporting biases

To minimise risk of publication bias, a comprehensive search was performed in multiple databases, including searching for unpublished studies. If more than 10 RCTs were identified, we planned to assess the existence of publication bias by constructing a funnel plot (Higgins 2011).

Data synthesis

Trials that did not report comparable outcomes were considered clinically heterogeneous and results were not pooled in meta-analysis. In this case, we performed critical interpretive synthesis of data from individual studies.

The duration of follow-up in trials varied considerably. If the range of follow-up was considered too large to pool results for meta-analysis, the data were divided into smaller time periods and separate meta-analyses were conducted for each period. The overall estimate was calculated using a fixed-effect model in the absence of statistical heterogeneity. In the presence of substantial statistical heterogeneity (I² value of 50% or higher), a random-effects model was used (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We conducted only one meta-analysis including two trials. We were therefore unable to analyse subgroups. We reported the results of subgroup analyses in the included studies.

Sensitivity analysis

We conducted no sensitivity analyses.

R E S U L T S

Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia (Review)

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Description of studies

See Characteristics of included studies; Characteristics of excluded studies; and Table 3.

Results of the search

Searches for this update identified 101 records after a de-duplication and first assessment performed by CDCIG information specialists; an ongoing study identified in the 2013 review was also assessed for inclusion. We removed 13 duplicate records (n = 89 records). We excluded 76 records following assessment of title and abstract (n = 13 full-text reports). Following assessment, we excluded 12 full-text articles that did not meet inclusion criteria (see Characteristics of excluded studies). We included one additional randomised controlled trial (RCT) involving 19 participants (Bergh 2011) for this update (Figure 2).

Figure 2.   Inclusions of trials of study flow diagram 2018
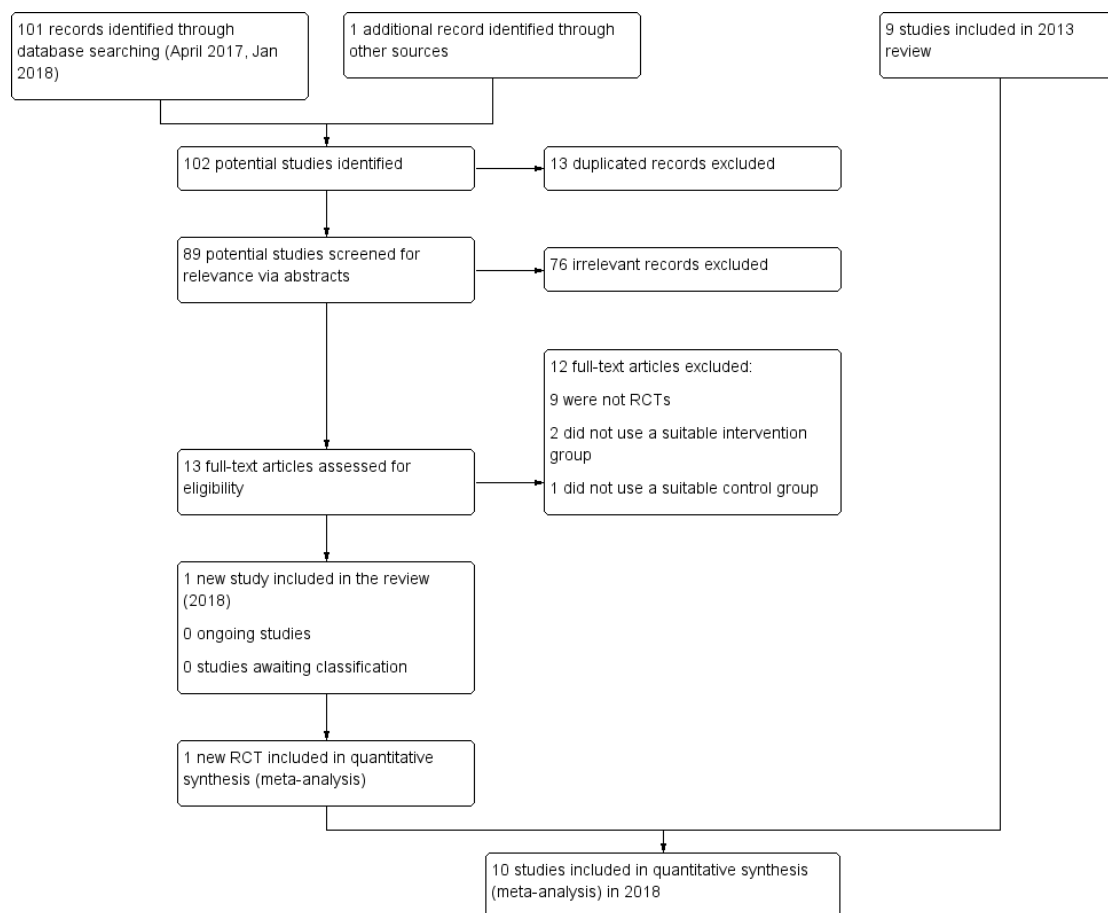
Included studies

The 2013 review (Declercq 2013) included nine studies (Ballard 2004; Ballard 2008; Bridges-Parlet 1997; Cohen-Mansfield 1999; Devanand 2011; Devanand 2012; Findlay 1989; Ruths 2008; van Reekum 2002). One additional study was added for this update (Bergh 2011). The 10 included studies involved a total of 632 participants (Characteristics of included studies; Table 3).

Overview

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The included trials were very diverse in terms of study participants (such as the case definition applied and the severity of dementia of the participants), types and dosages of antipsychotics used before withdrawal, exclusion criteria, interventions (i.e. method of discontinuation), outcomes, and times of assessment.

Design

Nine studies were parallel-group RCTs. One study was a crossover RCT (Cohen-Mansfield 1999).

Sample size

All 10 studies included small numbers of participants. Seven studies included fewer than 100 participants; three studies included between 100 and 200 participants (Ballard 2004; Ballard 2008; Devanand 2012).

Study setting

Eight studies included participants in nursing homes. One pilot study included participants with Alzheimer's disease and psychosis, agitation or aggression who were living in the community (Devanand 2011). One study included participants with Alzheimer's disease and psychosis, agitation or aggression who were living in the community or were residents of assisted-living facilities or nursing homes (Devanand 2012).

Participants

Clinical characteristics at baseline

See Characteristics of included studies

1. Age status at baseline

Participants' average age was 80 years or over in most studies.

2. Sex status at baseline

Most studies included higher proportions of female participants. Findlay 1989 recruited only female participants.

3. Dementia status at baseline

Different methods were used to diagnose dementia.
- Ballard 2004 and Ballard 2008 included only participants with Alzheimer's disease who fulfilled the National Institute of Neurological and Communicative Diseases and Stroke/

Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for possible or probable Alzheimer's disease.
- Bergh 2011 included participants with dementia due to Alzheimer's disease or vascular type or mixed type according to ICD-10 clinical criteria.
- Bridges-Parlet 1997 included residents with diagnoses of dementia or possible or probable dementia.
- Cohen-Mansfield 1999 had no explicit diagnostic standard for dementia; the study included nursing home residents aged over 70 years receiving haloperidol, thioridazine, and lorazepam. The study author confirmed by email that the residents participating in the study met the inclusion criteria dementia (Declerck 2009a [pers comm]).
- Devanand 2011 and Devanand 2012 included participants with diagnoses of dementia using DSM-IV and probably Alzheimer's Disease by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.
- Findlay 1989 included participants with Alzheimer's disease classified according to ICD-9 criteria, assessed by a consultant psychiatrist and based on medical history.
- Ruths 2008 included participants with diagnoses of dementia according to ICD-10 clinical criteria.
- van Reekum 2002 included participants with all forms of dementia based on chart review.

4. Cognitive status at baseline

At baseline, participants in most of the studies were described as having moderate to severe dementia. A variety of methods were used to measure baseline cognitive severity. Several studies had inclusion criteria based on cognitive severity at baseline.
- Ballard 2008 included participants with a Standardised Mini-Mental State Examination (SMMSE) score of 6 or a Severe Impairment Battery (SIB) score > 30.
- In Devanand 2011, study participants had SMMSE scores ranging from 5 to 26.
- Participants living in the community in the Devanand 2012 study had SMMSE scores of 5 to 26; participants residing in nursing homes had scores between 2 to 26.
- Cohen-Mansfield 1999 used the Brief Cognitive Rating Scale (BCRS) at baseline to determine participants' cognitive function without criteria.
- Findlay 1989 used the Cognitive Assessment Scale (CAS) for measuring cognitive status without criteria.
- There were no clear cut-off values reported to indicate the severity of cognitive status severity in seven studies (Ballard 2004; Bergh 2011; Bridges-Parlet 1997; Cohen-Mansfield 1999; Findlay 1989; Ruths 2008; van Reekum 2002.

5. Behavioural status at baseline

Several trials applied inclusion criteria based on severity of behavioural problems at baseline. This was not an inclusion criterion for this review.

- Ballard 2004 included participants with individual scores on the Neuropsychiatric Inventory (NPI) that were not higher than 7 at the time of evaluation.
- In Bridges-Parlet 1997, participants were selected by nurse supervisors who identified physically aggressive participants with dementia treated with antipsychotics.
- In the Devanand 2011 pilot trial, participants needed to have signs of psychosis, agitation or aggression or both to be included in the study. Psychosis was identified using the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD) and the Brief Psychiatric Rating Scale (BPRS) (psychosis factor of at least 4). Agitation and aggression was measured on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavioural Rating Scale for Dementia (score > 3 and present for at least 10 days per month, on one or more of the items for agitation, purposeless wandering, verbal aggression or physical aggression).
- Participants in the Devanand 2012 trial had scores on the NPI of 4 or more at both screening and baseline on the delusions or hallucinations subscale (psychosis score) or the agitation and aggression subscale (agitation/aggression score) (with scores on NPI subscales ranging from 0 to 12).
- Ruths 2008 included all potential participants regardless of individual neuropsychiatric symptoms (absent = 0, mild = 1, moderate = 2, severe = 3), providing a NPI-Q sum score ranging from 0 to 36.
- In van Reekum 2002, participants were included if they had "stable" behaviour.

Four studies (Ballard 2008; Bergh 2011; Cohen-Mansfield 1999; Findlay 1989) did not use severity of behaviour problems as a criterion for inclusion.

6. Global status at baseline

Several studies specified global functional status at time of inclusion in the study.

- In Ballard 2004, participants had Clinical Dementia Rating (CDR) Scale severity of stage 1 or greater.
- In Bergh 2011, inclusion was limited to Dementia Rating 1, 2 or 3 without further specification.
- van Reekum 2002 used the Clinical Global Impression scale (CGI) without further specifications.

No other studies reported measurements of global functioning at baseline.

Intervention

Antipsychotic treatments to be withdrawn and withdrawal schedules

The included studies used different antipsychotics at different dosages. Antipsychotics used were thioridazine, chlorpromazine, haloperidol, trifluoperazine (classified as 'typical antipsychotics') and risperidone or olanzapine (classified as 'atypical antipsychotics').

Three studies used an abrupt withdrawal schedule (Ballard 2004; Ballard 2008; Ruths 2008).

Two studies (Bridges-Parlet 1997; Devanand 2012) withdrew most participants abruptly from antipsychotic drugs, but used a tapering schedule when the baseline dose exceeded the equivalent of 50 mg of chlorpromazine. Bridges-Parlet 1997 did this by halving the baseline antipsychotic dose during week one and discontinuing the antipsychotic drug completely at the beginning of week two. In Devanand 2012, when the baseline dose was 2 mg risperidone or more daily, one-week tapering was used by means of a sequential double-blind placebo substitution (e.g. one 2 mg tablet of risperidone was switched to one 1 mg tablet and then to one placebo tablet).

The other studies used a tapering schedule.

- Most participants in Ballard 2008 were taking risperidone or haloperidol at variable dosages: participants were taking at least 10 mg chlorpromazine equivalents of a typical neuroleptic or at least 0.5 mg daily of risperidone. Dosages were defined as high, low, or very low:
  - very low: risperidone 0.5 mg daily, chlorpromazine 12.5 mg once daily, trifluoperazine 0.5 mg once daily; haloperidol 0.75 mg once daily;
  - low: risperidone 0.5 mg twice daily, chlorpromazine 12.5 mg twice daily, trifluoperazine 0.5 mg twice daily; haloperidol 0.75 mg twice daily; and
  - high: risperidone 1 mg twice daily; chlorpromazine 25 mg twice daily; trifluoperazine 1 mg twice daily; haloperidol 1.5 mg twice daily.
- Most participants in Ballard 2004 took risperidone or thioridazine at variable dosages. Participants used (mean ± SD dose): risperidone 1.3 mg ± 0.7 mg, thioridazine 38.0 mg ± 26.2 mg, haloperidol 0.9 mg ± 0.4 mg, trifluoperazine 3.0 mg ± 1.4 mg or chlorpromazine 20 mg (no SD value for chlorpromazine as there was only one person taking this drug).
- In Cohen-Mansfield 1999, participants took haloperidol, thioridazine and lorazepam at variable dosages (mean dosage haloperidol 1.34 mg, thioridazine 27.0 mg and lorazepam 0.94 mg, no SD given). The cross-over design of this trial led to a three-week dose-tapering period followed by seven weeks of placebo. After this placebo period, the placebo group was titrated back to the original dose and groups were switched for the procedure. Participants were withdrawn from antipsychotics

(haloperidol and thioridazine), and also from lorazepam, which is a benzodiazepine. Because of the dual drug cross-over design, it was difficult to interpret the results of this study.

- In Devanand 2011, participants in a community setting with Alzheimer's disease and symptoms of psychosis, agitation or aggression were included and treated with haloperidol in phase A. In phase B (discontinuation trial) only participants who responded well to haloperidol in phase A were included. Criteria for clinical response were minimum 50% reduction from baseline in the sum score of the three most prominent symptoms of psychosis, agitation or aggression, a sum score of 6 or less on these three items (range 0 to 18), and minimal or greater improvement on the Clinical Global Impression scale (CGI-C) rated only for symptoms of psychosis, agitation and aggression. Doses of haloperidol used in phase B varied (4 mg daily, 2 mg to 3 mg daily, 0.5 mg to 1 mg daily). According to these different dosages there was a two-week tapering period (4 mg daily switched to 2 mg daily for one week, 1 mg daily for the next week and then to placebo; participants on 2 mg to 3 mg daily switched to 1 mg daily for two weeks and then to placebo, and participants who received 0.5 mg or 1 mg daily were switched directly to placebo without a tapering period).

- In Devanand 2012, phase A participants were given flexible-dose risperidone for 16 weeks: risperidone therapy was initiated at a dose of 0.25 mg to 0.5 mg daily and could be increased to 3 mg daily, depending on the response and side effects. Participants who had a response in phase A entered phase B of the study (discontinuation trial with three regimens: continued risperidone therapy for 32 weeks (group 1), risperidone therapy for 16 weeks followed by placebo for 16 weeks (group 2) or placebo for 32 weeks (group 3)).

- Findlay 1989 used a half-dose reduction during the first week and a total placebo substitution over the next week. Original dosages that participants had been receiving were stable dosages between 10 mg and 100 mg thioridazine for at least two months.

- van Reekum 2002 did not define antipsychotic drug classes and included residents who had been taking typical or atypical antipsychotics for at least six months. In this study, all participants received a standard order for lorazepam (0.5 mg to 1.0 mg) on an as-needed basis for agitation. The study used a tapering schedule of two weeks in which original medication was halved for the first week and the remaining dose halved during the second week followed by a six-month study period.

- In Ruths 2008, participants were taking risperidone 1.0 mg (median; range 0.5 mg to 2.0 mg), olanzapine 5.0 mg (2.5 mg to 5.0 mg), and haloperidol 1.0 mg (0.5 mg to 1.5 mg).

- In Bergh 2011, all participants were taking risperidone at inclusion. The doses of the continuation group was determined by the participant's dose of antipsychotics prior to recruitment to the study. The study used a tapering schedule over one week for the discontinuation group. Participants received 50% of their original medication dose on day 1, reduced to 25% on day 4 and 12.5% on day 6 and fully discontinued on day 7. The mean dose at inclusion was risperidone 0.92 mg/day.

Outcome measures

Outcome measures were very diverse across included studies and therefore difficult to compare. We could not calculate a standardised mean difference (SMD) for any outcome when different scales were used, because we did not consider the scales to be measuring identical constructs.

Four studies reported outcomes as mean differences with SDs (Ballard 2004; Ballard 2008; Bergh 2011; Ruths 2008). Five studies (Bridges-Parlet 1997; Cohen-Mansfield 1999; Devanand 2011; Devanand 2012; van Reekum 2002) reported outcomes as means, but only three also reported SDs (Bridges-Parlet 1997; Devanand 2011; Devanand 2012). Findlay 1989 reported outcomes as means with a range and number of observations.

Primary outcomes

1. Success of withdrawal from antipsychotics in the short-term (4 weeks or less) and long-term (more than 4 weeks)

We defined successful withdrawal as ability to complete the study in the allocated study group (i.e. no withdrawal due to worsening of neuropsychiatric symptoms (NPS), or no relapse to antipsychotic drug use during the trial).

- Ballard 2004 and Ballard 2008 reported the participant flow in results sections and reasons for withdrawal from the study, for example, withdrawal because of behavioural deterioration. Unfortunately, relapse to antipsychotic drug use was not mentioned.

- Bridges-Parlet 1997 reported participants completing the study and relapse to antipsychotic drug use after completion of the trial.

- Cohen-Mansfield 1999 reported the participant flow in the results section and reasons why participants discontinued before study completion.

- Devanand 2011: phase B reported relapse using criteria of 50% worsening of the three target symptoms of psychosis, agitation and aggression, and a severity score ≥ 6 on these three items (range 0 to 18), and minimal or greater worsening on the Clinical Global Impression scale (CGI-C) (rated for psychosis, agitation and aggression). Time to relapse was also measured in Devanand 2011 phase B.

- Devanand 2012: phase B reported relapse using criteria of increase in the Neuropsychiatric Inventory (NPI) core score of 30% or more, or a 5-point increase from the score at the end of phase A, and a score of 6 (much worse) or 7 (very much worse) on the CGI-C scale. The NPI-core score is the sum of the

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subscale scores for agitation-aggression, hallucinations and delusions. The CGI-C scale ranged from 1 to 7, with higher scores indicating less improvement for overall psychosis, agitation or aggression.

- Findlay 1989 did not report withdrawal from the study in the text, but results can be extracted from the table.
- van Reekum 2002 reported early withdrawals from the study, but did not mention relapse to antipsychotic drugs.
- Ruths 2008 mentioned relapse of antipsychotic drug use after withdrawal from antipsychotic drugs.
- Bergh 2011 reported participant flow in the results section and reasons for withdrawal from the study, but relapse to antipsychotic drug use was not mentioned.

2. Behavioural and psychological symptoms (especially agitation, aggression and psychotic symptoms)

Behavioural and psychological symptoms (especially agitation, aggression and psychotic symptoms) were assessed by different scales across included studies:

- Behavioural and psychological symptoms measured with NPI and NPI-Q

Two trials using the Neuropsychiatric Inventory (NPI) or Neuropsychiatric Inventory Questionnaire (NPI-Q) score as a primary outcome performed NPI-subscore analysis (Ballard 2004; Ballard 2008).

Ruths 2008 assessed agitation as a subscore of the NPI-Q and Ballard 2004 assessed agitation as subscore of Neuropsychiatric Inventory (NPI) total score.

Only Devanand 2012 reported the effect on the NPI core score, that is, the sum of the NPI-subscale for agitation and aggression, hallucinations, and delusions.

The NPI covers 12 domains of behavioural and neurovegetative symptoms to assess outcome. Each subscore is rated on a 12-point scale, assessing severity (0 to 3) and frequency (0 to 4) of a domain, with a theoretical maximum of 144 (i.e. 12 x 12) (range 1 to 144). The NPI-Q (Neuropsychiatric Inventory Questionnaire) assesses only the severity of each of the same 12 domains (theoretically maximum of 36, range 0 to 36) and can be considered as a shorter version of the NPI.

Bergh 2011 used the primary endpoint changes in the Neuropsychiatric Inventory (NPI-10). The authors reported NPI-10, this assesses 10 items out of 12 NPI domains (no sleep/night time behaviour changes and no appetite/eating changes).

- Behavioural and psychological symptoms measured with other scales

Bergh 2011 used also the primary endpoint changes in Cornell Scale for Depression in Dementia (CSDD) (minimum score 0 and maximum score 38) assesses depressive symptoms of the participants with dementia. A score of 8 points and above is regarded as a sign of a depressive disorder, while a score of 13 and above is

regarded as a sign of a severe depressive disorder. The CSDD was divided into two subscales, mood (sadness, anxiety, pessimism, suicidal thoughts, poor self esteem and delusion) and non-mood (remaining 13 symptoms).

Bridges-Parlet 1997 used the physically aggressive behaviour scale (PAB) as the main outcome measure. The PAB scale assesses aggressive behaviour identified by type (coded by a barcode system). Five different types of behaviour are identified: hitting, biting, scratching, kicking and pushing. The study authors also assessed verbal aggressiveness, defined as an instance of speaking in an angry tone of voice, swearing or yelling in anger.

Cohen-Mansfield 1999 used behaviour and agitation measured by different scales. The primary outcome Brief Psychiatric Rating Scale (BPRS) assesses somatic concern, anxiety, emotional withdrawal, conceptual disorganisation, guilt feelings, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behaviour, motor retardation, uncooperativeness, unusual thought content, and blunted effect (scale 1 = not present to 7 = extremely severe). Agitation was measured with the Cohen-Mansfield Agitation Inventory scale (CMAI). This nurse-rated questionnaire consists of 29 agitated behaviours, each rated on a 7-point scale of frequency.

van Reekum 2002 used behavioural, cognitive, functional and extrapyramidal signs as outcome measures, but reported the BEHAVE-AD (Behavioural Pathology in Alzheimer's disease Rating Scale) measurements only in a figure (no means or SDs reported). Aggression was assessed by the ROAS scale (Retrospective Overt Aggression scale).

3. Presence or absence of withdrawal symptoms in the first four weeks after withdrawal

None of the studies assessed these specific outcomes although it is not easy to distinguish between a withdrawal phenomenon and a relapse of NPS.

4. Adverse events of antipsychotics

Total adverse events likely to be related to antipsychotic use, such as falls, extrapyramidal symptoms, cognitive dysfunction, metabolic changes (including weight gain and diabetes), cardiovascular events and others were not systematically reported in the included studies.

- Ballard 2008 measured parkinsonism using the Modified Unified Parkinson's Disease Rating Scale (M-UPDRS).
- Bridges-Parlet 1997 gave some attention to observations of tardive dyskinesia but no measurement scales were used. The entire study was based on direct observations by experienced personnel who were blinded to the assigned treatment.
- Cohen-Mansfield 1999 reported adverse events as secondary outcomes in a table (without reporting an SD), using

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the Abnormal Involuntary Movement Scale (AIMS): assessment of neurological and physical side effects associated with psychotropic drug use (9 items: e.g. movement of the face and oral cavity, extremities and trunk, global judgements of abnormal movements). A list of adverse effects (sedation, extrapyramidal reactions, orthostatic hypotension and anticholinergic effects) was provided to the nursing staff, who indicated frequency of occurrence. Nurse managers checked lists of psychomotor adverse effects, including 13 items describing pseudoparkinsonism, akathisia, acute dystonic reaction, and tardive dyskinesia.

• Devanand 2011 assessed somatic side effects with the Treatment Emergent Symptom Scale (TESS; range from 0 to 26, with higher scores indicating more somatic symptoms), extrapyramidal signs using the Unified Parkinson's Disease Rating Scale (UPDRS) and tardive dyskinesia with the Rockland Tardive Dyskinesia scale. No data were reported for the discontinuation trial.

• Devanand 2012 assessed extrapyramidal signs using the Simpson-Angus scale (range from 0 to 40, with higher scores indicating more extrapyramidal signs); tardive dyskinesia using the AIMS (range from 0 to 35, with higher scores indicating more severe symptoms) and general somatic symptoms developing during treatment using the TESS.

• Findlay 1989 provided additional information on mobility, range of mobility, transferring, response to chest pushing and balance and position sense, vibration sense, reading of a sway for participants standing with eyes open, systolic and diastolic blood pressure, and heart rate. Findlay 1989 reported lying and standing blood pressure and heart rate, the sum of the mobility outcomes, balance while standing, balance on turning head, balance on turning whole body through 360 °.

• van Reekum 2002 assessed extrapyramidal signs using the Extrapyramidal Symptom Rating Scale (ESRS).

• Bergh 2011 measured extrapyramidal adverse effects after prescription of antipsychotics using the M-UPDRS but these results were not reported.

2. Secondary outcomes

1. Cognitive function (e.g. short-term memory, frontal executive function, language)

• Ballard 2008 measured cognition using the SMMSE and the SIB, which was the main outcome for this trial. Frontal executive function was assessed by the FAS verbal fluency test, assessing phonemic verbal fluency. Language was assessed by using the Sheffield Test for Acquired Language Disorder (STALD receptive and STALD expressive skill).

• Cohen-Mansfield 1999, Devanand 2011 and Devanand 2012 assessed cognitive function using the MMSE. Devanand 2012 also used the Alzheimer's Disease Assessment Scale -

cognitive score (ADAS-cog, range from 0 to 70, with higher scores indicating worse cognition).

• Findlay 1989 assessed cognitive function with the Cognitive Assessment Scale (CAS) scored by a psychiatrist.

• van Reekum 2002 assessed cognitive function with the MMSE and the Mattis Dementia Rating Scale (MDRS).

2. Quality of life (QoL) of participants, carers, family of participants, or a combination

• Ballard 2004 scored QoL using Dementia Care Mapping (DCM) as a measure of participants' well-being. The method quantifies activity category codes, which are recorded every five minutes over a six hour period of observation during one day.

• Bergh 2011 assessed changes after 25 weeks on the Quality of Life - Alzheimer disease (QoL-AD) scale. The QoL-AD scale evaluates the quality of life of the patient using 13 items which are scored on a 4-point scale from 'bad' to 'excellent'.

3. Time, in days, until prescription of any psychotropic agent

Time, in days, until repeat prescription of any psychotropic agent with the exception of antipsychotics was not reported systematically. Only Ruths 2008 reported medication changes in a subgroup analysis.

4. Use of physical restraint

Only Bridges-Parlet 1997 reported use of physical restraint.

5. Mortality

Only Ballard 2008 and Devanand 2012 reported mortality. Mortality data in one of the two papers describing Ballard 2008 were reported at 12, 24 and 36 months follow-up after randomisation. Devanand 2012 assessed mortality at 16 weeks (4 months) and 32 weeks (8 months).

6. Other secondary outcomes
6.1. Global functioning

• Ballard 2008 reported global functioning with the BADLS (Bristol Activities of Daily Living Scale) and FAST (Functional Assessment Staging).

• Cohen-Mansfield 1999 reported residents' functioning as secondary outcomes by rating levels of activity and positive mood.

- Devanand 2011 assessed impairment in activities of daily living using the modified Blessed Functional Activity Scale (BFAS).
- Devanand 2012 assessed physical function with the use of the Physical Self-Maintenance Scale (PSMS; range from 1 to 30, with higher scores indicating worse functioning).
- van Reekum 2002 assessed functional outcome with the Blessed Dementia Scale (BDS).

6.2. Sleep

- Ruths 2008 (and subgroup analysis in Ruths 2004) and Bridges-Parlet 1997 reported effects on sleep.
- Cohen-Mansfield 1999 reported the effect on sleep and activity level (daytime sleep, time to fall asleep and activity level). Daytime sleep was an average of the items "How often does the resident appear drowsy or sleepy during the day?" and "How frequently does the resident actually sleep during the day?" Both items were rated on a frequency scale ranging from 1 (never) to 7 (several times an hour). Time to fall asleep was measured by "On the average, how long did it take the resident to fall asleep at night (from the time he/she went to bed until the time the resident fell asleep)?" and rated on a scale ranging from 1 (falls asleep immediately) to 6 (nearly never sleeps at night). Activity level was an average of 2 items: "How often did the resident participate in social activities?" and "How frequently was the resident involved in activities which is meaningful for his/her level of functioning?" and rated on a frequency scale ranging from 1 (never) to 6 (several times a day).

6.3 Clinical global impression

- Ballard 2008 reported clinical global impression using CGI-C (Clinical Global Impression-Change).
- Cohen-Mansfield 1999 reported clinical global impressions as secondary outcomes using the CGI-C scale.
- Findlay 1989 reported a psychiatric assessment using the Sandoz Clinical Assessment Geriatric Scale (SCAGS)
- In Devanand 2012, relapse was reported as a predefined deterioration on the NPI and the CGI-C. The CGI-C was also measured at different time points, but was not reported in the paper.

Co-variables

Only Ballard 2008 conducted a post hoc subgroup analysis by type of antipsychotic drug (typical versus atypical).

Time of assessment of outcome measurements

Outcomes were assessed at different times.
- Ballard 2004 assessed outcomes at three months.
- Ballard 2008 assessed outcomes in a first paper at 1, 3, 6 and 12 months: only the data assessed at six months were reported. Analysis at 12 months was limited to the two main

outcomes: cognitive function and neuropsychiatric features. In a second paper, Ballard assessed the outcome mortality at 12, 24 and 36 months (Ballard 2011). To pool the NPI data we asked Professor Ballard to provide data from the DART-AD study assessed at three months (Declerck 2009c [pers comm]). These data were extracted from the DART-AD database by Ly-Mee Yu from the Oxford Centre for Statistics in Medicine.
- Bridges-Parlet 1997 reported outcomes at one, two and four weeks.
- Cohen-Mansfield 1999, a cross-over study, reported that participants were assessed at five time points: one week after start of dosage tapering (week 1), phase one tapering (week 3), phase one end point (week 10), phase two tapering (week 13) and phase two end point (week 20). Results were reported as paired data for time points three and five (comparison of assessments of each phase in the cross-over study).
- Devanand 2011 assessed outcomes in phase B at 0, 2, 4, 8, 12, 16, 20 and 24 weeks.
- Devanand 2012: phase B assessed outcomes at 16 weeks (4 months) and 32 weeks (8 months).
- Findlay 1989 reported outcomes at two and four weeks.
- Ruths 2008 assessed outcomes at four weeks (1 month).
- van Reekum 2002 reported outcomes only in a figure from visit 1 (baseline) to visit 15 (6 months).
- Bergh 2011 reported outcomes at baseline and after 25 weeks.

Excluded studies

We excluded 12 studies for this update. Of these, eight were commentaries (Devanand 2013; Garner 2015; Gill 2013; Gnjidic 2013; Ling 2013; Lolk 2014; Power 2013; Renard 2014). Two studies did not investigate interventions that were relevant for this review (discontinuation of memantine (Ballard 2015) and discontinuation of antidepressants (Bergh 2012). Patel 2017 was not a randomised controlled trial (presented a post hoc analysis of Devanand 2012). Azermai 2013 did not use a suitable control intervention (it was a pilot study without a control group).
Five studies were excluded in the review 2013 (Other published versions of this review). Horwitz 1995; Westbury 2011; Wessels 2010 were excluded because these were not randomised controlled discontinuation trials. One trial was excluded because it analysed the Findlay 1989 cohort for outcomes that are not relevant to our review (McLennan 1992). Another study was excluded as it seems to be the registration of a not (yet) published (and perhaps still ongoing) trial and further searching did not reveal additional information about this trial (Rule 2003).
See Characteristics of excluded studies and Figure 2.

Risk of bias in included studies

We assessed risk of bias of included studies according to six specific domains using the Cochrane 'Risk of bias' assessment tool (Higgins 2011) (Figure 3; Figure 4).

Figure 3.   Risk of bias graph for the 10 included studies in the review.

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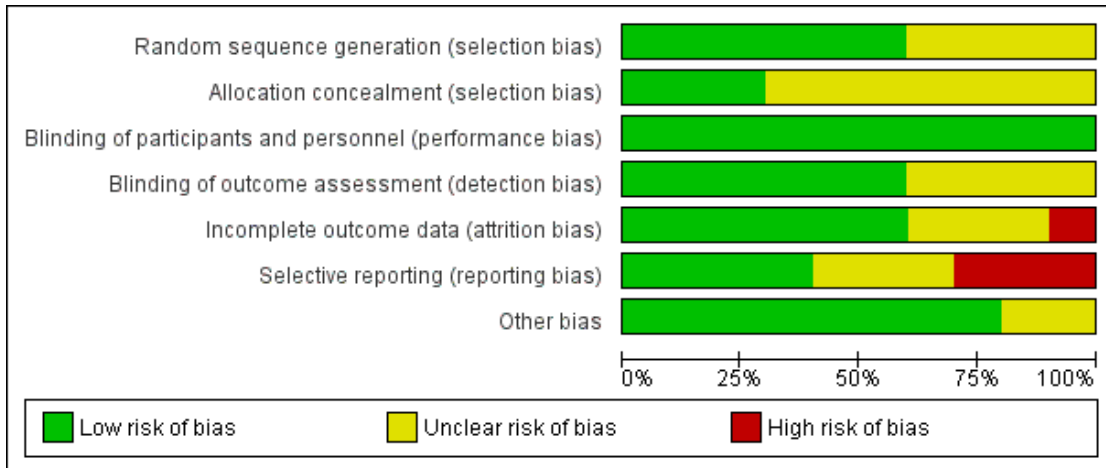**Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study in the review.**

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Most studies were assessed at low or unclear risk of bias. Only Ballard 2008 was assessed at low risk of bias for all domains. Bergh 2011 was judged to be at high risk of bias in two domains. Cohen-Mansfield 1999 and van Reekum 2002 were each assessed at high risk of bias in one domain. The most common unclear risk of bias domains were selection bias, detection bias, attrition bias and reporting bias.

See Characteristics of included studies.

Allocation

Randomisation sequence generation was described and adequate in six trials (Ballard 2008; Bergh 2011; Bridges-Parlet 1997; Devanand 2012; Ruths 2008; van Reekum 2002) and unclear in four trials (Ballard 2004; Cohen-Mansfield 1999; Devanand 2011; Findlay 1989).

Allocation concealment was only described in sufficient detail to assess the risk of bias as low in three studies (Ballard 2008; Bergh 2011; Devanand 2012). Risk of allocation concealment bias was unclear in seven studies (Ballard 2004; Bridges-Parlet 1997; Cohen-Mansfield 1999; Devanand 2011; Findlay 1989; Ruths 2008; van Reekum 2002).

Blinding

All included studies were double-blinded. The overall risk of performance bias was low. All studies adequately described methods of blinding participants and personnel. We assessed four studies (Devanand 2011; Findlay 1989; Ruths 2008; van Reekum 2002) at unclear risk of detection bias; information on blinding of outcome assessors was not reported. In these trials, there were several subjective outcomes, so a lack of blinding of outcome assessors could have had an influence.

Incomplete outcome data

Six trials reported the issue of incomplete outcome data, with no unequal numbers across the groups and with adequate reasons provided for dropouts and losses to follow-up (Ballard 2004; Ballard 2008; Bridges-Parlet 1997; Devanand 2011; Devanand 2012; van Reekum 2002). In Bergh 2011, attrition bias was judged as high risk due to the high dropout rate with unequal numbers across the groups (7 dropouts of 9 participants in the discontinuation group and no dropouts of 10 participants in the continuation group) and missing data. We considered the risk of incomplete outcome data bias to be unclear in three studies (Cohen-Mansfield 1999; Findlay 1989; Ruths 2008).

Selective reporting

We judged four studies at low risk of selective reporting bias (Ballard 2004; Ballard 2008; Bridges-Parlet 1997; Ruths 2008).

Findlay 1989 did not describe the primary outcome and was unclear if all outcomes were reported. In van Reekum 2002, some outcomes mentioned in the methods sections of the paper were not reported in the results. In Bergh 2011, an unpublished study, the authors reported that they did not perform an observed case analysis due to the high dropout rate and missing data. In Devanand 2012 the CGI-C data were not fully reported. Devanand 2011 and Devanand 2012 reported numeric data for several continuous outcomes at the time of randomisation into the discontinuation phase, but only dichotomous data at later time points. In Cohen-Mansfield 1999, outcome data were not reported separately for each medication discontinued in the trial (i.e. haloperidol, thioridazine or lorazepam).

Other potential sources of bias

It was unclear if participants in the two groups were similar in Ruths 2008. In the Findlay 1989 study there was a baseline imbalance between the placebo group and continuation group in one of the three cognitive/behavioural rating scales used to measure outcomes. It was unclear if this had an impact on the results.

Effects of interventions

See: **Summary of findings for the main comparison** Discontinuation compared to continuation of antipsychotic medication for behavioural and psychological symptoms in older people with dementia

We included 10 RCTs with 632 participants. However, although Cohen-Mansfield 1999 met inclusion criteria, we were unable to use any data from this study. Cohen-Mansfield 1999 did not report outcome data separately for the different medications discontinued in the trial (which included the benzodiazepine lorazepam as well as the antipsychotics haloperidol and thioridazine). We contacted the study author by for further data, but have not received a response (Declerck 2009b [pers comm]).

For all outcomes, our conclusions were based on studies that reported quantitative data, or on conclusions made by the study authors if data were not provided.

The result and the evidence quality for each outcome for the main comparison (discontinuation compared to continuation of antipsychotic drug use for behavioural and psychological symptoms in older participants with dementia) are described in Summary of findings for the main comparison.

Primary outcomes

1. Success of antipsychotic withdrawal

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We defined success of withdrawal as the ability to complete the study, i.e. no dropout due to worsening of neuropsychiatric symptoms (NPS) or no relapse to antipsychotic drugs use during the trial. This was not reported in any of the included studies. Several studies reported the number of participants completing and not completing the study, but did not report the number of participants who failed to complete the study due to worsening NPS or the number of participants who restarted antipsychotics. Therefore, we used the difference between groups in the number of non-completers of the study as a proxy for our primary outcome. However, we could not pool data because the studies were too heterogeneous clinically and there were considerable discrepancies in the way the success of antipsychotic withdrawal was measured.

Nine studies (575 participants) reported data relevant to this outcome (Ballard 2004; Ballard 2008; Bergh 2011; Bridges-Parlet 1997; Devanand 2011; Devanand 2012; Findlay 1989; Ruths 2008; van Reekum 2002).

In seven studies (446 participants) discontinuation of the antipsychotic made little or no difference to the ability of participants to complete the study (Ballard 2004; Ballard 2008; Bridges-Parlet 1997; Devanand 2011; Findlay 1989; Ruths 2008; van Reekum 2002).

In three studies (149 participants) there was some evidence in favour of the continuation group (Devanand 2011; Devanand 2012; Bergh 2011). Although Devanand 2011 reported no difference between groups in the numbers of participants leaving the study group early due to symptomatic relapse (a worsening of psychosis, agitation or aggression), the study also reported that time to a symptomatic relapse was shorter in the discontinuation group than in the continuation group. Devanand 2012 reported a higher rate of participants leaving the study group early due to symptomatic relapse in the discontinuation group compared with the continuation group and that discontinuation led to increased risk of symptomatic relapse (increase in the NPI-core score at 4 months and 8 months follow-up). Bergh 2011 reported a very high dropout rate (7 of 9 participants) in the discontinuation group compared to no dropouts (among 10 participants) in the continuation group.

We assessed the overall quality of the evidence for this outcome to be low, downgraded one level for indirectness, as not all included studies directly measured the outcome of our interest, and one level for risk of reporting bias. Several studies did not report the number of participants who failed to complete the study due to worsening NPS or the number of participants who relapsed to antipsychotic use.

In Ballard 2008, we extracted data from the study flow diagram on the same proxy outcome as reported in the pilot study of Ballard 2004 i.e. the number of participants not completing the study (based on intention-to-treat (ITT) analysis). In this study, there was a high number of participants not completing the study: 45/82 participants (56%) in the discontinuation group and 43/83 (51%) participants in the continuation group. Three participants

in the discontinuation group and four in the continuation group did not complete the study because their behavioural condition deteriorated. No difference between groups was reported. No data were reported for relapse to antipsychotic use.

Ballard 2004 reported the number of non-completers of the study based on ITT analysis and the proportion of participants developing pronounced behavioural symptoms. About a third (14/46, 30%) participants in the discontinuation group and 14/54 (26%) participants in the continuation group did not complete the study (P = 0.62). Six of 46 participants in the discontinuation and 5/54 participants in the continuation group did not complete the study due to behavioural deterioration (P = 0.55). In this study, there was no difference in completion rates between groups. No data were reported for relapse to antipsychotic use.

In Bergh 2011 there was a high dropout rate and imbalance between the discontinuation and continuation groups: 7/9 participants in the discontinuation group and 0/10 participants in the continuation group failed to complete the study. This could be interpreted as failure of completing the study in the discontinuation group due to worsening NPS. The study authors reported that results were inconclusive.

Bridges-Parlet 1997 reported the numbers of participants completing the four-week trial, the number of non-completers of the study due to increased NPS and also the number of participants relapsing to antipsychotic use. Two of 22 participants (9%) in the discontinuation group and 0/14 participants in the continuation group failed to complete the study. There was no difference in successful completion between groups (Chi² > 0.05). One non-completer experienced a pronounced increase in behavioural symptoms and was reverted to antipsychotic drug use.

Devanand 2011 reported the total number of participants not completing the study, the rate of leaving the study group early due to symptomatic relapse, and the time to symptomatic relapse. There was a higher rate of participants leaving the study group early due to symptomatic relapse in the discontinuation group (8/10, 80%) compared to the continuation group (4/10, 40%), but the difference in relapse rates between the groups was not statistically significant (Chi² = 3.3, P = 0.07). There was, however, a statistically significantly shorter time to relapse in the discontinuation group: mean 5.8 weeks (SD 6.7) in the discontinuation group compared to mean 8.0 weeks (SD 6.7) in the continuation group (Chi² = 4.1, P = 0.04). The severity of agitation or aggression in the open haloperidol treatment phase of the study did not predict the likelihood of symptomatic relapse in the discontinuation trial.

Devanand 2012 reported the total number of participants not completing the study and the rate of participants leaving the study early due to symptomatic relapse (an increase in the NPI-core score of 30% or more). During the first 16 weeks of the study (N = 110), 27/40 participants in the discontinuation group and 30/70 participants in the continuation group did not complete the study. The rate of participants leaving the study early due to symptomatic relapse (including relapse, imminent relapse, or mortality)

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was higher in the discontinuation group (24/40, 60%) than in the continuation group (23/70, 33%) (P = 0.004). The discontinuation group had an increased risk of leaving the study early due to symptomatic relapse compared with the continuation group (hazard ratio (HR) 1.94, 95% CI 1.09 to 3.45, P = 0.02). Crude (unstratified) rates of relapse at four months were 6.5 and 3.0 per 100 patient-weeks of follow-up for the discontinuation and continuation groups, respectively. During the subsequent 16 weeks (N = 40), 13/27 participants did not complete the study in the discontinuation group and 3/13 participants did not complete the study in the continuation group. The rate of participants leaving the study early due to symptomatic relapse was higher in the discontinuation group (13/27, 48%) than in the continuation group (2/13, 15%) (HR 4.88, 95% CI 1.08 to 21.98, P = 0.02). At eight months, crude rates of relapse were 4.3 and 1.1 per 100 patient-weeks of follow-up for the discontinuation and the continuation groups respectively. The total number of participants completing the eight months discontinuation trial was very low: 10/40 participants in the discontinuation group and 10/32 participants in the continuation group. No difference was reported by the study authors.

In Findlay 1989, all 36 participants (18 in each group) completed the four week study. We therefore assumed that no participants left the study early due to worsening NPS or relapsed to antipsychotic use.

The main outcome measure in Ruths 2008 was successful antipsychotic discontinuation, i.e. still off antipsychotics in the discontinuation group at the end of the one month study. In the discontinuation group 23/27 participants were still off antipsychotics. Four participants did not complete the study in the discontinuation group (4/27) and three participants did not complete the study in the continuation group (3/28) (P = 0.7). There were two non-completers in the discontinuation group due to behavioural deterioration.

van Reekum 2002 reported that 10/17 participants stopped the allocated treatment early in the discontinuation group and 6/17 stopped early in the continuation group (ITT analysis). The difference in the rate of early stopping between the groups was not significant (RR 1.57, 95% CI 0.76 to 3.26), nor was the difference in number of participants stopping early due to exacerbation of NPS (4/17 in the discontinuation group, 3/17 in the continuation group, P > 0.1.) There were no data on relapse to antipsychotic use.

2. Behavioural and psychological symptoms

Seven studies (519 participants) contributed data for this outcome (Ballard 2004; Ballard 2008; Bergh 2011; Bridges-Parlet 1997; Devanand 2012; Ruths 2008; van Reekum 2002).

Two studies (265 participants) used the NPI to assess NPS and were considered suitable to pool for meta-analysis (Ballard 2004; Ballard 2008). There was little or no difference in NPS between

groups after three months (negative values favour discontinuation): MD -1.49, 95% CI -5.39 to 2.40; participants = 194; studies = 2 (Analysis 1.1 and Figure 1). Initially, assessments of the NPI scores in these two Ballard studies were not made at the same time (Ballard 2004 assessed at three months and Ballard 2008 assessed at 1, 3, 6 and 12 months, but data in the publication were only available for six months). With the permission of Clive Ballard and the help of Ly-Mee Yu we calculated means and mean differences from individual participant data of the DART-AD trial for the NPI score at three months using SPSS software (Declerck 2009c [pers comm]).

We could not pool data from five studies because they were clinically too heterogeneous (different outcomes, different outcome scales, different time of follow-up) or reported insufficient data. However, results from these five studies (254 participants) also suggested that discontinuation may make little or no difference to NPS (Bergh 2011; Bridges-Parlet 1997; Devanand 2012; Ruths 2008; van Reekum 2002).

Overall, we considered the quality of evidence relating to this outcome to be low, downgraded one level for imprecision due to the wide confidence interval and small number of participants and one level for risk of reporting bias (study authors' conclusions were not supported with reported data in four studies).

Subgroup analyses of Ballard 2004 and Ballard 2008 suggested that the effect of antipsychotic discontinuation may differ depending on the severity of NPS at baseline. Ballard 2004 reported that some participants with less severe NPS (NPI score $\leq$ 14) may benefit from discontinuation of antipsychotics in terms of agitation (a subscore of the NPI). Ballard 2008 and Ballard 2004 suggest that some participants with more severe NPS (total NPI > 14) may benefit from continuing antipsychotic treatment.

Behavioural and psychological symptoms measured with versions of the NPI

Pooled studies

There was no difference between groups in change on the NPI total score after three months in Ballard 2004 or the key psychiatric/behavioural factors of agitation, mood and psychosis. Results were reported for on-treatment-analysis only (i.e. all participants who completed the study).

In the subgroup of participants with baseline NPI scores at or below the median ($\leq$ 14) there was a trend that the discontinuation group was less likely to develop pronounced behavioural or psychiatric symptoms (Chi² = 3.6; P = 0.06) although there was no difference in the total NPI score between groups (Mann-Whitney U test z = 1.7; P = 0.9). A pronounced behavioural problem was defined as a score of 8 or above on an individual item of the NPI (Declerck 2009c [pers comm]). There was a greater reduction of agitation (a subscore of the NPI) in the discontinuation group:

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1.0 point (SD 3.1) improvement in the discontinuation group and 1.5 point (SD 2.5) deterioration in the continuation group (Mann-Whitney U test z = 2.4; P = 0.018).

A subgroup of participants with higher baseline NPI scores (> 14) were more likely to develop pronounced behavioural problems if antipsychotics were discontinued (Chi² = 6.8; P = 0.009). There were no differences in total NPI score (Mann-Whitney U test z = 0.34; P = 0.73) or agitation (Mann-Whitney U test z = 0.82; P = 0.38).

In the Ballard The DART-AD Trial 2008 there was no difference between groups in the estimated mean change in NPI scores between baseline and six months. However, there was a significant difference between groups in the estimated mean change in NPI scores between baseline and 12 months. Results are reported for the modified intention-to-treat (mITT) analysis (i.e. only participants who had at least one dose of treatment were included in the analysis).

For all participants, there was no clear difference between groups in the estimated mean change in NPI scores between baseline and six months: 4.5 points (SD 17.6) deterioration for the discontinuation group (N = 53) compared to 1.3 points (SD 15.5) deterioration for the continuation group (N = 56); estimated mean difference in NPI change (favouring continue treatment) 2.4, 95% CI -8.2 to 3.5, adjusted for baseline value: P = 0.4.

For participants with baseline NPI ≤ 14, the change in NPI over six months was very similar between groups (estimated mean difference in NPI change 0.49, 95% CI -5.63 to 6.60).

For participants with baseline NPI ≥ 14, there was no clear difference between groups in the estimated mean change in NPI scores between baseline and 6 months (estimated mean difference in NPI change -5.33, 95% CI -15.82 to 5.17).

For all participants, continuation leads to small advantages at 12 months for those who continued antipsychotics: 11.4 points (SD 17.7) deterioration in the discontinuation group (N = 31) compared to 1.4 points (SD 22.1) deterioration in the continuation group (N = 28); estimated mean difference in NPI change (favouring continuation group) -10.9, 95% CI -20.1 to -1.7, adjusted for baseline: P = 0.02. Over 12 months there was a large amount of missing data, which could limit the validity of the results.

For participants with baseline NPI ≤ 14, there was no clear difference between groups in the estimated mean change in NPI scores between baseline and 12 months: estimated mean difference in NPI change (favouring continuation of treatment) -5.2, 95% CI -15.8 to 5.4.

For participants with baseline NPI > 14, continuation lead to advantages at 12 months for those who continued on antipsychotics: estimated mean difference in NPI change (favouring the continuation group) -16.9, 95% CI -32.5 to -1.2. The study authors mentioned that the test for interaction (although underpowered) was not significant (P = 0.2) and therefore concluded there was no evidence of interaction between treatment group and severity of symptoms at baseline (Ballard 2008).

Studies that could not be pooled

Bergh 2011 reported NPI-10 as a primary outcome, measuring 10 of the 12 NPI items, but without a score for sleep/nighttime behaviour and appetite/eating changes. The mean total score for the NPI-10 decreased by 3.50 (SD 13.53) in the discontinuation group and decreased by 5.40 (SD 10.78) in the continuation group (P = 0.76).

Devanand 2012 measured and reported the NPI core score for both groups at baseline and at the time of randomisation, and measured but not reported at later time points, although change in the NPI core score was used to define relapse. The study authors reported that the total NPI score at baseline did not predict a relapse during the first 16 weeks of phase B and that the presence of psychosis at baseline or randomisation did not predict a relapse after discontinuation of risperidone.

Ruths 2008 used the NPI-Q, which measures severity but not frequency of NPS, as a primary outcome. The NPI-Q scores were reported for all 55 participants at one month follow-up. Changes from baseline did not differ significantly between groups for total NPI-Q scores, or the 12 individual symptoms of the NPI, or the agitation subscore. There was no difference between groups in the number of participants whose NPI-Q scores remained stable or decreased (18/27 in the discontinuation group, 24/28 in the continuation group, P = 0.18). Participants with behavioural deterioration after antipsychotic cessation used higher daily drug doses at baseline (P = 0.042).

van Reekum 2002 used the NPI as an outcome but did not report data in the paper. The study authors reported no conclusions relating to NPI score.

Behavioural and psychological symptoms measured with other scales

We could not pool data from any of the studies using other scales to assess behavioural and psychological symptoms.

Bergh 2011 reported depression measured with the CSDD. They found no evidence of a difference between groups. The mean change from baseline to 25 weeks on the CSDD was a small deterioration of 5.83 points (SD 36.40) in the discontinuation group and a small improvement of 5.30 points (SD 11.25) in the continuation group (P = 0.375).

Bridges-Parlet 1997 concluded there was no difference between continuation and discontinuation groups in observed instances of physically aggressive behaviour: discontinuation group 1.27 (SD 3.95) versus continuation group 4.50 (SD 8.83), P > 0.05. Verbally aggressive behaviour was reported not to differ significantly between groups, although no data were provided to support this conclusion made by the study authors.

van Reekum 2002 reported no statistically significant difference in BEHAVE-AD (measuring behaviour) and ROAS (measuring physical aggression towards themselves or others) scores between the discontinuation and continuation groups (P > 0.05). The dis-

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continuation group showed more apathy than the continuation group (P = 0.04). However, not all of the study authors' conclusions were supported by data reported.

3. Presence of withdrawal symptoms or withdrawal syndrome in the first four weeks after withdrawal

No studies reported withdrawal symptoms or withdrawal syndrome in participants who discontinued antipsychotics.

4. Adverse events

Five studies (381 participants) (Ballard 2008; Bridges-Parlet 1997; Devanand 2012; Findlay 1989; van Reekum 2002) contributed data on adverse events. Devanand 2011 reported adverse events only for the initial phase of open treatment with haloperidol and not for the discontinuation phase. None of the studies systematically reported all adverse and serious adverse events. Studies reported only a selection of adverse events such as parkinsonism, movement disorders, falls, mobility, balance, extrapyramidal symptoms, heart rate and blood pressure. We could not pool data because of the diverse ways adverse events were assessed.

Discontinuation may make little or no difference to adverse events (Devanand 2012; Ballard 2008; Bridges-Parlet 1997; Findlay 1989; van Reekum 2002). Overall, we considered the quality of evidence for this outcome to be low, downgraded one level for indirectness because only a selection of adverse events was systematically assessed and one level for risk of bias because there was a high dropout in two studies (Ballard 2008; Devanand 2012) and risk of reporting bias (no data were provided to support the authors' conclusions in two studies).

Ballard 2008 measured change in severity of parkinsonism from baseline to six months using the MUPDRS. There was a small 0.4 point (SD 3.2) improvement in the discontinuation group and a small 0.8 point (SD 4.1) deterioration in the continuation group. The study authors reported that this difference was not statistically significant: estimated mean difference (favouring placebo): 1.1, 95% CI 0.4 to 2.6, adjusted for baseline value: P = 0.1. This may be due to the small sample size and high dropout.

Bridges-Parlet 1997 reported that three participants in the discontinuation group experienced adverse events (2 participants had behaviour deterioration and 1 had tardive dyskinesia). There were no adverse events reported for the continuation group.

In Devanand 2012 all adverse events (extrapyramidal signs, akathisia or restlessness, sedation, insomnia, confusion, agitation-aggression, falls, nausea or vomiting and other) and serious adverse events (death, cardiovascular event, neurologic event, agitation-aggression, pulmonary event, fall or fracture and other) were reported in a separate table, and an expanded version of this table was provided in the Supplementary appendix. Only this study assessed falls. A serious adverse event was defined as an adverse event that resulted in any of the following outcomes: death, a life-threatening

condition, hospital admission or prolongation of hospital stay or an unexpected event leading to clinically significant disability or incapacity. There were no differences in rates of serious adverse events, adverse events and death. There was no difference in adverse events measured with the Simpson-Angus, AIMS, TESS, although comparisons were based on small numbers of participants, especially during the final 16 weeks and on truncated observation period for adverse events in the case of participants who had an early relapse. No data for difference between groups was reported. Findlay 1989 reported numerical data for mobility, range of mobility, transferring, response to chest pushing and balance and position sense, vibration sense, reading of a sway for the participants standing with eyes open, systolic and diastolic blood pressure and heart rate, lying and standing blood pressure and heart rate, the sum of the mobility outcomes, balance while standing, balance on turning head, balance on turning whole body through 360 °. Only means, ranges and numbers of observations were reported for each of these outcomes. The study authors concluded that discontinuation had no apparent effect on mental function, mobility or balance, and that the drugs had few side effects.

van Reekum 2002 assessed extrapyramidal signs using ESRS, but reported results for this outcome only at baseline and not at the end of the study. The study authors concluded that both groups scored similarly on the assessment measures. The data to support this conclusion were not reported.

Secondary outcomes

1. Cognitive function

We included five studies (365 participants) for this outcome (Ballard 2008; Devanand 2011; Devanand 2012; Findlay 1989; van Reekum 2002). Outcome measures differed across studies and we could not pool data for this outcome.

Discontinuation may make no difference to cognitive function (Ballard 2008; Devanand 2011; Devanand 2012; Findlay 1989; van Reekum 2002). However, one trial found that discontinuation improves measures of verbal fluency (Ballard 2008). Overall, we assessed the quality of the evidence for this outcome to be low, downgraded one level for imprecision (no meta-analysis and most included studies had few participants) and one level for risk of reporting bias (no data were provided to support the authors' conclusions in 4 studies).

Ballard 2008 reported four outcomes measuring aspects of cognitive function. One outcome, the FAS, measuring verbal fluency, favoured the discontinuation group after six months: the estimated change in FAS totals between baseline and six months was a 0.6 point (SD 6.2) improvement in the discontinuation group and a 3.2 points (SD 6.6) deterioration in the continuation treatment group: estimated mean difference (favouring discontinuation) -4.5, 95% CI -7.3 to -1.7, adjusted for baseline: P = 0.002. For the

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main outcome, the SIB, used to assess overall cognition, there was no evidence of a difference between groups. The mean change from baseline to six months was a deterioration of 5.7 points (SD 14.2) in the discontinuation group and a deterioration of 6.2 points (SD 16.0) in the continuation group (estimated difference -0.4, 95% CI -6.4 to 5.5, adjusted for baseline: P = 0.9). For the SMMSE, used to assess overall cognition, there was also no evidence of a difference between groups. The mean change from baseline to six months for the SMMSE was a deterioration of 1.0 point (SD 4.2) in the discontinuation group and a deterioration of 1.8 point (SD 3.6) in the continuation group (estimated MD -1, 95% CI -2.7 to 0.7, adjusted for baseline: P = 0.2). For the STALD (receptive), used to assess receptive language skills, there was no evidence of a difference between the continuation and discontinuation groups. The mean change in STALD scores was 0.3 points (SD 2.1) deterioration for the discontinuation group and a 0.5 point (SD 1.7) deterioration for the continuation group: estimated MD -0.2, 95% CI -1.1 to 0.6, adjusted for baseline value: P = 0.6. For the STALD (expressive), used to assess expressive language skills, there was no clear evidence of a difference between the continuation and discontinuation groups. The mean change in receptive language scores between baseline and six months was a 0.2 point (SD 2.5) improvement in the discontinuation group and a 0.6 point (SD 1.8) deterioration in the continuation group: estimated MD -1.0, 95% CI -2.0 to 0.04, adjusted for baseline: P = 0.06.

In Devanand 2011 the study authors reported that cognition measured by change in MMSE did not differ by treatment group in phase B. No data were provided to support this conclusion. MMSE cognitive scores were measured and reported only at baseline (phase A) and at time of randomisation into phase B, and measured but not reported at other time points or at the end of the study.

In Devanand 2012 the study authors reported that the changes in MMSE and ADAS-cog score did not differ between the continuation and discontinuation groups. Data were not reported to support these conclusions. Total MMSE and ADAS-cog scores were measured and reported only at baseline of the open risperidone treatment and at the time of randomisation into the discontinuation trial and measured but not reported at other time points or at the end of the study.

Findlay 1989 concluded there was no difference in cognitive function measured by CAS over a four-week study period. Outcomes were reported only as means with a range and number of observations. However, the difference between the discontinuation and continuation groups at baseline could have influenced the result.

van Reekum 2002 concluded there was no difference between the continuation and discontinuation groups in cognition, measured by MMSE and MDRS. Data were not reported to support these conclusions.

2. Quality of life of participants, carers, families or a

combination

Quality of life was reported in two studies (119 participants) (Ballard 2004; Bergh 2011). We could not pool data because different outcome measures were used.

There may be no difference in quality of life between groups, but we considered the quality of the evidence for this outcome to be low, downgraded one level for imprecision and one level for risk of bias (high risk of attrition bias and reporting bias in Bergh 2011). There was no clear evidence of a difference between groups in well-being measured by Dementia Care Mapping in Ballard 2004. There was a small improvement in well-being (mean -0.18 (SD 1.72)) in the discontinuation group and a slight worsening (mean 0.35 (SD 2.41)) in the continuation group (MD -0.53, 95% CI -1.42 to 0.36).

Bergh 2011 reported there were no statistically significant differences in QoL-AD between groups. No data were provided to support this conclusion.

3. Time, in days, until repeat prescription for any psychotropic or any antipsychotic agent

Time in days until repeat prescription for any psychotropic or any antipsychotic agent was reported for a subgroup 30 participants in one nursing home. Ruths 2008 reported that standing orders for antidepressants, hypnotic and anxiolytic medications remained unchanged for all participants during the intervention, but did not provide supporting data. We considered this to be very low-quality evidence, downgraded one level for imprecision (single study with a small number of participants) and two levels for risk of bias (unclear risks of selection, detection bias and reporting bias; no data provided to support conclusion).

4. Use of physical restraint

Use of physical restraint was reported as an outcome in Bridges-Parlet 1997 (36 participants). The study authors reported no difference in time being restrained between the discontinuation and continuation groups, but provided no supporting data. We considered the quality of this evidence to be very low, downgraded one level for imprecision (single study with a small number of participants) and two levels for risk of bias (no data reported to support conclusion and unclear risk of selection).

5. Mortality

Mortality was reported as an outcome in two studies (275 participants) (Ballard 2008; Devanand 2012). We could not pool data due to heterogeneity of the outcome measures. It was not possible to draw conclusions about the effect of discontinuation on mortality because of the very low-quality of the evidence, downgraded one level for imprecision (small numbers of participants and events in both studies) and two levels for risk of attrition bias (high dropout in both studies).

Ballard reported mortality data as *cumulative probability of survival* at 12, 24 and 36 months in a long-term follow-up for participants randomised in the 12 month discontinuation trial (Ballard 2008). In a mITT analysis including participants who received at least one dose of treatment, there was no evidence of a difference between groups. The cumulative probability of survival during the first 12 months was 70% (95% CI 58% to 80%) in the continuation group compared with 77% (95% CI 64% to 85%) in the discontinuation group. The small sample size meant a lack of power to detect differences. The difference between groups in cumulative survival rate became more pronounced after the 12 month randomised phase of the trial. The cumulative survival rate was higher in the discontinuation group (71%) compared to the continuation group (46%) after 24 months follow-up, and also higher in the discontinuation group (59%) compared to the continuation group (30%) after 36 months follow-up (reported as a significant difference between groups, no further details reported). Due to high dropout and uncertainty about the use of antipsychotics, Ballard 2008 reported that the lower mortality in the discontinuation group should be interpreted with caution. The survival rates were similar in additional analyses that focused on the participants who continued their allocated treatment for at least 12 months.

In Devanand 2012 mortality measured after 16 and 32 weeks did not differ between the continuation and discontinuation groups. Three deaths (1 in the discontinuation group and 2 in the continuation group) occurred during the discontinuation trial. There were small numbers of participants, especially during weeks 16 to 32.

6. Other secondary outcomes

6.1 Global functioning

We included four studies (329 participants) for this outcome (Ballard 2008; Devanand 2011; Devanand 2012; van Reekum 2002). Outcome measures differed among included studies and data could not be pooled for this outcome.

Discontinuation may make no difference to global functioning. Overall, we assessed the quality of the evidence for this outcome to be low, downgraded one level for imprecision (studies with small numbers of participants) and one level for risk of reporting bias in three studies.

In Ballard 2008 global function assessed with the BADLS showed no clear difference between continuation and discontinuation groups: there was an improvement in function of 0.2 points (SD 7.2) in the discontinuation group and an improvement of 1.8 points (SD 8.9) in the continuation group. However there was no difference between groups (estimated MD 1.7, 95% CI -1.2 to 4.6, adjusted for baseline: P = 0.2). For the change on FAST, which measures global outcome, there were no differences between the

continuation and discontinuation groups in terms of the dementia stage (P = 0.9).

Devanand 2011 reported no evidence of a difference in BFAS scores between the continuation and discontinuation groups in phase B, although the supporting data were not reported.

Devanand 2012 reported no evidence of a difference in physical function between groups on the Physical Self-Maintenance Scale, although the supporting data were not reported.

van Reekum 2002 concluded that discontinuation of antipsychotics did not lead to differences between groups on the BDS, measuring activities of daily living and motivational behaviour. Supporting data were not provided.

6.2 Sleep

We included two studies (66 participants) for this outcome (Bridges-Parlet 1997; Ruths 2008). Outcome measures differed and we could not pool data for this outcome.

Discontinuation may make no difference to sleep (Bridges-Parlet 1997; Ruths 2008). Overall, we assessed the quality of evidence for this outcome to be low, downgraded one level for imprecision (only 2 studies with few participants) and one level for risk of bias (conclusions were from subgroup analyses and there was a risk of reporting bias in Ruths 2008).

In a subgroup of the Ruths 2008 study, sleep was measured by actigraphy in 30 participants over four weeks. Abrupt discontinuation of antipsychotics was associated with slightly reduced average sleep efficiency from 86% to 75% (i.e. 54 minutes less sleep), but there was no difference between groups (P = 0.29).

In Bridges-Parlet 1997, the study authors reported no difference in time sleeping between treatment groups. No data were provided to support the conclusion.

6.3 Clinical global impression

We included three studies (311 participants) for this outcome (Ballard 2008; Devanand 2012; Findlay 1989). Outcome measures differed among included studies and we could not pool data for this outcome.

Based on these three studies, we are uncertain whether discontinuation improves clinical global functioning. Overall, we assessed the quality of the evidence for this outcome to be low, downgraded one level for imprecision (small number of participants) and one level for risk of reporting bias (data not provided to support conclusion in either study).

In Ballard 2008, there was no evidence of differences between the continuation and discontinuation groups in clinical global impression rated on the CGI-C (P = 0.9).

Findlay 1989 reported no difference in global impression using the Sandoz Clinical Assessment Geriatric Scale (SCAGS). Authors' conclusions were not supported with extractable data; results were given only as means, ranges and numbers of observations.

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In Devanand 2012, the CGI-C was also measured at different times, but assessment at the end of the discontinuation trial was not reported in the paper, although this score was a criterion of the predefined threshold score for relapse in the discontinuation trial. No conclusions were made by the study authors.

Covariables

In a post hoc analysis reported in Ballard 2008 (N = 100, follow-up 3 months) there was no indication of a difference between participants taking typical or atypical antipsychotics. Most participants were taking risperidone or haloperidol; the number of participants taking other drugs was too small for any meaningful comparison.

DISCUSSION

Summary of main results

We included 10 studies that included a total of 632 participants. One new trial was added for this update (19 participants).

Our conclusions for all outcomes were based on studies that reported quantitative data, or on conclusions made by the study authors if data were not provided.

Pooling was only possible for behavioural outcomes assessed by Neuropsychiatric Inventory score (NPI) and not possible for all other outcomes due to the clinical heterogeneity of the studies, and considerable discrepancies in the ways outcomes were measured. The results and quality of evidence assessment for each outcome in the main comparison (discontinuation compared to continuation of antipsychotic drug use for behavioural and psychological symptoms in older participants with dementia) are described in Summary of findings for the main comparison.

Primary outcomes

Our predefined outcome success of withdrawal was not reported in the included studies. Therefore, we used the difference between groups in the number of non-completers of the study as a proxy for our primary outcome. Low-quality evidence in seven studies suggests little or no overall difference in the ability of participants to complete the study. However, in two studies of participants with psychosis, aggression or agitation who had responded to antipsychotic treatment, we found there may be a benefit from continuing antipsychotics. One small study reported that a high proportion of participants in the discontinuation group failed to complete the study.

We found low-quality evidence in two pooled studies and five non-pooled studies for the outcome behavioural and psychological symptoms. In the two pooled studies, there was no difference in NPI scores between groups. In five non-pooled studies, discontinuation may make little or no difference in scales measuring overall behaviour and psychological symptoms between groups. The two pooled studies performed subgroup analyses according to baseline NPI-score ($\leq$ 14 or > 14). In one study, some participants with milder symptoms at baseline were less agitated at three months in the discontinuation group. Both studies suggest that participants with more severe neuropsychiatric symptoms (NPS) (total NPI above 14) may benefit from continuing antipsychotic treatment. No studies reported withdrawal symptoms.

Low-quality evidence from five studies suggested discontinuation may make little or no difference in adverse events between groups.

Secondary outcomes

Low-quality evidence from five studies suggested discontinuation may make no difference to cognitive function. However, one trial found that discontinuation improved measures of verbal fluency. Low-quality evidence from two studies indicated there may be no difference in quality of life between discontinuation and continuation group participants.

It remains unclear if discontinuation reduced time to repeat prescription of any psychotropic or antipsychotic agent (1 study) or discontinuation increased use of physical restraint (1 study).

We found low-quality evidence that discontinuation may make no difference to global functioning (4 studies), in sleep (2 studies) and clinical global functioning (3 studies).

Based on very low-quality evidence from two studies, It was not possible to draw conclusions about the effect of discontinuation on mortality.

Overall completeness and applicability of evidence

The main limitation of this review was the lack of consistency regarding study participants (such as the case definition applied and the severity of dementia of the participants), types and dosages of antipsychotics used before withdrawal, exclusion criteria, interventions (i.e. method of withdrawal), outcomes, and times of assessment among the individual studies.

We included all types and grades of dementia severity, regardless of the method of diagnosis. This reflects the current situation in clinical practice where many nursing home residents with dementia are not formally diagnosed. We believe that including all potential participants will make the review findings as widely applicable as possible.

It is possible that the profile of the original symptoms (i.e. a specific cluster of NPS) for which the antipsychotics were prescribed influenced the assessed outcome. Therefore, it would be useful to know why the antipsychotics were prescribed. Devanand 2011 and Devanand 2012 tried to overcome this problem by including

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only participants with symptoms of psychosis, agitation or aggression who had responded to antipsychotic treatment.

Most of the available evidence only applies to nursing home residents or to people in long-stay psychogeriatric or geriatric wards (i.e. hospital setting). Only one small pilot study and its larger subsequent trial included participants living in the community (outpatients). Therefore, the results of this review may not be applicable to community settings.

Adverse events, withdrawal symptoms or syndromes, initiation of other psychoactive drug use after withdrawal and baseline antipsychotic dose were not systematically reported. Consequently, the effect of these on clinical outcomes is unknown, which is a major gap in the evidence. It was not possible to draw conclusions about the comparative efficacy of a tapered withdrawal schedule or abrupt withdrawal.

This review assessed the effect of antipsychotic withdrawal only. The results cannot be extrapolated to other drug types which may be prescribed for NPS in dementia and which are also potentially inappropriate or harmful, such as benzodiazepines.

Quality of the evidence

Overall, data on the effect of withdrawal of antipsychotics in older participants with dementia and NPS remain very sparse. We summarised the quality of evidence for comparisons in Summary of findings for the main comparison. Evidence for all outcomes was low- or very low-quality. The reasons for downgrading were imprecision, risk of bias and indirectness.

Limitations in study design or execution

Many included studies had methodological limitations. Only one RCT was assessed at low risk of bias for all domains (Ballard 2008). In almost half of the studies, there was insufficient information on random sequence generation or allocation concealment or both. Participants and personnel were blinded in all studies, but information on blinding of outcome assessment was unclear for four studies, although we thought this was unlikely to seriously alter the results. One study had a high dropout rate with imbalance between groups which could influence the results. Three studies were identified as having a potential risk of reporting bias, although most results reported were negative, suggesting they were not tending to favour the reporting of positive results. We judged three studies to be at high risk of reporting bias, possibly influencing results. Because of these limitations, we downgraded the level of evidence by one or two levels for risk of bias.

Mortality outcomes were measured in two studies from four months to 12 months (Ballard 2008; Devanand 2012). In a long-term follow-up of 36 months, after the 12 months randomised discontinuation trial, we were uncertain whether discontinuation led to a decreased mortality (Ballard 2008). These two studies were

possibly too short-term to detect an effect of discontinuation of antipsychotics on mortality rates.

Other limitations of study design were a lack of information about the indications for antipsychotic use and a lack of systematic reporting of adverse events which may be related to antipsychotics use, such as falls, extrapyramidal symptoms, cognitive dysfunction, metabolic changes, cardiovascular events and others. Only one study assessed falls (Devanand 2012).

Inconsistency of results

The two studies that reported our primary outcome NPS and provided data that could be pooled for meta-analysis, showed consistency of results between the studies. On the whole, the diversity of the studies and their outcome measures precluded meta-analyses. We therefore summarised evidence in a narrative synthesis, showing good consistency of conclusions across studies.

Indirectness

We defined success of withdrawal as the ability to complete the study (i.e. no withdrawal due to worsening of NPS or no relapse to antipsychotic drugs use during the trial). However none of the studies included this outcome defined in this way. Therefore, we used the number of non-completers of the study and the difference between groups as a proxy for our primary outcome. We downgraded the quality of evidence for this outcome by one level due to this indirectness.

Most of the included trials assessed a wide range of neuropsychiatric symptoms (anxiety, apathy, depression, delusions, wandering, repetitive vocalisations, shouting, disinhibition, aberrant motor behaviour and appetite behaviour and many other symptoms). Two RCTs (Devanand 2011; Devanand 2012) focused on participants with psychosis, agitation or aggression. This could limit generalisability of the results of these studies, although we did not think this had an impact on the overall conclusions, because this subgroup was small. We discussed this subgroup separately because it may be clinically relevant.

We downgraded quality by one level for indirectness when considering the outcome adverse events because the included studies measured only a selection of potential adverse events.

Imprecision

All included studies had problems including 'frail' older participants (a group with high mortality) and had small sample sizes. Therefore, the statistical power of the studies was low, and very few outcomes showed clinical differences between the groups. Because it was not possible to pool data for most outcomes due to variability in outcome measures, the potential benefit of a meta-analysis to produce a more precise effect estimate could not be realised.

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The effect estimate for the two pooled studies on NPS had a wide 95% confidence interval which includes the null effect of no difference between treatments. This means NPS could get either better or worse after discontinuation.

Publication bias

We conducted a comprehensive search for published and unpublished studies that would have reduced the risk of publication bias. Funnel plots could not be constructed because we included only 10 studies.

Potential biases in the review process

We searched a wide range of databases with no restriction of language. We identified one unpublished study. We may have missed relevant studies; however, we think it is unlikely that we did not capture all available RCT evidence in this review.

Three review authors independently conducted all data selection and extraction; another review author acted as arbiter to minimise the risk of error and bias.

We pooled two studies that used the same NPI scale, although assessed at different times. It was unclear whether this difference in time of assessment had an important impact on the conclusions. A critical narrative synthesis of the results could introduce bias, although there was consistency in the effects of the intervention across studies.

Overall, data on the effect of withdrawal of antipsychotics in older people with dementia and NPS remain very sparse, and conclusions should be interpreted with caution.

None of the review authors was involved in the included trials or had conflicts of interest in the field of antipsychotics.

Agreements and disagreements with other studies or reviews

A systematic review of 10 studies (Pan 2014) found that discontinuation of antipsychotics had no effect on behavioural and psychological symptoms severity, early study termination and mortality. Pan 2014 did not identify the unpublished study by Bergh 2011. One cluster RCT (Ballard 2016) in participants with dementia living in nursing homes found advantages on quality of life if antipsychotic review is combined with non-pharmacological interventions (social interaction or exercise) compared with antipsychotic review without non-pharmacological interventions. This reinforces the urgency to establish safe and effective pharmacological and non-pharmacological alternatives to antipsychotics in older people with dementia and NPS.

A literature review by Banerjee 2009 revealed an increase in absolute mortality risk of approximately 1% after antipsychotic treatment in older people with dementia. We found insufficient data to determine whether discontinuation of antipsychotic medication has any effect on mortality.

AUTHORS' CONCLUSIONS

Implications for practice

There is low-quality evidence that antipsychotics may be discontinued in older people with dementia who have been taking these drugs for at least three months, and that discontinuation may have little or no important effect on behavioural and psychological symptoms. This approach is consistent with the observation that most behavioural complications of dementia are intermittent and do not persist for longer than three months. Discontinuation also may have little or no effect on overall cognitive function, although one study reported an improvement in verbal fluency. It may make no difference to adverse events and quality of life. We are uncertain whether discontinuation of antipsychotics leads to a decrease in mortality at short- or long-term follow-up.

Subgroup analyses in some of the included trials suggest that discontinuation may reduce agitation for participants with less severe neuropsychiatric symptoms (NPS) and continuation may benefit participants with more severe NPS.

We also found that in two studies, participants with psychosis, aggression or agitation who had responded well to long-term antipsychotic drug use may benefit from continuation of antipsychotics.

Nevertheless, because of limitations in the quality of the evidence, further research on the benefits and harms of withdrawing antipsychotics from participants with milder and severe symptoms is required.

The overall conclusions of the review are unchanged since this review was published 2013 and the number of available trials is still low.

Implications for research

The available studies have low statistical power due to lower than expected recruitment and high mortality in this frail group of older people. This could explain the absence of a clinically important effect for several outcomes. However, the sample of participants included in these studies reflects everyday reality. Conducting trials in this context of frail older people requires a delicate balance between methodological rigor and feasibility. Future trials need to be rigorous in design and delivery, with subsequent reporting to include a comprehensive description of all aspects of methodology to enable appraisal and interpretation of results with sufficient follow-up. A pragmatic trial, designed to evaluate the effectiveness of interventions in real-life routine practice conditions, may add significant value.

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None of the included studies addressed acute withdrawal effects of antipsychotics. Abrupt drug discontinuation may contribute to observed withdrawal effects and tapering medication may produce different effects, particularly in participants taking high doses of antipsychotics at baseline. More studies focusing on different methods of withdrawal are needed to provide the evidence base for clinical recommendations.

A focus on the NPS cluster with predominantly psychotic symptoms (i.e. hallucinations, irritability, agitation and anxiety) could be clinically relevant and an appropriate primary outcome for studies assessing the effect of withdrawal from antipsychotics in participants with dementia. It is likely that scales other than the NPI scale (e.g. the agitation NPI subscore) will correspond better with this symptom cluster and should, therefore, be used in further trials.

Studies are needed to explore the effects of withdrawal on different aspects of cognitive function and to determine whether any cognitive effects have an impact on the ability of participants to carry out daily activities.

Characteristics other than low baseline behavioural scores (Ballard 2004), for example, low antipsychotic baseline dose, or no use of benzodiazepines or antidepressants, may predict beneficial outcomes after antipsychotic cessation (Meador 1997). Future trials could examine how outcomes for discontinuation of antipsychotics depend on the agent and on drug interactions and concomitant drugs. Thus, other psychotropic medications such as benzodiazepines, should be considered systematically as well.

Important adverse effects such as falls, extrapyramidal symptoms and involuntary movements are not systematically measured in most of the available studies. The reduction of adverse events related to long-term antipsychotic drug use is another potential benefit of discontinuing antipsychotics and should be evaluated more systematically.

The perceptions and beliefs of carers and families may influence inclusion of participants in withdraw interventions. Smith 2011 reported that in the Ballard 2008 study, consent was withdrawn in 16% of the eligible cases before blinding, either by the participant, the family practitioner or the family. In addition, Cohen-Mansfield 1999 reported that half of the nursing staff feared that drug withdrawal would lead to deterioration of behaviour. More studies are needed to elicit barriers and enabling factors and explore their impact on success of the intervention.

Our review reinforces the urgency to establish safe and effective pharmacological and non-pharmacological alternatives to antipsychotics in older people with dementia and NPS. Meanwhile, action is needed in several domains of dementia care to reduce long-term and potentially inappropriate use of antipsychotics in frail older people (McCleery 2012).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ballard 2004

Methods	**Design:** double-blind, placebo-controlled study **Duration**: 3 months
Participants	**Country:** UK **Centres:** 2 **Setting:** residents of 2 long-term care facilities **Total number of participants**: 100 (46 intervention, 54 control) **Analysis:** completed at least 1 follow-up randomisation **Gender distribution (F%):** 76 % intervention = 76%, control = 87% **Mean age (years):** intervention = 83.1 (SD 7.1), control = 83.6 (SD 9.3) **Cognitive function (Mean MMSE):** intervention = 5.5 (SD 6.8), control = 5.5 (SD 6.5) **Total NPI**: intervention = 13.3 (SD 9.3), control = 15.7 (SD 8.3) **Inclusion criteria:** older participants (aged > 65 years) care facility residents, probable or possible Alzheimer's disease by the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association Criteria), a Clinical Dementia Rating Scale stage 1 or greater and no severe behavioural symptoms (no individual scores above 7) on the NPI at time of evaluation, taking neuroleptics (thioridazine, chlorpromazine, haloperidol, trifluoperazine or risperidone) for more than 3 months (median prescription time longer than 1 year) **Exclusion criteria:** no severe behavioural disturbances, taking neuroleptics for longer than 3 months, having severe behavioural symptoms (individual scores above 1) and no severe behavioural symptoms (individual scores above 7 on 1 of the 12 items of the NPI-scale)
Interventions	**Intervention 1:** abrupt discontinuation of antipsychotics (intervention group) **Intervention 2:** continuing antipsychotics (control group) No dose reduction of tapering
Outcomes	**Duration of follow-up:** 3 months (0, 1 and 3 months) **Outcomes measured:** behavioural and psychiatric symptoms (NPI), quality of life (DCM)
Notes	Funding provided by Research into Aging (London, UK) and Age Concern (London, UK) Conflicts of interests were not reported.
Risk of bias	

Bias	Authors' judgement	Support for judgement

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Random sequence generation (selection bias)	Unclear risk	Comment: method of sequence generation is not reported Quote: "Subjects were then randomised to neuroleptic (N = 54) or placebo (N = 46)"
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment is not described Quote: "...Dispensing was coordinated by the pharmacy departments at the 2 centres. Prescriptions were written prior to randomisation in a twice daily regimen, allocating to each participant the closest dose. .."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study is described as double-blinded, unlikely that blinding could have been broken. Encapsulation of the administered drugs ensured blinding of participants and doctors/nurses Quote: "The study was conducted using a double-blind design. All study neuroleptics were encapsulated by an independent company to maintain blind, and dispensing was coordinated by the pharmacy departments at the 2 centres. Prescriptions were written prior to randomisation in a twice-daily regimen, allocating to each participant the closest dose to their pre-existing prescription from the doses encapsulated"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: study is described as double-blinded, unlikely that blinding could have been broken. Blinding of the outcome raters is not described Quote: "...using a double blind design...the centre coordinator, blinded to neuroleptic status, decided whether the patient needed to be withdrawn from the study to receive "rescue" medication."
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	Comment: reasons for dropouts reported and similar for both groups Quote: "All evaluations were undertaken at baseline. The NPI and DCM assessments were also completed at 1 and 3 month follow-up. Study withdrawals and the proportion of participants developing marked (pronounced or manifest) behavioural symptoms are described and

		compared between groups using the chi-square test. Fourteen participants (26% active treatment, 30% placebo) withdrew from the study in each group. There were only 6 withdrawals in the placebo-treated group (13%) and 5 withdrawals in the active treatment group (9%) because of behavioural deterioration. Other withdrawals were because of physical health problems (active group: 3 (6%), placebo group: 3 (7%)), protocol violation (active group: 2 (4%), placebo group: 1(2%)) or withdrawal of consent (active group: 3 (6%), placebo group: 2 (4%)). Eighty-two (82%) of the participants completed at least 1 follow-up evaluation and were included in the primary outcome analysis. For all participants who completed at least 1 follow-up assessment, the last evaluation was carried forward"
Selective reporting (reporting bias)	Low risk	Comment: behavioural and psychiatric symptoms and well-being reported on all measured time points, cognition was only assessed at start of the study
Other bias	Low risk	No other bias

Ballard 2008

Methods	**Design:** randomised, blinded, placebo-controlled parallel 2-group treatment discontinuation study **Duration**: 12 months
Participants	**Country:** UK **Setting:** residents of 5 long-term care facilities **Total number of participants**: 165 (82 discontinuation, 83 continuation) **Gender distribution (women %):** 75.6 % discontinuation, 77.1% continuation **Mean Age, SD (years):** 84.9 (SD 6.1) discontinuation, 84.4 (SD 7.0) continuation **Inclusion criteria:** participants lived in a nursing or residential home, patient fulfilled the NINCDS/ADRDA criteria for possible or probable Alzheimer's Disease, patient had either a MMSE score > 6 or a Severe Battery Impairment score > 30, patient was taking at least 10mg chlorpromazine equivalents of a typical neuroleptic or at least 0.5 mg daily of risperidone **Exclusion criteria:** participants unable to complete primary outcome measures at baseline assessment, clinician responsible for care or study clinician considered the person with any physical condition that would have made participation in the trial distressing or likely to have more physical problems, patient was currently taking thioridazine and showing a prolonged QTc on electrocardiogram, patient was likely to be unable to take

	capsules
Interventions	**Intervention 1:** abrupt discontinuation of neuroleptics and switch to placebo (placebo group) **Intervention 2:** continuation of neuroleptics (continuation group) Three fixed dosages (very low-low-high) were chosen for each of the permitted neuroleptic drugs and were maintained during the 12 months
Outcomes	**Duration of follow-up:** 12 months **Primary outcome:** **Cognitive function:** total Severe Impairment Battery (SIB) score (0, 6, 12 months) **Secondary outcomes:** neuropsychiatric symptoms: NPI (0, 6, 12 months) cognitive function: Standardised Mini-Mental State Examination (SMME) (0, 6 months) adverse effects: Modified Unified Parkinson's disease Rating Scale (M-UPDRS) (0, 6 months) FAS test (0, 6 months) Bristol Activities of Daily Living Scale (BADLS) (0, 6 months) Sheffield Test for Acquired Language Disorders (STALD)(0, 6 months) Functional Assessment Staging (FAST)(0, 6 months) Clinician's Global Impression of Change (CGIC) (0, 6 months)
Notes	Clive Ballard, first author, has received honoraria en research grants from different companies Study was possible by a grant from the Alzheimer's Research Trust, Cambridge, UK There are several factors limiting the generalisability of the interpretation of this trial First, recruitment focused on participants living in residential care where moderate and severe dementia usually predominates, and the participants generally are older and frailer than their counterparts in other settings. Thus, the results are not easily extrapolated to individuals who are cared for in other community settings Second, 89% of the participants were taking haloperidol or risperidone, but pharmacological profiles of neuroleptics differ, so that the study might not adequately represent the effects of discontinuation of other neuroleptics Furthermore, polypharmacy is common in residential care, and the study did not consider other psychotropic prescriptions Finally, high participant attrition sharply reduced the statistical power and scope for analysis of outcomes at 12 months. Imputation procedures and sensitivity analyses established robustness of estimates, but they cannot account for type II errors (i.e. false-negative interpretation) Individual participant data at three months from was kindly provided by the authors to allow pooling of the data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comments: randomisation was done by computer random number generator Quote: "Randomisation was performed

		centrally at the Centre for Statistics in Medicine in Oxford (CSMO), using dedicated computer software (MINIM). The randomisation programme included a minimisation algorithm to ensure balanced allocation of participants across the intervention groups for important prognostic factors"
Allocation concealment (selection bias)	Low risk	Comment: central allocation concealment Quote: "The statistician carrying out the randomisation had no direct contact with patients and allocation was, therefore, totally independent of patient recruitment. The clinician responsible for randomisation of a patient faxed a randomisation form to the CSMO (or sent e-mail) in exceptional circumstances) and provided details appropriate and sufficient for establishing eligibility. If a person was eligible and informed consent/assent had been obtained and baseline assessments had been completed, the patient was randomised by the statistician either to continue taking medication or to discontinue (placebo group). The statistician directly communicated the allocation to the relevant trial pharmacy, ensuring concealment."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study is described as double-blinded, unlikely that blinding could have been broken Quote: "The clinicians, those administering the trial medication, the carers, the relatives and the participants themselves, and those assessing the outcomes were all blinded to treatment allocation. Each antipsychotic was over-encapsulated to maintain the double-blind design. Placebo capsules were identical to the over-encapsulated antipsychotics,.."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: study is described as double-blinded, unlikely that blinding could have been broken Quote: "... those assessing the outcomes were blinded to treatment allocation..."

Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	Comment: flow of participants is included. Missing data is balanced across groups and similar reasons Quote: "Primary analysis was done performed on patients with complete data at both baseline and week 26, including those who did not adhere tot the protocol. To give a completed data set the imputation method was used "filling in" missing data with plausible values. A sensitivity analysis was used to test the robustness of the SIB result. This analysis was limited to those participants for whom the risk of possible floor and ceiling effects was smallest, i.e. SIB baseline cut-off values ≥ 40 but ≤ 90. "
Selective reporting (reporting bias)	Low risk	Comment: all intended primary and secondary outcomes are reported in the first and the follow-up study
Other bias	Low risk	No other bias

Bergh 2011

Methods	**Design:** randomised double-blind placebo-controlled trial with two sub-studies: the antidepressant discontinuation placebo-controlled study group (Bergh 2012) and the antipsychotic discontinuation placebo controlled study group (Bergh 2011). The antipsychotic discontinuation study (Bergh 2011) met inclusion criteria and was included in the review. **Duration:** 25 weeks
Participants	**Country:** Norway **Setting:** residents of 15 nursing homes **Total number of randomised participants**: 19 (9 discontinuation, 10 continuation) **Mean age (years):** 81.7 discontinuation, 82.6 continuation **Gender distribution (% women):** 37.5 discontinuation, 70 continuation **Median CSDD score (range 0 to 38):** 5.5 discontinuation, 6 continuation **Median NPI-10 (range 0 to 144):** 22 discontinuation, 21 continuation **Inclusion criteria:** vascular or Alzheimer dementia, or mixed Alzheimer's disease/vascular dementia, nursing homes resident for 3 months or more, given risperidone for 3 months or more, Clinical Dementia rating 1, 2 or 3 **Exclusion criteria:** dementia of other origin, psychiatric disease (schizophrenia, depression or any severe), life expectancy less than 3 months, acute infection last 10 days, unstable diabetes mellitus, terminal disease
Interventions	**Treatment 1:** discontinuation risperidone after titrated out over one week **Treatment 2:** continuation of risperidone (dose in each patient varied, according to the

	dose the participants were prescribed at inclusion, mean dose at inclusion was 0.92 mg/d **Concomitant therapy:** all kinds of concomitant therapy were allowed before, during and after the study
Outcomes	**Primary outcomes:** neuropsychiatric symptoms: changes in Neuropsychiatric Inventory-10 (0 weeks, 25 weeks; range 0 to 120), depressive symptoms of a patient with dementia: changes in Cornell's Depression Scale (0 week, 25 weeks; range 0 to 38), safety analyses: changes on the Unified Parkinson Disease Rating Scale (UPDRS, six-item version) (0 weeks, 25 weeks) **Secondary outcomes:** Quality of life - Alzheimer's disease (QoL-AD), the Severe Impairment Battery (SIB), the Lawton & Brody's Physical Self-Maintenance scale (PSMS) , the Clinical Dementia Rating Scale (CDR)
Notes	Sponsor: Innlandet Hospital Trust. There is no conflict of interest of the author reported. It is unclear if the author received grants. Provider of study drugs is not described This was an unpublished study. We requested results by email communication with the author on 8 June 2017 (Van Leeuwen 2017 [pers comm]). We received study results on 10 June 2017. The study arm with antidepressants was published in 2012 as a separate paper. The antipsychotics discontinuation arm was never published as paper. The study results were known in 2011 and reported to the Norwegian Medicines Agency. This study was not included in the 2013 review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: participants randomised centrally Quote: "...using computer generated randomisation (1:1) in block of four..."
Allocation concealment (selection bias)	Low risk	Comment: pharmacist was responsible for allocation Quote: "... patients were allocated to placebo or active treatment group by centralized allocation in blocks of four (1:1) by Sykehusapotekene Gjøvik, who also kept the randomisation list, computer derived, until the statistical analyses were completed.."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study was described as double-blinded, probably blinding will be successfully done Quote: "Study blinding was maintained as no other involved partner of the study knew the randomisation list than Syke-husapoteket Gjøvik. All statistical analy-

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		ses were performed before the randomisation groups were unblended. The bottles with active medication and placebo were identical labelled...replaced by placebo in a blinded way or replaced by a study drug containing active medication (same kind, same dose) as before..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: probably blinding of assessment outcomes was successfully done. The study involved 57 study nurses which could have biased the results Quote: "Data collection was done by research nurses. All statistical analyses were performed before the randomisation groups were unblended. A sealed code envelope was stored in the patient's medical journal at the nursing homes, and could only be opened in case of medical emergencies as a serious adverse event."
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	High risk	Comment: all randomised participants (19) are described in the flowchart. Very high dropout and withdrawal in the discontinuation group (7/9) suggests high risk of bias. Dropouts were more frequent in the ApDG (7/9, 77.8%) than in the ApCG (0/10, 0.0%) (P = 0.001). The analysis was based on modified ITT: participants in efficacy analysis: 16, participants included in safety analysis: 18. Unpublished data and high dropouts suggests high risk of attrition bias
Selective reporting (reporting bias)	High risk	Comment: protocol was registered in ClinicalTrials.gov, outcome measurements were not all reported as per protocol paper. Study is unpublished, no peer reviewing to valid results suggests high risk of bias Quote: " ... The number of primary endpoints were reduced from three to two: Cornell Scale of Depression in Dementia and the Neuropsychiatric Inventory...the changes were made prior to breaking the blind, and have limited implications for study interpretation... no observe case analysis en no interim analyses as planned in the protocol."

Other bias	Low risk	No other bias

Bridges-Parlet 1997

Methods	**Design:** double-blind, baseline treatment neuroleptic-controlled pilot study
	Duration: 4 weeks

Participants	**Country:** USA
	Setting: residents of long-term care facilities
	Participants: 36 (22 discontinuation, 14 continuation)
	Inclusion criteria: participants with diagnosis of possible or probable Alzheimer's dementia (criteria were given), participants receiving a neuroleptic (any traditional neuroleptic was acceptable) and who had been on a stable dose for 3 months prior to the study, a history of physically aggressive behaviour according to the referring nursing supervisor, participants residing in a nursing home, participants on antidepressants were permitted to participate if medication doses had been stable
	Exclusion criteria: participants with primary psychiatric diagnoses, mental retardation and terminal illness or other recent acute, changes in health status (e.g. recent broken hip)

Interventions	**Intervention 1:** withdrawal neuroleptics (discontinuation)
	Intervention 2: no withdrawal neuroleptics (continuation)
	Abrupt withdrawal or tapering off a neuroleptic when baseline dose exceeded the equivalent of 50 mg of chlorpromazine. The tapering was done by dropping the baseline neuroleptic dose by half during week 1 and then discontinuing the neuroleptic completely at the beginning of week 2
	Neuroleptic drugs: haloperidol (21), thioridazine (9), thiothixene (3), trifluoperazine (1), mesoridazine (1), loxapine (1)

Outcomes	**Primary outcome:** completion of the 4 weeks of study (numbers completing the 4 week study), behavioural symptoms: change in the amount of observed physically aggressive behaviour (mean, mean difference) (0, 1, 2, 4 weeks)
	Secondary outcomes: use of physical restraint, verbally aggressive behaviour, walking, amount of time spent sleeping and sitting, verbal aggressiveness, physically aggressive acts observed by experienced study personnel and by using a portable barcode reader capable of storing several hours of observation (0, 1, 2, 4 weeks)

Notes	Research grant from the Alzheimer's Association.
	There may have been selective recruitment limiting the generalisation of the results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: randomisation was done by random number table
		Quote: "Assignment was based on a predetermined sequence such that three patients

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		were assigned to withdrawal for every two not withdrawn. At the end of week 1, subjects were randomly assigned to either withdrawal or no withdrawal."
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment is not described, and may not have been blinded. Participant groups were well matched for age, chlorpromazine-equivalent neuroleptic dose and physically aggressive behaviour at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study is described as double-blinded, unlikely that blinding could have been broken. Nursing staff was involved in decision to discontinue the programme. They were blinded for the treatment allocated, thus outcome assessment may have been adequately blinded Quote: "Patients in both groups received identical-appearing capsules prepared at the University of Minnesota Hospital Pharmacy. Patients receiving their medication in crushed form, received in the placebo group tablets of vitamin C instead of capsules. The patient receiving intramuscular mesoridazine daily was given intramuscular saline from a nurse not directly involved in the patient's care"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: study is described as double-blinded, unlikely that blinding could have been broken. Participants were directly observed by study personnel, who were blinded to treatment assignments and recording behaviour was done by using a portable bar-code reader capable of storing several hours of observation
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	Comment: dropouts were described Quote: "Of the 22 patients who were withdrawn, 20 (91%) completed the 4-week double-blinded withdrawal. Two patients were restarted on medication on the recommendation of the nursing staff; only one went back on a neuroleptic. Of the 14 patients not withdrawn, all completed the 4-week trial. Of the 576 observation periods there were seven in which the bar-

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		code reader failed. Handwritten back-up notes were used for physically aggressive behaviour frequency."
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes were reported
Other bias	Low risk	No other bias

Cohen-Mansfield 1999

Methods	**Design:** double-blind cross-over study **Duration:** seven weeks followed by seven weeks cross-over
Participants	**Country:** USA **Setting:** residents of one nursing home **Diagnosis**: the diagnosis of dementia was not mentioned **Number of participants:** 58 **Inclusion criteria:** nursing home residents; aged over 70 years; had received at least four weeks haloperidol, thioridazine or lorazepam for agitation **Exclusion criteria:** concomitant administration of other antipsychotic or anti-anxiety drugs other than low-dose trazodone hydrochloride for sleep, life expectancy less than three months due to obvious causes as judged by the nursing home staff member responsible for direct care psychiatric diagnosis of a major affective disorder of schizophrenia according to DSM-III, acute infection within 10 days before entry, expectancy of leaving the nursing home within three months, uncontrolled hyperglycaemia or hypoglycaemia
Interventions	**Tapering period:** withdrawal of antipsychotic and lorazepam use by tapering to placebo during a three-week period **Intervention 1:** seven weeks of taking placebo followed by seven weeks of taking antipsychotic medication **Intervention 2:** seven weeks of taking medication followed by seven weeks of placebo **Antipsychotics**: haloperidol, thioridazine
Outcomes	**Time of measurements:** one week after start of dosage tapering (week 1), phase one tapering (week 3), phase one end point (week 10), phase two tapering (week 13), phase two end point (week 20) **Primary outcomes:** behavioural symptoms (BPRS) (mean), agitation (CMAI) (mean) **Secondary outcomes (mean):** adverse effects (AIMS), cognitive function (MMSE), global impression scale (GCI-S), sleep and activity level ratings **Time of assessment:** one week after start of dosage tapering (week 1), phase one tapering (week 3), phase one end point (week 10), phase two tapering (week 13), phase two end point (week 20)
Notes	Several different analyses were used to assess the robustness of the result. However, it was not clear if an intention-to-treat analysis was used. We were unable to use any data from this study. Cohen-Mansfield 1999 did not report outcome data separately for the different medications discontinued in the trial (which included the benzodiazepine

Cohen-Mansfield 1999   (*Continued*)

lorazepam as well as the antipsychotics haloperidol and thioridazine)
This study was supported by grants AG00547 and AG10172 from the National Institute on Aging, Bethesda, MD, USA
No conflicts of interest reported.
Because diagnosis of dementia was not mentioned in the paper, we emailed the first author (Declerck 2009a [pers comm] on 21 april 2009 to ask her whether the participants included had dementia and her answer was positive (referring to the MMSE scores)
We have asked the author by email for more results (SDs of the means…) on 1 July 2009, but we have not received any response on our last e-mail (Declerck 2009b [pers comm]).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of sequence generation is not described Quote "…half the residents were randomly assigned to have their medication dose tapered during a 3-week period, followed by receipt of a placebo (the other half continued their usual medication dosage). Residents were randomly assigned to the placebo versus medication group and stratified both by level of cognitive function and by psychotropic medication."
Allocation concealment (selection bias)	Unclear risk	Comment: allocation is not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study is described as blinded, unlikely that blinding was broken Quote: "Study medications (usual medication and placebo) were administered as identical liquids to ensure blindness by the care team. Only the dispensing pharmacist, who was not an employee of the nursing home, knew which medication was administered. The care team, residents, family caregivers, and research team were blinded to which group a participant was assigned."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: study is described as blinded, unlikely that blinding was broken Quote: "The care team, … and research team were blinded to which group a participant was assigned. Primary outcome data BPRS was assessed by daytime and evening nursing staff. "

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Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Unclear risk	Comment: rates and reason for dropout were described. However we were uncertain how many participants discontinued in the discontinuation or continuation group in the first part of the study Quote: "Twenty-three participants discontinued participation in the study before completion for the following reasons: death or dying (3), hospitalisation (1), not eating or weight loss (3), increased agitation (9), lethargy (2), withdrawal of consent (4), facial asymmetry (1) and fall (3); some had multiple reasons. For 12 participants, discontinuation occurred during the original drug dosage, for 9 while taking placebo, and for 2 during titration from drug to placebo. Most discontinuations (20 of 23) occurred in the first part of the study, before the cross-over."
Selective reporting (reporting bias)	High risk	Comment: no distinction is made for number of withdrawals in each group during the first part of the trial. it is not clear how they analyse these outcome. By not making difference in outcome reporting between discontinuation of antipsychotics, namely haloperidol and thioridazine, versus discontinuation of lorazepam, a benzodiazepine, it is impossible to retain robust conclusions from this withdrawal study Quote: "Participants who discontinued the study were similar in demographic characteristics to those who stayed. Although their levels of agitation at baseline were higher than those who stayed in the study, these differences did not reach statistical significance. Most withdrawals from the study occurred in the first part of the study (no numbers given)."
Other bias	Low risk	No other bias

Devanand 2011

Methods	Design: a six-month, randomised, double-blind, placebo-controlled discontinuation trial (phase B) following response to haloperidol open treatment during 20 weeks (phase A)
Participants	**Country:** USA **Setting:** participants living in the community who presented to a memory disorders clinic or an affiliated behavioural neurology practice group **Total number of participants**: 44 participants included in phase A, 22 responders of phase A were eligible for randomisation in phase B (discontinuation trial), 20 in phase B (10 discontinuation, 10 continuation) **Gender distribution (female):** 77% **Mean (years):** 75 (SD 8.0) **Inclusion criteria:** aged 50 to 95 years, clinical diagnosis of dementia by DSM-IV criteria and probable Alzheimer's disease by NNCDS-ADRA criteria, MMSE range between 5 and 26, current symptoms of psychosis, agitation or aggression **Exclusion criteria:** acute unstable medical condition, delirium, alcohol or substance abuse or dependence during the prior year, clinical evidence of stroke, other dementias including vascular or Lewy body or frontotemporal dementia, multiple sclerosis, Parkinson's disease, Huntington's disease, tardive dyskinesia, diagnosis of a psychotic disorder predating the onset of dementia, antipsychotic medication usage during the 4 weeks before study entry, and contra-indication to the use of haloperidol
Interventions	**Phase A:** open treatment (20 weeks): 44 participants living in the community with Alzheimer's disease and psychosis, agitation or aggression receiving psychotropic medication had a 1-week washout before entering phase A. During phase A flexible doses of haloperidol 0.5 to 5 mg daily were individually titrated to maximise therapeutic response and minimise side effects, especially extrapyramidal side effects. Visits occurred at 0, 2, 4, 8, 12, 16 and 20 weeks **Phase B:** discontinuation trial (24 weeks): 20 phase A responders were double-blind randomised to a continuation versus placebo (i.e. discontinuation) group. For participants randomised to placebo, there was a 2-week double-blind sequential placebo substitution tapering period to placebo
Outcomes	**Phase A:** the 3 most prominent targets of psychosis, agitation or aggression, scored on a 7-point scale (0 = absent to 6 = extreme) and tracked during the study. Criteria for response (primary outcome) were minimum 50% reduction from baseline in the sum score of these 3 target symptoms, a sum score ≤ 6 on these 3 items (range 0 to 18), and minimal or greater improvement on the CGI-C score (rated only for symptoms of psychosis, agitation or aggression) **Phase B** **Primary outcome:** relapse, assessed at any single time point during phase B. Criteria for relapse were minimum 50% worsening from the sum score of the 3 target symptoms at the end of phase A, a sum score ≥ 6 on these 3 items (range 0 to 18), and minimal or greater worsening on the CGI-C score (rated for psychosis and agitation/aggression) **Secondary outcomes:** somatic side effects assessed by the TESS, extrapyramidal signs assessed by the UPDRS and tardive dyskinesia assessed by the Rockland TD scale. Cognition was assessed by change in MMSE and impairment in ADL was assessed by the modified BFAS Time points of assessment during phase B: 0 (same as end of phase A), 2, 4, 8, 12, 16, 20 and 24 weeks (i.e. 6 months)

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	Pretrial: a 1-week washout prior to entering phase A.
Notes	Disclosures: authors had financial links with several pharmaceutical companies. Study supported by NIH grant The discontinuation trial included only participants who responded to haloperidol. Non-responders after the first 20 weeks (phase A) were excluded from the discontinuation phase (B). This limits the generalisability of the results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described in the study
Allocation concealment (selection bias)	Unclear risk	Comment: no description of the blinding of random allocation Quote: "Responders by end-Phase A were eligible for Phase B, a 24-week, random assignment (1:1 assignment of haloperidol and placebo), double-blind, trial of continuation haloperidol (same dose as end-Phase A) versus switch to placebo."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study is described as double-blinded, unlikely blinding could have been broken Quote: "Haloperidol and placebo were made up in identical looking opaque white capsules."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding of outcome raters is not described. In these trial, they were several subjective outcomes, so a lack of blinding of outcome assessors could had an influence The protocol (Devanand 2012a) for the subsequent study (Devanand 2012) mentions: Quote: "The blind is maintained after study exit to avoid biasing raters. A code-break is authorized only if needed in cases of overdose or medical emergency... raters remained unaware of the group assignments of all patients during the entire study."
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	Comment: non-completers data were described and balanced between the groups Attrition at end of phase A fully accounted

		for; quote: "There were 15 Phase A non-completers (34%), with all early terminations attributed either to lack of efficacy (n = 9) or side effects (n = 6)." Attrition at end of phase B accounted for and ITT included; quote: "Twenty of the 21 patients randomised in Phase B to continuation haloperidol or placebo had at least one follow-up visit after randomisation and were included in the Phase B analysis. Among patients who did not relapse, reasons for early study termination prior to 24 weeks in Phase B were side effects (n = 2), moving out of the area (n = 1), medical illness (n = 1) and noncompliance (n = 1). All data from these patients were included in the intent-to-treat, last observation carried forward, analyses. "
Selective reporting (reporting bias)	Unclear risk	Comment: several outcomes were measured at baseline of the open haloperidol treatment and at time of the discontinuation period, but no results were reported at later times of assessment
Other bias	Low risk	No other bias

Devanand 2012

Methods	Phase A: flexible dose risperidone open treatment for 16 weeks Phase B: six-month, randomised, double-blind, placebo-controlled discontinuation trial, following response to phase A Duration: 48 weeks
Participants	**Country:** USA **Setting:** outpatients through physician referrals and advertising; and residents of assisted-living facilities (memory clinics (including Alzheimer's research centres), geriatric psychiatry clinics and clinics at Veterans' Affairs medical centres) or nursing home **Total number of participants**: 253 participants screened **Phase A**: 180 received risperidone, participants who had a response in phase A entered phase B **Phase B:** 110 randomised **Group 1**: continue risperidone: 32 participants at start, 13 received risperidone at 16 weeks, 10 completed 48 weeks without relapse **Group 2:** continue risperidone for 16 weeks and then placebo: 38 participants at start, 27 received placebo at 16 weeks, 14 completed 48 weeks without relapse **Group 3:** start placebo in phase B: 40 participants at start, 13 received placebo at week 16, 10 completed 48 weeks without relapse **Gender distribution at baseline:** 59%

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	Mean (years) at baseline: 79.6 (SD 7.6) **Inclusion criteria:** outpatients or residents of assisted-living facilities or nursing homes, aged 50 to 95 years, met the criteria for dementia of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition ([DSM-IV](#)) and the criteria for probable Alzheimer's disease of the NINCDS-Alzheimer's Disease and Related Disorders Association, a score on the Neuropsychiatric Inventory (NPI) of 4 or more at both screening and baseline on the delusions or hallucinations subscale (psychosis score) or the agitation/aggression subscale (agitation score) (with scores on all NPI subscales ranging from 0 to 12 and higher scores indicating more pronounced symptoms), a score of 5 to 26 on the Mini-Mental State Examination (MMSE, with scores ranging from 0 to 30) in the case of outpatients, a score of 2 to 26 in the case of nursing home residents (with the lower range reflecting the greater severity of dementia in nursing homes) **Exclusion criteria:** history of stroke, transient Ischaemic attack, or uncontrolled atrial fibrillation
Interventions	Participants with Alzheimer's disease and psychosis, agitation or aggression received open-label treatment with risperidone for 16 weeks. Those who had a response to risperidone therapy were then randomly assigned, in a double-blind fashion, to one of three regimens: continued risperidone therapy for 32 weeks (group 1), risperidone therapy for 16 weeks followed by placebo for 16 weeks (group 2), or placebo for 32 weeks (group 3) **Phase A:** open-label treatment with flexible dose risperidone for 16 weeks, participants who had a response entered phase B **Phase B:** 110 randomised in phase B **Group 1:** continue risperidone **Group 2** continue risperidone for 16 weeks and then placebo **Group 3:** discontinuation of antipsychotics **Concomitant treatment:** quote: "If washout was not feasible ... stable doses of selective serotonin-reuptake inhibitors or low-dose trazodone or of sedatives or hypnotic agents were permitted ... Lorazepam, at a dose of 1 mg or less per day, was permitted if needed. ... cholinesterase inhibitors and memantine at stable dose were permitted"
Outcomes	**Primary end point:** the time to relapse of psychosis and agitation/aggression during weeks 0 to 16 of phase B, the time to relapse psychosis and agitation/aggression during weeks 17 to 32 of phase B **Phase A**: participants were considered to have had a response if they had a reduction of 30% or more from baseline on the NPI score (the sum of the sub-scores for agitation-aggression, hallucinations, and delusions) and a score of one (very much improved) or two (much improved) on the Clinical Global Impression of Change (CGI-C) scale (which ranges from one to seven, with higher scores indicating less improvement) for overall psychosis, agitation or aggression **Phase B:** participants were considered to have had a relapse if they had an increase in the NPI core score of 30% or more, or a 5-point increase from the score at the end of phase A, and a score of six (much worse) or seven (very much worse) on the CGI-C **Secondary outcomes:** assessments of extrapyramidal signs, with the use of the Simpson-Angus scale (which ranges from 0 to 40, with higher scores indicating more extrapyramidal signs), tardive dyskinesia, with the use of the Abnormal Involuntary Movement Scale (AIMS, which ranges from 0 to 35, with higher scores indicating more severe symptoms), general somatic symptoms developing during treatment, as assessed with the use of the Treatment Emergent Symptoms Scale (TESS, which ranges from 0 to 26, with

		higher scores indicating more somatic symptoms), cognitive status, as assessed with the use of the MMSE and the Alzheimer's Disease Assessment Scale (ADAS)-cognitive score (which ranges from 0 to 70, with higher scores indicating worse cognition), physical function, as assessed with the use of the Physical Self-Maintenance Scale (PSMS, which ranges from 1 to 30, with higher scores indicating worse functioning) and adverse events
Notes		Outcome symptoms slightly unevenly distributed in randomised groups in phase B: 9% agitation-aggression in group 1 (continue risperidone) versus 19% in group 2 (switch to placebo after 16 weeks) and 18% in group 3 (placebo throughout phase B) High rates of discontinuation of risperidone (38% in phase A; 68% in group 1 and 29% in group 2) Funding sources: quote "...Johnson & Johnson, donated the risperidone tablets and matching placebo but had no role in the conduct of the study or the analysis or reporting of the data... Supported by grants from the National Institutes of Health (R01 AG021488 and R01 AG17761) and the Department of Veterans Affairs." Conflict of interest: not reported in the paper, but included in the Supplementary Appendix available online (add link). The first author received grants from several pharmaceutical companies (inside and outside the submitted work). The discontinuation trial only included only participants who responded to risperidone. Non-responders after first 16 weeks (phase A) were excluded from the discontinuation phase (B). This limits the generalisability of the results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: block randomisation is described Quote: "The study statistician prepared a randomised permuted-blocks procedure, with blocks of three or six, to balance the group assignment in each of four (2 × 2) strata, with stratification within each site according to the presence or absence of psychosis at baseline and residence (assisted-living facility or nursing home vs. home)."
Allocation concealment (selection bias)	Low risk	Comment: central allocation by pharmacist Quote: "Patients who had a response entered phase B of the study and were randomly assigned...The central pharmacy of the New York State Psychiatric Institute maintained the assignment code, and clinicians and raters remained unaware of the group assignments of all patients during the entire study."

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study is described as double-blinded and unlikely that blinding could have been broken Quote: "...double-blind fashion... clinicians and raters remained unaware of the group assignments of all patients during the entire study ... all tablets identical in appearance ... Immediately before the end of phase A, the pharmacy dispensed pre-packaged blister packs of risperidone or placebo tablets that were identical in appearance for patients eligible for randomisation in phase B. The number of tablets the patient was receiving daily at the end of phase A was the number he or she received throughout phase B."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: study is described as double-blinded and unlikely that blinding could have been broken. The blind is maintained after study exit to avoid biasing raters. A code-break is authorized only if needed in cases of overdose or medical emergency Quote: "...raters remained unaware of the group assignments of all patients during the entire study..."
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	Comment: all randomised participants accounted for in the flowchart Quote: "The dropout rates did not differ significantly among the randomised groups (Fig. 1)"
Selective reporting (reporting bias)	Unclear risk	Comment: the results for the CGI-C were not reported in the study, the total NPI scores and the NPI core score were measured at baseline (phase A) and at time of randomisation (phase B), but no results were reported at later times of assessment
Other bias	Low risk	No other bias.

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Findlay 1989

Methods	**Design:** randomised double-blind placebo-controlled trial **Duration**: 4 weeks
Participants	**Country:** UK **Setting:** residents from one long stay of psychogeriatric ward of hospital **Total number of participants**: 36 **Gender distribution:** 100% women **Mean age (years):** 65 years or older **Inclusion criteria:** senile dementia, Alzheimer type, according to ICD-9, receiving a stable dose of between 10 mg and 100 mg of thioridazine per day for at least 2 months **Exclusion criteria:** male, multi-infarct dementia and antipsychotic agents other than thioridazine
Interventions	**Intervention 1:** withdrawal of thioridazine **Intervention 2:** continuation of thioridazine **Antipsychotic drug**: thioridazine **Pre-trial:** tapering to half of the daily dose in the first week and to placebo over the next week **Post-trial:** all participants were restored to half their original dose of thioridazine with any subsequent alterations being made by their regular medical attendant on an empirical base **Concomitant treatment**: chlormethiazole
Outcomes	**Primary outcomes:** cognitive function: CAS (0, 2, 4 weeks), cognitive and behavioural dysfunction: LPRS (0, 2, 4 weeks), functioning: SCAGS (0, 2, 4 weeks) **Secondary outcomes:** systolic BP and heart rate (0, 2, 4 weeks) Results only given as means, ranges and numbers of observations
Notes	Conflict of interest and source of funding were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: methods of sequence generation were not described Quote "...matching active and placebo (liquid) formulations of thioridazine were used, each subject being entered separately and allocated by a random code to the active or placebo group in a double-blind manner"
Allocation concealment (selection bias)	Unclear risk	Comment: study described as 'randomised', the randomisation process was not completely successful Quote: "...each subject being allocated by a random code to the active or placebo group in a double-blind manner ... The

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		starting difference in Cognitive Assessment Scale scores between active-continued and placebo-substituted groups represents an artefact of the randomisation process."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study described as "double blinded", unlikely that blinding was been broken Quote: "matching active and placebo (liquid) formulations were used ... During the first week patients in the 'placebo' group received placebo substitution for half of their daily dose of thioridazine and over the next week a total substitution. Similar mock substitutions with thioridazine were given to the 'active' group, so that initial medication was continued but the trial remained double-blind. After four weeks all patients were restored to half their original dose of thioridazine with any subsequent alterations being made by their regular medical attendant on an empirical basis ... as it was not possible to break the code in the middle of the trial "
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: study is described as double-blinded, blinding of the outcome assessors is not described. Assessment was done by clinicians and nurses with psychiatric training. In these trial, they were several subjective outcomes, so a lack of blinding of outcome assessors could had an influence
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Unclear risk	Comment: information of dropouts is not reported in the study
Selective reporting (reporting bias)	Unclear risk	Comment: primary outcome is not described, it is unclear if a selection of measured outcomes was reported
Other bias	Unclear risk	Comment: the randomisation procedure unfortunately resulted in a baseline imbalance in 1 of the 3 cognitive/behavioural rating scales (starting difference in cognitive assessment scale (CAS) between active continued was 4.2 treatment and 9.8 in the placebo-substituted groups. The author noted: "Difference represents an artefact of

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		the randomisation process." It is unclear if this has had an impact on outcomes

Ruths 2008

Methods	**Design:** randomised, placebo-controlled, double-blinded study **Duration:** 4 weeks
Participants	**Country:** Norway **Setting:** residents of 13 nursing homes **Diagnosis:** dementia diagnosis according to the clinical criteria of ICD-10 **Number of participants:** 55 (27 intervention, 28 reference) **Gender distribution (F)** (number, %): 20 (74%) intervention, 23 (82%) reference **Mean age (years):** 83.6 (SD 8.1) intervention, 84.6 (SD 5.9) reference **Inclusion criteria:** older participants, aged 65 years and over, dementia diagnosis according to the clinical criteria of ICD-10 residence in the facility for at least 3 months before inclusion, taking haloperidol, risperidone or olanzapine for nonpsychotic symptoms for at least 3 months before the study as standing medication in stable doses **Exclusion criteria:** participants with antipsychotic use for a primary diagnosis of major psychotic disorder, mental retardation, terminal illness with life expectancy judged to be shorter than 3 months and recent major changes in health status
Interventions	Intervention group: abrupt discontinuation of antipsychotic medication Reference group: no discontinuation of antipsychotic medication Note: same dose of initial daily dose of antipsychotic drugs in intervention group: risperidone 1.0 (0.5 to 2.0) mg, haloperidol 1.0 (0.5 to 1.5) mg or olanzapine 5.0 (2.5 to 5.0) mg
Outcomes	Behavioural and psychological symptoms measured by the NPI-Q (second baseline period, week 1, week 4). The NPI-Q covers 12 symptoms: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour (restlessness, e.g. purposeless wandering and inappropriate activity), sleep problems and eating disorders. Information on participants' symptoms was obtained by interview with the primary nurse informant. Individual symptoms were scored as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe), providing an NPI-Q sum score rating from 0 to 36. Three separate ratings were conducted for all the participant. These ratings included symptoms occurring during the 7-day period before assessment Sleep/wake activity was recorded continuously during baseline and intervention (i.e. over 6 weeks) using an Actiwatch portable recorder (second baseline week, week 1, week 4). The Actiwatch is a small wrist-worn device containing an accelerometer that is optimised for highly effective sleep-week inference from wrist activity. Actigraphically measured wrist activity is a feasible and reliable method for sleep/wake evaluation in nursing home residents. The following actigraphic parameters were calculated: total sleep time, total wake time, sleep efficiency (proportion of sleep during night window, i.e. 11 pm to 7 am), daytime activity and night-time activity. The ratio of day-to-night-time activity was calculated and expressed as a light/dark ratio. Mean 24-hours activity and peak times of activity were calculated. Analyses of sleep/wake activity were based on 3 x 7-day records

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Notes	Conflict of interests and funding were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: method of randomisation is done computer random number generator Quote: "Participants were assigned to antipsychotic drug discontinuation (intervention group) or no discontinuation (reference group) by means of computer generated, random, permuted blocks of 4… "
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment was provided central, no further details were reported Quote: "…an independent researcher … participants were consecutively assigned to antipsychotic drug discontinuation or no discontinuation…"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: blinding of participants and personnel is described, unlikely that blinding could have been broken Quote: "In the intervention group, patients received inert placebo capsules consisting of lactose, whereas reference group patients received identically looking capsules containing continued antipsychotic drug treatment at current dose … all study medications were provided by an independent pharmacy to maintain blindness … Sealed envelopes, containing details of study medication for each patient, were available for the nursing home physicians in case of serious health events."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: study is described as double-blinded. Blinding of the assessment interviewers is not described. In these trial, they were several subjective outcomes, so a lack of blinding of outcome assessors could had an influence Quote: "NPI rating was based on interviews with patient' prime nurse on her observations of BPSD the previous week. The interviews were conducted by spe-

Ruths 2008 (*Continued*)

		cially trained medical students... Sealed envelopes... At the completion of the intervention, randomizations codes were broken."
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Unclear risk	Comments: all 55 participants completed at least the week one evaluation were included in study analysis. No statistical difference in dropout between intervention and reference group Quote: "Seven patients completed the study prematurely, due to unblinding for randomisation code, behavioural deterioration, restless legs or delirium."
Selective reporting (reporting bias)	Low risk	Comment: all intended outcomes reported in accordance with the methods section
Other bias	Unclear risk	Comment: the selection of participants may have been biased. It is not clear if the participating nursing homes participants are different from non-participating nursing home patients

van Reekum 2002

Methods	**Design:** randomised, double-blind, placebo-controlled trial **Duration:** 26 weeks
Participants	**Country:** Canada **Setting:** residents of two nursing homes and geriatric chronic care floor of an academic health science centre **Total number of participants**: 34 (17 placebo, 17 active) **Gender distribution (male):** 47.1% placebo; 56.3% active **Mean (SD) age, years:** 84.4 (SD 4;6) placebo, 82.9 (SD 6.9) active **Inclusion criteria:** any form of dementia, receiving antipsychotics for 6 months or longer, stable behaviour **Exclusion criteria:** history of antipsychotic discontinuation having failed within the past 6 months, a history of schizophrenia, antipsychotic use for nausea, diagnosis of delirium (DSM-IV criteria), a global rating scale of 3 on the BEHAVE-AD rating scale at the time of the screening, 1 week prior to the start of the study or within the 2 weeks of the pre-trial period
Interventions	**Placebo group:** discontinuation antipsychotics **Active treatment:** continuing antipsychotic treatment with the same dose **Antipsychotics:** risperidone, thioridazine, loxapine, perphenazine, haloperidol, olanzapine, nozinan **Note:** pre-trial period: 2-week pre-trial period and a 2 week dose reduction period by tapering (dose reduction with original medication halved for the first week of the dose

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	reduction period and the remaining dose halved for the second week) **Concomitant medication:** lorazepam 0.5 mg to 1 mg every 8 hours on a per need basis for agitation
Outcomes	Behavioural outcome measures: BEHAVE-AD, the NPI and the ROAS (each visit: 15 times) Cognitive functioning: MMSE (0, 4, 8, 12, 14, 16, 20, 24 weeks), MDRS (0, 24 weeks) Functional level: BDS, ADL and motivational behaviour subscale (0, 4, 8, 12, 14, 16, 20, 24 weeks) Extrapyramidal signs: ESRS (0, 4, 8, 12, 14, 16, 20, 24 weeks) Clinical impression of severity of behavioural disturbance: CGI (all visits). The CGI quantified the clinical impression of severity of behavioural disturbance on a 7-point, verbally anchored scale. The degree of change from baseline was also ranked on a similar scale All outcome data were obtained by a trained research assistant upon interview of the prime nurse or the subject as appropriate for the instrument
Notes	Funding source and conflict of interests were not reported in study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: participants randomly assigned to treatment by random number table Quote: "A random number table was used to allocate subjects to receive either continued antipsychotic treatment at the current dose or to receive identical placebo"
Allocation concealment (selection bias)	Unclear risk	Comment: no reference made to the method in which allocation concealment was ensured
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: study is described as "double blind" and unlikely blinding could have been broken Quote: "A randomised double blind placebo controlled study design was used ... During all study periods, medications, including placebo, were placed into identical capsules to maintain blindness."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: study is described as double-blinded, blinding of the research team is not described. In these trial, they were several subjective outcomes, so a lack of blinding of outcome assessors could had an influence

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		Quote: "All outcome data were obtained by a trainee research assistant upon interview of the prime nurse or the subject as appropriate for the instrument... if the clinical staff observed significant behavioural worsening that they thought warranted early withdrawal from the study, the ware asked to contact the research team immediately and the outcome measures were repeated at that time."
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	Comment: rates and reasons for dropouts were reported. Analysis is done by intention-to-treatment principle Quote: "The total number of subjects who were withdrawn from the study early was 10/17 in the placebo group and 6/17 in the active treatment group. The difference in the rate of early study withdrawal was not statistically significant. Subjects were withdrawn due to medical illness (3), death (3), extrapyramidal symptoms (3), and exacerbations of behavioural problems (4 in the placebo and 3 in the active group)."
Selective reporting (reporting bias)	High risk	Comments: some data of the continuation and the discontinuation group for several outcomes is not completely given in numerical results but only in descriptive figures. NPS assessed by NPI, aggression assessed by the ROAS, extrapyramidal signs assessed by the ESRS, cognitive functioning assessed by MMSE and functional outcome assessed by the BDS were not reported in the paper
Other bias	Low risk	No other bias.

ADL: activities of daily living; BDS: Blessed Dementia Scale; BEHAVE-AD: Behavioural Pathology in Alzheimer's disease; BFAS: Blessed Functional Activity Scale; BP: blood pressure; BPRS: Brief Psychiatric Rating Scale; CAS: Cognitive Assessment Scale; CGI: Clinical Global Impression; CGI-C: Clinical Global Impression-Change; CMAI: Cohen-Mansfield Agitation Inventory; DCM: Dementia Care Mapping; DSM-III: Diagnostic and Statistical Manual of Mental Disorders - 3th Edition; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders - 4th Edition; ESRS: Extrapyramidal Symptom Rating Scale; LPRS: London Psychogeriatric Rating Scale; MDRS: Mattis Dementia Rating Scale; MMSE: Mini-Mental State Examination; NIH: National Institutes of Health; NPI: Neuropsychiatric Inventory; NPQ-I: Neuropsychiatric Inventory Questionnaire; NPS: neuropsychiatric symptoms; RCT: randomised controlled trial; SCAGS: Sandoz Clinical Assessment Geriatric Scale; SIB: Severe Impairment Battery; TESS: Treatment Emergent Symptom Scale; ROAS: Retrospective Overt Aggression Scale; UPDRS: Unified Parkinson's Disease Rating Scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Azermai 2013	Not an RCT but a clinical trial without a suitable control group
Ballard 2015	Intervention was discontinuation of memantine
Bergh 2012	Intervention was discontinuation of antidepressants
Devanand 2013	Commentary
Garner 2015	Commentary
Gill 2013	Commentary
Gnjidic 2013	Commentary
Horwitz 1995	Not a clinical trial, but a naturalistic study
Ling 2013	Commentary
Lolk 2014	Commentary
McLennan 1992	This trial reports a primary outcome (prolactin response to withdrawal of thioridazine assessed in the Findlay 1989 cohort), which has no relationship with the neuropsychiatric symptom in which we were interested
Patel 2017	Not an RCT; post hoc analysis of Devanand 2012
Power 2013	Commentary
Renard 2014	Commentary
Rule 2003	This reference probably refers to the registration of a discontinuation study which has not been published until now (no more information found on this reference)
Wessels 2010	This trial was not a discontinuation trial
Westbury 2011	This trial was a follow-up study and not a discontinuation trial

RCT: randomised controlled trial

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DATA AND ANALYSES

Comparison 1.   Discontinuation versus continuation of long-term antipsychotic drug use (continuous data, analysis method mean difference)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Behavioural assessment	2	194	Mean Difference (IV, Fixed, 95% CI)	-1.49 [-5.39, 2.40]

Analysis 1.1.   Comparison 1 Discontinuation versus continuation of long-term antipsychotic drug use (continuous data, analysis method mean difference), Outcome 1 Behavioural assessment.

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Comparison: 1 Discontinuation versus continuation of long-term antipsychotic drug use (continuous data, analysis method mean difference)

Outcome: 1 Behavioural assessment

Study or subgroup	Discontinuation		Continuation		Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)			
Ballard 2004	36	-1.3 (9.4)	46	0.2 (12)		70.9 %	-1.50 [-6.13, 3.13]
Ballard 2008	54	2.04 (18.2)	58	3.52 (20.78)		29.1 %	-1.48 [-8.70, 5.74]
Total (95% CI)	**90**		**104**			**100.0 %**	**-1.49 [-5.39, 2.40]**

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable

-100   -50   0   50   100

Favours discontinuation   Favours continuation

ADDITIONAL TABLES

Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia (Review)

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Table 1. Antipsychotic drug classes

Phenothiazines with aliphatic side chain
Phenothiazines with piperazine structure
Fhenothiazines with piperidine structure
Butyrophenone derivatives
Indole derivatives
Thioxanthene derivatives
Diphenylbutylpiperidine derivatives
Diazepines, Oxazepines and Thiazepines
Benzamides
Other antipsychotics

Table 2. Antipsychotic drugs with defined daily doses

Phenothiazines with aliphatic side-chain
N05AA01 Chlorpromazine 0.3 g per os
N05AA02 Levomepromazine 0.3 g per os
N05AA03 Promazine 0.3 g per os
N05AA04 Acepromazine 0.1 g per os
N05AA05 Triflupromazine 0.1 g per os
N05AA06 Cyamemazine
N05AA07 Chlorproethazine

Phenothiazines with piperazine structure
N05AB01 Dixyrazine 50 mg per os
N05AB02 Fluphenazine 10 mg per os
N05AB03 Perphenazine 30 mg per os
N05AB04 Prochlorperazine 0.1 g per os
N05AB05 Thiopropazate 60 mg per os
N05AB06 Trifluoperazine 20 mg per os
N05AB07 Acetophenazine 50 mg per os
N05AB08 Thioproperazine 20 mg per os
N05AB09 Butaperazine 10 mg per os
N05AB10 Perazine 0.1 g per os
N05AB20 Homophenazine

Phenothiazines with piperidine structure
N05AC01 Periciazine 50 mg per os
N05AC02 Thioridazine 0.3 g per os
N05AC03 Mesoridazine 0.2 g per os
N05AC04 Pipotiazine 10 mg per os

Butyrophenone derivatives
N05AD01 Haloperidol 8 mg per os
N05AD02 Trifluperidol 2 mg per os
N05AD03 Melperone* 0.3 g per os
N05AD04 Moperon 20 mg per os
N05AD05 Pipamperone 0.2 g per os

Table 2. Antipsychotic drugs with defined daily doses   (*Continued*)

N05AD06 Bromperidol 10 mg per os
N05AD07 Benperidol 1.5 mg per os
N05AD08 Droperidol
N05AD09 Fluanisone

N05AE Indole derivatives
N05AE01 Oxypertine 0.12 g per os
N05AE02 Molindone 50 mg per os
N05AE03 Sertindole* 16 mg per os
N05AE04 Ziprasidone* 80 mg per os

Thioxanthene derivatives
N05AF01 Flupentixol 6 mg per os
N05AF02 Clopenthixol 0.1 g per os
N05AF03 Chlorprothixene 0.3 g per os
N05AF04 Tiotixene 30 mg per os
N05AF05 Zuclopenthixol 30 mg per os

Diphenylbutylpiperidine derivatives
N05AG01 Fluspirilene
N05AG02 Pimozide 4 mg per os
N05AG03 Penfluridol 6 mg per os

Diazepines, Oxazepines and Thiazepines
N05AH01 Loxapine 0.1 g per os
N05AH02 Clozapine* 0.3 g per os
N05AH03 Olanzapine* 10 mg per os
N05AH04 Quetiapine* 0.4 g per os

Benzamides
N05AL01 Sulpiride 0.8 g per os
N05AL02 Sultopride 1.2 g per os
N05AL03 Tiapride 0.4 g per os
N05AL04 Remoxipride 0.3 g per os
N05AL05 Amisulpride* 0.4 g per os
N05AL06 Veralipride
N05AL07 Levosulpiride 0.4 g per os

Other antipsychotics
N05AX07 Prothipendyl 0.24 g per os
N05AX08 Risperidone* 5 mg per os
N05AX09 Clotiapine 80 mg per os
N05AX10 Mosapramine*
N05AX11 Zotepine* 0.2 g per os
N05AX12 Aripiprazole* 15 mg per os
N05AX13 Paliperidone*
*atypical antipsychotics

* Atypical antipsychotic agents.

Table 3. Characteristics of included studies

Study IDI	Setting	Duration	Ran-domised number	Discon-tinuation group	Continua-tion group	Discon-tinuation schedule	Control	Be-havioural inclusion criteria	Notes
Ballard 2004	Residents in long-term care facilities	3 months	100	46	54	Abrupt	Typical AP[a] or risperidone	NPI[b] not higher than 7	
Ballard 2008	Residents in long-term care facilities	6 months 12 months	165	82	83	Abrupt	Typical and risperidone	NR[c]	
Bergh 2011	Residents in nursing homes	25 weeks	19	9	10	Tapering over 2 week	Risperidone	NR[c]	Unpublished study
Bridges-Parlet 1997	Residents in long-term care facilities	1 month	36	22	14	Abrupt + tapering over 2 weeks	Typical AP[a]	Physically aggressive participants identified by nurse supervisors	
Cohen-Mansfield 1999	Residents in nursing homes	7 weeks followed by 7 weeks cross-over	58	29	29	Tapering over 3 weeks	Typical AP[a] + lorazepam	NR[c]	Cross-over study
Devanand 2011	Residents in the community	6 months (primary analysis) 12 months	20	10	10	Abrupt + tapering over 2 weeks	Haloperidol	Current symptoms of psychosis, agitation or aggression	Participants had a response to haloperidol open treatment for 20 weeks
Devanand 2012	Residents in the community and nursing homes	4 months 8 months	110	70	40	Abrupt + tapering over 2 week	Risperidone	NPI[b] score higher than 4 on psychosis or agitation/aggression subscale	Participants had a response to risperidone open treatment for 16 weeks

Table 3. Characteristics of included studies *(Continued)*

Findlay 1989	Residents in nursing homes	1 month	36	18	18	Ta-pering over 1 week	Thiori-dazine	NR[c]	
Ruths 2008	Residents in nursing homes	1 month	55	27	28	Abrupt	Haloperi-dol risperi-done, olanzapine	All partic-ipants re-gardless in-dividual symptoms	
van Reekum 2002	Residents in nursing homes	26 weeks	34	17	17	Ta-pering over 2 weeks	Typical AP [a]	Stable be-haviour	

[a] AP: antipsychotic drug.
[b] NPI: Neuropsychiatric Inventory.
[c] NR: not reported.

APPENDICES

Appendix 1. Initial search: 9 February 2009

Source	Date range searched	Hits retrieved
MEDLINE (PubMed)	Up to 9 Feb 2009	108
Embase (Ovid SP)	Up to 10 Feb 2009	37
PsycINFO (Ovid SP)	Up to 10 Feb 2009	20
CINAHL (Ovid SP)	Up to 11 Feb 2009	16
LILACS (Bireme)	Up to 9 Feb 2009	0
CDCIG SR*	Searched 9 Feb 2009	163
CENTRAL (*Cochrane Library*)	Issue 1 2009	75
ISTP Conference Proceedings portal.isiknowledge.com/portal.cgi	Up to 11 Feb 2009	105

(Continued)

Australian Digital Theses Program adt.caul.edu.au/	Searched 12 Feb 2009	0
Canadian Theses and Dissertations www.collectionscanada.ca/thesescanada/index-e.html	Searched 12 Feb 2009	0
WHO ICTRP	Searched 11 Feb 2009	4
Current Controlled trials: MetaRegister of Controlled trials (mRCT) www.controlled-trials.com/	Searched 11 Feb 2009	1
ISRCTN Register	Searched 12 Feb 2009	0
Nederlands Trial Register www.trialregister.nl/trialreg/index.asp	Searched 12 Feb 2009	0
ClinicalTrials.gov www.ClinicalTrials.gov	Included in WHO portal	//
IPFMA Clinical Trials Register www.ifpma.org/clinicaltrials.html	Searched 12 Feb 2009	0
UMIN Japan Trial Register www.umin.ac.jp/ctr/	Searched 12 Feb 2009	0
OPENsigle	Searched 12 Feb 2009	0

Appendix 2. Updated search: 11 March 2011

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Antipsychotic OR neuroleptic OR APSY	126
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950 to 11 March 2011 (Ovid SP)	1. antipsychotic*.ti,ab. 2. "anti-psychotic*".ti,ab. 3. Antipsychotic Agents/ 4. neuroleptic*.ti,ab. 5. phenothiazines.ti,ab. 6. Phenothiazines/ 7. butyrophenones.ti,ab. 8. Butyrophenones/ 9. risperidone.ti,ab. 10. Risperidone/	86

Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia (Review)

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(Continued)

11. Risperdal*.ti,ab.
12. olanzapine.ti,ab.
13. (Zyprexa* or Zalasta* or Zolafren* or Olzapin* or Oferta* or Zypadhera*).ti,ab
14. haloperidol.ti,ab.
15. Haloperidol/
16. (Aloperidin* or Bioperidolo* or Brotopon* or Dozic* or Duraperidol*).ti,ab
17. prothipendyl.ti,ab.
18. methotrimeprazine.ti,ab.
19. Methotrimeprazine/
20. (Nosinan* or Nozinan* or Levoprome*).ti,ab.
21. clopenthixol.ti,ab.
22. Clopenthixol/
23. (Sordinol* or clopentixol).ti,ab.
24. flupenthixol.ti,ab.
25. Flupenthixol/
26. (flupentixol or depixol* or fluanxol*).ti,ab.
27. clothiapine.ti,ab.
28. metylperon.ti,ab.
29. melperon.ti,ab.
30. droperidol.ti,ab.
31. Droperidol/
32. (Droleptan* or Dridol* or Inapsine* or Xomolix*).ti,ab.
33. pipamperone.ti,ab.
34. Dipiperon*.ti,ab.
35. benperidol.ti,ab.
36. Benperidol/
37. Anquil*.ti,ab.
38. bromperidol.ti,ab.
39. Bromidol*.ti,ab.
40. fluspirilene.ti,ab.
41. Fluspirilene/
42. (Redeptin* or Imap*).ti,ab.
43. pimozide.ti,ab.
44. Pimozide/
45. orap*.ti,ab.
46. penfluridol.ti,ab.
47. Penfluridol/
48. (Semap* or Micefal*).ti,ab.
49. sulpiride.ti,ab.
50. Sulpiride/
51. veralipride.ti,ab.
52. (Agreal* or Agradil*).ti,ab.
53. levosulpiride.ti,ab.

54. sultopride.ti,ab.
55. (Barnetil* or Barnotil* or Topral*).ti, ab.
56. aripiprazole.ti,ab.
57. (Abilify* or Aripiprex*).ti,ab.
58. clozapine.ti,ab.
59. Clozapine/
60. (Clozaril* or Azaleptin* or Leponex* or Fazaclo* or Froidir* or Denzapine* or Zaponex* or Klozapol* or Clopine*).ti,ab
61. quetiapine.ti,ab.
62. (Seroquel* or Ketipinor*).ti,ab.
63. thioridazine.ti,ab.
64. Thioridazine/
65. (Mellaril* or Novoridazine* or Thioril*).ti,ab.
66. or/1-65
67. exp Dementia/
68. Delirium/
69. Wernicke Encephalopathy/
70. Delirium, Dementia, Amnestic, Cognitive Disorders/
71. dement*.mp.
72. alzheimer*.mp.
73. (lewy* adj2 bod*).mp.
74. deliri*.mp.
75. (chronic adj2 cerebrovascular).mp.
76. ("organic brain disease" or "organic brain syndrome").mp
77. ("normal pressure hydrocephalus" and "shunt*").mp.
78. "benign senescent forgetfulness".mp.
79. (cerebr* adj2 deteriorat*).mp.
80. (cerebral* adj2 insufficient*).mp.
81. (pick* adj2 disease).mp.
82. (creutzfeldt or jcd or cjd).mp.
83. huntington*.mp.
84. binswanger*.mp.
85. korsako*.mp.
86. or/67-85
87. 66 and 86
88. (discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*).ti,ab
89. 87 and 88
90. randomized controlled trial.pt.
91. controlled clinical trial.pt.
92. randomized.ab.

	93. placebo.ab. 94. drug therapy.fs. 95. randomly.ab. 96. trial.ab. 97. groups.ab. 98. or/90-97 99. (animals not (humans and animals)). sh. 100. 98 not 99 101. 89 and 100 102. (2009* or 2010* or 2011*).ed. 103. 101 and 102	
3. Embase 1980 to 2011 week 12 (Ovid SP)	1. antipsychotic*.ti,ab. 2. "anti-psychotic*".ti,ab. 3. Antipsychotic Agents/ 4. neuroleptic*.ti,ab. 5. phenothiazines.ti,ab. 6. Phenothiazines/ 7. butyrophenones.ti,ab. 8. Butyrophenones/ 9. risperidone.ti,ab. 10. Risperidone/ 11. Risperdal*.ti,ab. 12. olanzapine.ti,ab. 13. (Zyprexa* or Zalasta* or Zolafren* or Olzapin* or Oferta* or Zypadhera*).ti,ab 14. haloperidol.ti,ab. 15. Haloperidol/ 16. (Aloperidin* or Bioperidolo* or Brotopon* or Dozic* or Duraperidol*).ti,ab 17. prothipendyl.ti,ab. 18. methotrimeprazine.ti,ab. 19. Methotrimeprazine/ 20. (Nosinan* or Nozinan* or Levoprome*).ti,ab. 21. clopenthixol.ti,ab. 22. Clopenthixol/ 23. (Sordinol* or clopentixol).ti,ab. 24. flupenthixol.ti,ab. 25. Flupenthixol/ 26. (flupentixol or depixol* or fluanxol*).ti,ab. 27. clothiapine.ti,ab. 28. metylperon.ti,ab. 29. melperon.ti,ab. 30. droperidol.ti,ab. 31. Droperidol/ 32. (Droleptan* or Dridol* or Inapsine* or	178

(Continued)

Xomolix*).ti,ab.
33. pipamperone.ti,ab.
34. Dipiperon*.ti,ab.
35. benperidol.ti,ab.
36. Benperidol/
37. Anquil*.ti,ab.
38. bromperidol.ti,ab.
39. Bromidol*.ti,ab.
40. fluspirilene.ti,ab.
41. Fluspirilene/
42. (Redeptin* or Imap*).ti,ab.
43. pimozide.ti,ab.
44. Pimozide/
45. orap*.ti,ab.
46. penfluridol.ti,ab.
47. Penfluridol/
48. (Semap* or Micefal*).ti,ab.
49. sulpiride.ti,ab.
50. Sulpiride/
51. veralipride.ti,ab.
52. (Agreal* or Agradil*).ti,ab.
53. levosulpiride.ti,ab.
54. sultopride.ti,ab.
55. (Barnetil* or Barnotil* or Topral*).ti,
ab.
56. aripiprazole.ti,ab.
57. (Abilify* or Aripiprex*).ti,ab.
58. clozapine.ti,ab.
59. Clozapine/
60. (Clozaril* or Azaleptin* or Leponex*
or Fazaclo* or Froidir* or Denzapine* or
Zaponex* or Klozapol* or Clopine*).ti,ab
61. quetiapine.ti,ab.
62. (Seroquel* or Ketipinor*).ti,ab.
63. thioridazine.ti,ab.
64. Thioridazine/
65. (Mellaril* or Novoridazine* or Thio-
ril*).ti,ab.
66. or/1-65
67. exp dementia/
68. Lewy body/
69. delirium/
70. Wernicke encephalopathy/
71. cognitive defect/
72. dement*.mp.
73. alzheimer*.mp.
74. (lewy* adj2 bod*).mp.
75. deliri*.mp.

(Continued)

	76. (chronic adj2 cerebrovascular).mp. 77. ("organic brain disease" or "organic brain syndrome").mp 78. "supranuclear palsy".mp. 79. ("normal pressure hydrocephalus" and "shunt*").mp. 80. "benign senescent forgetfulness".mp. 81. (cerebr* adj2 deteriorat*).mp. 82. (cerebral* adj2 insufficient*).mp. 83. (pick* adj2 disease).mp. 84. (creutzfeldt or jcd or cjd).mp. 85. huntington*.mp. 86. binswanger*.mp. 87. korsako*.mp. 88. CADASIL.mp. 89. or/67-88 90. 66 and 89 91. (discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*).ti,ab 92. 90 and 91 93. randomized controlled trial/ 94. randomi?ed.ab. 95. controlled clinical trial/ 96. placebo.ab. 97. randomly.ab. 98. trial.ab. 99. groups.ab. 100. or/93-99 101. 92 and 100 102. (2009* or 2010* or 2011*).em. 103. 101 and 102	
4. PsycINFO 1806 to March week 3 2011 (Ovid SP)	1. antipsychotic*.ti,ab. 2. "anti-psychotic*".ti,ab. 3. neuroleptic*.ti,ab. 4. phenothiazines.ti,ab. 5. butyrophenones.ti,ab. 6. risperidone.ti,ab. 7. Risperidone/ 8. Risperdal*.ti,ab. 9. olanzapine.ti,ab. 10. (Zyprexa* or Zalasta* or Zolafren* or Olzapin* or Oferta* or Zypadhera*).ti,ab 11. haloperidol.ti,ab. 12. Haloperidol/ 13. (Aloperidin* or Bioperidolo* or Brotopon* or Dozic* or Duraperidol*).ti,ab 14. prothipendyl.ti,ab.	110

(Continued)

15. methotrimeprazine.ti,ab.
16. (Nosinan* or Nozinan* or Levoprome*).ti,ab.
17. clopenthixol.ti,ab.
18. (Sordinol* or clopentixol).ti,ab.
19. flupenthixol.ti,ab.
20. (flupentixol or depixol* or fluanxol*).ti,ab.
21. clothiapine.ti,ab.
22. droperidol.ti,ab.
23. (Droleptan* or Dridol* or Inapsine* or Xomolix*).ti,ab.
24. pipamperone.ti,ab.
25. Dipiperon*.ti,ab.
26. benperidol.ti,ab.
27. bromperidol.ti,ab.
28. Bromidol*.ti,ab.
29. fluspirilene.ti,ab.
30. (Redeptin* or Imap*).ti,ab.
31. pimozide.ti,ab.
32. Pimozide/
33. orap*.ti,ab.
34. penfluridol.ti,ab.
35. (Semap* or Micefal*).ti,ab.
36. sulpiride.ti,ab.
37. Sulpiride/
38. veralipride.ti,ab.
39. levosulpiride.ti,ab.
40. sultopride.ti,ab.
41. (Barnetil* or Barnotil* or Topral*).ti,ab.
42. aripiprazole.ti,ab.
43. (Abilify* or Aripiprex*).ti,ab.
44. clozapine.ti,ab.
45. Clozapine/
46. (Clozaril* or Azaleptin* or Leponex* or Fazaclo* or Froidir* or Denzapine* or Zaponex* or Klozapol* or Clopine*).ti,ab
47. quetiapine.ti,ab.
48. (Seroquel* or Ketipinor*).ti,ab.
49. thioridazine.ti,ab.
50. Thioridazine/
51. (Mellaril* or Novoridazine* or Thioril*).ti,ab.
52. (discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*).ti,ab
53. or/1-51

	54. 52 and 53 55. exp Dementia/ 56. exp Delirium/ 57. exp Huntingtons Disease/ 58. exp Kluver Bucy Syndrome/ 59. exp Wernickes Syndrome/ 60. exp Cognitive Impairment/ 61. dement*.mp. 62. alzheimer*.mp. 63. (lewy* adj2 bod*).mp. 64. deliri*.mp. 65. (chronic adj2 cerebrovascular).mp. 66. ("organic brain disease" or "organic brain syndrome").mp 67. "supranuclear palsy".mp. 68. ("normal pressure hydrocephalus" and "shunt*").mp. 69. "benign senescent forgetfulness".mp. 70. (cerebr* adj2 deteriorat*).mp. 71. (cerebral* adj2 insufficient*).mp. 72. (pick* adj2 disease).mp. 73. (creutzfeldt or jcd or cjd).mp. 74. huntington*.mp. 75. binswanger*.mp. 76. korsako*.mp. 77. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp 78. or/55-77 79. 54 and 78 80. (2009* or 2010* or 2011*).up. 81. 79 and 80	
5. CINAHL (EBSCO host)	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer* S6 TX lewy* N2 bod* S7 TX deliri* S8 TX chronic N2 cerebrovascular S9 TX "organic brain disease" or "organic brain syndrome" S10 TX "normal pressure hydrocephalus" and "shunt*" S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient*	99

(Continued)

S14 TX pick* N2 disease
S15 TX creutzfeldt or jcd or cjd
S16 TX huntington*
S17 TX binswanger*
S18 TX korsako*
S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18
S20 TX "cognit* impair*"
S21 TX "cognit* defect*"
S22 (MH "Cognition Disorders+")
S23 TX MCI
S24 TX ACMI
S25 TX ARCD
S26 TX SMC
S27 TX CIND
S28 TX BSF
S29 TX AAMI
S30 AB MD
S31 AB LCD
S32 AB QD OR "questionable dementia"
S33 TX AACD
S34 TX MNCD
S35 TX "N-MCI" or "A-MCI" or "M-MCI"
S36 TX "preclinical AD"
S37 TX "pre-clinical AD"
S38 TX "preclinical alzheimer*" or "pre-clinical alzheimer*"
S39 TX aMCI OR MCIa
S40 TX "CDR 0.5" or "clinical dementia rating scale 0.5"
S41 TX "GDS 3" OR "stage 3 GDS"
S42 TX "global deterioration scale" AND "stage 3"
S43 TX "Benign senescent forgetfulness"
S44 TX "mild neurocognit* disorder*"
S45 TX prodrom* N2 dement*
S46 TX "age-related symptom*"
S47 TX cognit* N2 deficit*
S48 TX cognit* N2 deteriorat*
S49 TX cognit* N2 declin*
S50 TX cognit* N2 degenerat*
S51 TX cognit* N2 complain*
S52 TX cognit* N2 disturb*
S53 TX cognit* N2 disorder*
S54 TX memory N2 episod* or TX memory N2 los* or TX memory N2 impair* or

	TX memory N2 complain* S55 TX memory N2 disturb* or TX memory N2 disorder* or TX cerebr* N2 impair* or TX cerebr* N2 los* S56 TX cerebr* N2 complain* or TX cerebr* N2 deteriorat* or TX cerebr* N2 disorder* or TX cerebr* N2 disturb* S57 TX mental* N2 declin* or TX mental* N2 los* or TX mental* N2 impair* or TX mental* N2 deteriorat* S58 TX ”pre-clinical dementia“ or TX ”preclinical dementia“ S59 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 S60 S19 or S59	
6. ISI Web of Knowledge - all databases (includes: Web of Science (1945 to present); BIOSIS Previews (1926 to present); MEDLINE (1950 to present); Journal Citation Reports)	#1 Topic=(antipsychotic* OR neuroleptic* OR phenothiazines OR butyrophenones OR risperidone OR olanzapine OR haloperidol OR prothipendyl OR methotrimeprazine OR clopenthixol OR flupenthixol) #2 Topic=(clothiapine OR melperon OR droperidol OR pipamperone OR benperidol OR bromperidol OR fluspirilene OR pimozide OR penfluridol OR sulpiride) #3 Topic=(veralipride OR levosulipride OR sultopride OR aripiprazole OR clozapine OR quetiapine OR thioridazine) #4 Topic=(discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*) #5 #3 OR #2 OR #1 #6 #5 AND #4 #7 Topic=(dementia OR alzheimer* OR ”lew* bod*“ OR ”parkinson disease dementia“ OR VAD OR PDD) #8 #7 AND #6 #9 Topic=(randomly OR randomized OR randomised OR placebo* OR trial OR RCT) #10 #9 AND #8 #11 Topic=(#10) AND Year Published= (2009-2011)	90

(Continued)

7. LILACS (Bireme)	antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics [Words] and dementia OR demenc$ OR alzheimer$ [Words] and 2009 OR 2010 OR 2011 [Country, year publication]	17	
8. CENTRAL (*Cochrane Library*) (Issue 1, January 2011)	#1 "anti-psychotic*" #2 antipsychotic*:ti,ab #3 MeSH descriptor Antipsychotic Agents explode all trees #4 neuroleptic*:ti,ab #5 phenothiazines OR butyrophenones OR risperidone OR Risperdal* OR olanzapine #6 Zyprexa* OR Zalasta* OR Zolafren* OR Olzapin* OR Oferta* OR Zypadhera* #7 haloperidol #8 Aloperidin* OR Bioperidolo* OR Brotopon* OR Dozic* OR Duraperidol* #9 prothipendyl OR methotrimeprazine OR Nosinan* OR Nozinan* OR Levoprome* #10 clopenthixol OR Sordinol* OR clopentixol OR flupenthixol OR flupentixol OR depixol* OR fluanxol* #11 clothiapine OR metylperon OR melperon OR droperidol OR Droleptan* OR Dridol* OR Inapsine* OR Xomolix* #12 pipamperone OR Dipiperon* OR benperidol OR Anquil* OR bromperidol OR Bromidol* OR fluspirilene OR Redeptin* OR Imap* #13 pimozide OR orap* OR penfluridol OR Semap* OR Micefal* #14 sulpiride OR veralipride OR Agreal* OR Agradil* OR levosulpiride OR sultopride #15 Barnetil* OR Barnotil* OR Topral* #16 aripiprazole OR Abilify* OR Aripiprex* OR clozapine OR Clozaril* OR Azaleptin* OR Leponex* OR Fazaclo* OR Froidir* OR Denzapine* OR Zaponex* OR Klozapol* #17 quetiapine OR Seroquel* OR Ketipinor* #18 thioridazine OR Mellaril* OR Novoridazine* OR Thioril* #19 (#1 OR #2 OR #3 OR #4 OR #5 OR	46	

(Continued)

| | #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)
#20 Dement*
#21 Deliri*
#22 alzheimer*
#23 "organic brain disease" OR "organic brain syndrome"
#24 creutzfeldt OR jcd OR cjd
#25 huntington*
#26 binswanger*
#27 korsako*
#28 "parkinson* disease dementia*" OR PDD
#29 "lew* bod*" OR DLB OR LDB OR LBD
#30 MeSH descriptor Dementia explode all trees
#31 (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)
#32 (#19 AND #31), from 2009 to 2011 | |
| 9. Clinicaltrials.gov (www.clinicaltrials.gov) | Search 1: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop \| dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD \| antipsychotic OR neuroleptic OR risperidone OR olanzapine OR haloperidol OR prothipendyl OR clopenthixol \| received from 01/01/2009 to 03/31/2011
Search 2: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop \| dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD \| clothiapine OR droperidol OR pipamperone OR benperidol OR bromperidol OR fluspirilene OR pimozide \| received from 01/01/2009 to 03/31/2011
Search 3: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop \| dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD \| penfluridol OR sulpiride OR veralipride OR levosulpiride OR sultopride | 9 + 0 + 2 = 11 |

(Continued)

	OR aripiprazole OR clozapine OR quetiapine OR thioridazine | received from 01/01/2009 to 03/31/2011	
10. ICTRP Search Portal (apps.who.int/trialsearch) (includes: Australian New Zealand Clinical Trials Registry; ClinicalTrials.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; Netherlands National Trial Register)	Search 1: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop | dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | antipsychotic OR neuroleptic OR risperidone OR olanzapine OR haloperidol OR prothipendyl OR clopenthixol | received from 01/01/2009 to 03/31/2011 Search 2: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop | dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | clothiapine OR droperidol OR pipamperone OR benperidol OR bromperidol OR fluspirilene OR pimozide | received from 01/01/2009 to 03/31/2011 Search 3: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop | dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | penfluridol OR sulpiride OR veralipride OR levosulpiride OR sultopride OR aripiprazole OR clozapine OR quetiapine OR thioridazine | received from 01/01/2009 to 03/31/2011	13
TOTAL before de-duplication	776	
TOTAL after de-duplication and first-assess	70	

Appendix 3. Top-up searches: June 2012, November 2012, March 2017, January 2018

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois) [Date of most recent search: 10 January 2018]	Antipsychotic OR neuroleptic OR APSY	Jun 2012: 58 Nov 2012: 1 Mar 2017: 0 Jan 2018: 0

		Jun 2012: 60
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP) [Date of most recent search: 10 January 2018]	1. antipsychotic*.ti,ab. 2. "anti-psychotic*".ti,ab. 3. Antipsychotic Agents/ 4. neuroleptic*.ti,ab. 5. phenothiazines.ti,ab. 6. Phenothiazines/ 7. butyrophenones.ti,ab. 8. Butyrophenones/ 9. risperidone.ti,ab. 10. Risperidone/ 11. Risperdal*.ti,ab. 12. olanzapine.ti,ab. 13. (Zyprexa* or Zalasta* or Zolafren* or Olzapin* or Oferta* or Zypadhera*).ti,ab 14. haloperidol.ti,ab. 15. Haloperidol/ 16. (Aloperidin* or Bioperidolo* or Brotopon* or Dozic* or Duraperidol*).ti,ab 17. prothipendyl.ti,ab. 18. methotrimeprazine.ti,ab. 19. Methotrimeprazine/ 20. (Nosinan* or Nozinan* or Levoprome*).ti,ab. 21. clopenthixol.ti,ab. 22. Clopenthixol/ 23. (Sordinol* or clopentixol).ti,ab. 24. flupenthixol.ti,ab. 25. Flupenthixol/ 26. (flupentixol or depixol* or fluanxol*).ti,ab. 27. clothiapine.ti,ab. 28. metylperon.ti,ab. 29. melperon.ti,ab. 30. droperidol.ti,ab. 31. Droperidol/ 32. (Droleptan* or Dridol* or Inapsine* or Xomolix*).ti,ab. 33. pipamperone.ti,ab. 34. Dipiperon*.ti,ab. 35. benperidol.ti,ab. 36. Benperidol/ 37. Anquil*.ti,ab. 38. bromperidol.ti,ab. 39. Bromidol*.ti,ab. 40. fluspirilene.ti,ab. 41. Fluspirilene/	Nov 2012: 28 (plus suppl search hits) Mar 2017: 284 Jan 2018: 63

(Continued)

42. (Redeptin* or Imap*).ti,ab.
43. pimozide.ti,ab.
44. Pimozide/
45. orap*.ti,ab.
46. penfluridol.ti,ab.
47. Penfluridol/
48. (Semap* or Micefal*).ti,ab.
49. sulpiride.ti,ab.
50. Sulpiride/
51. veralipride.ti,ab.
52. (Agreal* or Agradil*).ti,ab.
53. levosulpiride.ti,ab.
54. sultopride.ti,ab.
55. (Barnetil* or Barnotil* or Topral*).ti,
ab.
56. aripiprazole.ti,ab.
57. (Abilify* or Aripiprex*).ti,ab.
58. clozapine.ti,ab.
59. Clozapine/
60. (Clozaril* or Azaleptin* or Leponex*
or Fazaclo* or Froidir* or Denzapine* or
Zaponex* or Klozapol* or Clopine*).ti,ab
61. quetiapine.ti,ab.
62. (Seroquel* or Ketipinor*).ti,ab.
63. thioridazine.ti,ab.
64. Thioridazine/
65. (Mellaril* or Novoridazine* or Thio-
ril*).ti,ab.
66. or/1-65
67. exp Dementia/
68. Delirium/
69. Wernicke Encephalopathy/
70. Delirium, Dementia, Amnestic, Cog-
nitive Disorders/
71. dement*.mp.
72. alzheimer*.mp.
73. (lewy* adj2 bod*).mp.
74. deliri*.mp.
75. (chronic adj2 cerebrovascular).mp.
76. ("organic brain disease" or "organic
brain syndrome").mp
77. ("normal pressure hydrocephalus" and
"shunt*").mp.
78. "benign senescent forgetfulness".mp.
79. (cerebr* adj2 deteriorat*).mp.
80. (cerebral* adj2 insufficient*).mp.
81. (pick* adj2 disease).mp.
82. (creutzfeldt or jcd or cjd).mp.

(Continued)

	83. huntington*.mp. 84. binswanger*.mp. 85. korsako*.mp. 86. or/67-85 87. 66 and 86 88. (discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*).ti,ab 89. 87 and 88 90. randomized controlled trial.pt. 91. controlled clinical trial.pt. 92. randomized.ab. 93. placebo.ab. 94. drug therapy.fs. 95. randomly.ab. 96. trial.ab. 97. groups.ab. 98. or/90-97 99. (animals not (humans and animals)).sh. 100. 98 not 99 101. 89 and 100 102. (2011* or 2012*).ed. 103. 101 and 102	
3. Embase 1980 to 2018 January 09 (Ovid SP) [Date of most recent search: 10 January 2018]	1. antipsychotic*.ti,ab. 2. "anti-psychotic*".ti,ab. 3. Antipsychotic Agents/ 4. neuroleptic*.ti,ab. 5. phenothiazines.ti,ab. 6. Phenothiazines/ 7. butyrophenones.ti,ab. 8. Butyrophenones/ 9. risperidone.ti,ab. 10. Risperidone/ 11. Risperdal*.ti,ab. 12. olanzapine.ti,ab. 13. (Zyprexa* or Zalasta* or Zolafren* or Olzapin* or Oferta* or Zypadhera*).ti,ab 14. haloperidol.ti,ab. 15. Haloperidol/ 16. (Aloperidin* or Bioperidolo* or Brotopon* or Dozic* or Duraperidol*).ti,ab 17. prothipendyl.ti,ab. 18. methotrimeprazine.ti,ab. 19. Methotrimeprazine/ 20. (Nosinan* or Nozinan* or Levoprome*).ti,ab. 21. clopenthixol.ti,ab.	Jun 2012: 109 Nov 2012: 35 (plus suppl search hits) Mar 2017: 533 Jan 2018: 133

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22. Clopenthixol/
23. (Sordinol* or clopentixol).ti,ab.
24. flupenthixol.ti,ab.
25. Flupenthixol/
26. (flupentixol or depixol* or fluanxol*).ti,ab.
27. clothiapine.ti,ab.
28. metylperon.ti,ab.
29. melperon.ti,ab.
30. droperidol.ti,ab.
31. Droperidol/
32. (Droleptan* or Dridol* or Inapsine* or Xomolix*).ti,ab.
33. pipamperone.ti,ab.
34. Dipiperon*.ti,ab.
35. benperidol.ti,ab.
36. Benperidol/
37. Anquil*.ti,ab.
38. bromperidol.ti,ab.
39. Bromidol*.ti,ab.
40. fluspirilene.ti,ab.
41. Fluspirilene/
42. (Redeptin* or Imap*).ti,ab.
43. pimozide.ti,ab.
44. Pimozide/
45. orap*.ti,ab.
46. penfluridol.ti,ab.
47. Penfluridol/
48. (Semap* or Micefal*).ti,ab.
49. sulpiride.ti,ab.
50. Sulpiride/
51. veralipride.ti,ab.
52. (Agreal* or Agradil*).ti,ab.
53. levosulpiride.ti,ab.
54. sultopride.ti,ab.
55. (Barnetil* or Barnotil* or Topral*).ti,ab.
56. aripiprazole.ti,ab.
57. (Abilify* or Aripiprex*).ti,ab.
58. clozapine.ti,ab.
59. Clozapine/
60. (Clozaril* or Azaleptin* or Leponex* or Fazaclo* or Froidir* or Denzapine* or Zaponex* or Klozapol* or Clopine*).ti,ab
61. quetiapine.ti,ab.
62. (Seroquel* or Ketipinor*).ti,ab.
63. thioridazine.ti,ab.
64. Thioridazine/

	65. (Mellaril* or Novoridazine* or Thioril*).ti,ab.	
	66. or/1-65	
	67. exp dementia/	
	68. Lewy body/	
	69. delirium/	
	70. Wernicke encephalopathy/	
	71. cognitive defect/	
	72. dement*.mp.	
	73. alzheimer*.mp.	
	74. (lewy* adj2 bod*).mp.	
	75. deliri*.mp.	
	76. (chronic adj2 cerebrovascular).mp.	
	77. ("organic brain disease" or "organic brain syndrome").mp	
	78. "supranuclear palsy".mp.	
	79. ("normal pressure hydrocephalus" and "shunt*").mp.	
	80. "benign senescent forgetfulness".mp.	
	81. (cerebr* adj2 deteriorat*).mp.	
	82. (cerebral* adj2 insufficient*).mp.	
	83. (pick* adj2 disease).mp.	
	84. (creutzfeldt or jcd or cjd).mp.	
	85. huntington*.mp.	
	86. binswanger*.mp.	
	87. korsako*.mp.	
	88. CADASIL.mp.	
	89. or/67-88	
	90. 66 and 89	
	91. (discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*).ti,ab	
	92. 90 and 91	
	93. randomized controlled trial/	
	94. randomi?ed.ab.	
	95. controlled clinical trial/	
	96. placebo.ab.	
	97. randomly.ab.	
	98. trial.ab.	
	99. groups.ab.	
	100. or/93-99	
	101. 92 and 100	
	102. (2011* or 2012*).em.	
	103. 101 and 102	
4. PsycINFO 1806 to January week 1 2018 (Ovid SP) [Date of most recent search: 10 January 2018]	1. antipsychotic*.ti,ab. 2. "anti-psychotic*".ti,ab. 3. neuroleptic*.ti,ab. 4. phenothiazines.ti,ab. 5. butyrophenones.ti,ab.	Jun 2012: 70 Nov 2012: 58 (plus suppl search hits) Mar 2017: 281 Jan 2018: 73

	6. risperidone.ti,ab. 7. Risperidone/ 8. Risperdal*.ti,ab. 9. olanzapine.ti,ab. 10. (Zyprexa* or Zalasta* or Zolafren* or Olzapin* or Oferta* or Zypadhera*).ti,ab 11. haloperidol.ti,ab. 12. Haloperidol/ 13. (Aloperidin* or Bioperidolo* or Brotopon* or Dozic* or Duraperidol*).ti,ab 14. prothipendyl.ti,ab. 15. methotrimeprazine.ti,ab. 16. (Nosinan* or Nozinan* or Levoprome*).ti,ab. 17. clopenthixol.ti,ab. 18. (Sordinol* or clopentixol).ti,ab. 19. flupenthixol.ti,ab. 20. (flupentixol or depixol* or fluanxol*).ti,ab. 21. clothiapine.ti,ab. 22. droperidol.ti,ab. 23. (Droleptan* or Dridol* or Inapsine* or Xomolix*).ti,ab. 24. pipamperone.ti,ab. 25. Dipiperon*.ti,ab. 26. benperidol.ti,ab. 27. bromperidol.ti,ab. 28. Bromidol*.ti,ab. 29. fluspirilene.ti,ab. 30. (Redeptin* or Imap*).ti,ab. 31. pimozide.ti,ab. 32. Pimozide/ 33. orap*.ti,ab. 34. penfluridol.ti,ab. 35. (Semap* or Micefal*).ti,ab. 36. sulpiride.ti,ab. 37. Sulpiride/ 38. veralipride.ti,ab. 39. levosulpiride.ti,ab. 40. sultopride.ti,ab. 41. (Barnetil* or Barnotil* or Topral*).ti,ab. 42. aripiprazole.ti,ab. 43. (Abilify* or Aripiprex*).ti,ab. 44. clozapine.ti,ab. 45. Clozapine/ 46. (Clozaril* or Azaleptin* or Leponex* or Fazaclo* or Froidir* or Denzapine* or	

(Continued)

	Zaponex* or Klozapol* or Clopine*).ti,ab 47. quetiapine.ti,ab. 48. (Seroquel* or Ketipinor*).ti,ab. 49. thioridazine.ti,ab. 50. Thioridazine/ 51. (Mellaril* or Novoridazine* or Thioril*).ti,ab. 52. (discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*).ti,ab 53. or/1-51 54. 52 and 53 55. exp Dementia/ 56. exp Delirium/ 57. exp Huntingtons Disease/ 58. exp Kluver Bucy Syndrome/ 59. exp Wernickes Syndrome/ 60. exp Cognitive Impairment/ 61. dement*.mp. 62. alzheimer*.mp. 63. (lewy* adj2 bod*).mp. 64. deliri*.mp. 65. (chronic adj2 cerebrovascular).mp. 66. ("organic brain disease" or "organic brain syndrome").mp 67. "supranuclear palsy".mp. 68. ("normal pressure hydrocephalus" and "shunt*").mp. 69. "benign senescent forgetfulness".mp. 70. (cerebr* adj2 deteriorat*).mp. 71. (cerebral* adj2 insufficient*).mp. 72. (pick* adj2 disease).mp. 73. (creutzfeldt or jcd or cjd).mp. 74. huntington*.mp. 75. binswanger*.mp. 76. korsako*.mp. 77. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp 78. or/55-77 79. 54 and 78 80. (2011* or 2012*).up. 81. 79 and 80	
5. CINAHL (EBSCO host) [Date of most recent search: 10 January 2018]	S1 (MH "Dementia+") S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders") S3 (MH "Wernicke's Encephalopathy") S4 TX dement* S5 TX alzheimer*	Jun 2012: 71 Nov 2012: 51 (plus suppl search hits) Mar 2017: 26 Jan 2018: 8

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S6 TX lewy* N2 bod*
S7 TX deliri*
S8 TX chronic N2 cerebrovascular
S9 TX "organic brain disease" or "organic brain syndrome"
S10 TX "normal pressure hydrocephalus" and "shunt*"
S11 TX "benign senescent forgetfulness"
S12 TX cerebr* N2 deteriorat*
S13 TX cerebral* N2 insufficient*
S14 TX pick* N2 disease
S15 TX creutzfeldt or jcd or cjd
S16 TX huntington*
S17 TX binswanger*
S18 TX korsako*
S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18
S20 TX "cognit* impair*"
S21 TX "cognit* defect*"
S22 (MH "Cognition Disorders+")
S23 TX MCI
S24 TX ACMI
S25 TX ARCD
S26 TX SMC
S27 TX CIND
S28 TX BSF
S29 TX AAMI
S30 AB MD
S31 AB LCD
S32 AB QD OR "questionable dementia"
S33 TX AACD
S34 TX MNCD
S35 TX "N-MCI" or "A-MCI" or "M-MCI"
S36 TX "preclinical AD"
S37 TX "pre-clinical AD"
S38 TX "preclinical alzheimer*" or "pre-clinical alzheimer*"
S39 TX aMCI OR MCIa
S40 TX "CDR 0.5" or "clinical dementia rating scale 0.5"
S41 TX "GDS 3" OR "stage 3 GDS"
S42 TX "global deterioration scale" AND "stage 3"
S43 TX "Benign senescent forgetfulness"
S44 TX "mild neurocognit* disorder*"
S45 TX prodrom* N2 dement*

	S46 TX "age-related symptom*" S47 TX cognit* N2 deficit* S48 TX cognit* N2 deteriorat* S49 TX cognit* N2 declin* S50 TX cognit* N2 degenerat* S51 TX cognit* N2 complain* S52 TX cognit* N2 disturb* S53 TX cognit* N2 disorder* S54 TX memory N2 episod* or TX memory N2 los* or TX memory N2 impair* or TX memory N2 complain* S55 TX memory N2 disturb* or TX memory N2 disorder* or TX cerebr* N2 impair* or TX cerebr* N2 los* S56 TX cerebr* N2 complain* or TX cerebr* N2 deteriorat* or TX cerebr* N2 disorder* or TX cerebr* N2 disturb* S57 TX mental* N2 declin* or TX mental* N2 los* or TX mental* N2 impair* or TX mental* N2 deteriorat* S58 TX "pre-clinical dementia" or TX "preclinical dementia" S59 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 S60 S19 or S59 S61 EM 2011 S62 EM 2012 S63 S61 OR S62 S64 S60 AND S63	
6. ISI Web of Knowledge - all databases (includes: Web of Science (1945 to present); BIOSIS Previews (1926 to present); MEDLINE (1950 to present); Journal Citation Reports) [Date of most recent search: 10 January 2018]	#1 Topic=(antipsychotic* OR neuroleptic* OR phenothiazines OR butyrophenones OR risperidone OR olanzapine OR haloperidol OR prothipendyl OR methotrimeprazine OR clopenthixol OR flupenthixol) #2 Topic=(clothiapine OR melperon OR droperidol OR pipamperone OR benperidol OR bromperidol OR fluspirilene OR pimozide OR penfluridol OR sulpiride) #3 Topic=(veralipride OR levosulpiride OR sultopride OR aripiprazole OR clozapine OR quetiapine OR thioridazine) #4 Topic=(discontinu* or withdraw* or	Jun 2012: 56 Nov 2012: 260 (plus suppl search hits) Mar 2017: 290 Jan 2018: 48

	cessat* or reduce* or reducing or reduct* or taper* or stop*) #5 #3 OR #2 OR #1 #6 #5 AND #4 #7 Topic=(dementia OR alzheimer* OR "lew* bod*" OR "parkinson disease dementia" OR VAD OR PDD) #8 #7 AND #6 #9 Topic=(randomly OR randomized OR randomised OR placebo* OR trial OR RCT) #10 #9 AND #8	
7. LILACS (Bireme) [Date of most recent search: 10 January 2018]	antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics [Words] and dementia OR demenc$ OR alzheimer$ [Words]	Jun 2012: 6 Nov 2012: 1 Mar 2017: 0 Jan 2018: 0
8. CENTRAL (*Cochrane Library*) (Issue 1, 2018) [Date of most recent search: 10 January 2018]	#1 "anti-psychotic*" #2 antipsychotic*:ti,ab #3 MeSH descriptor Antipsychotic Agents explode all trees #4 neuroleptic*:ti,ab #5 phenothiazines OR butyrophenones OR risperidone OR Risperdal* OR olanzapine #6 Zyprexa* OR Zalasta* OR Zolafren* OR Olzapin* OR Oferta* OR Zypadhera* #7 haloperidol #8 Aloperidin* OR Bioperidolo* OR Brotopon* OR Dozic* OR Duraperidol* #9 prothipendyl OR methotrimeprazine OR Nosinan* OR Nozinan* OR Levoprome* #10 clopenthixol OR Sordinol* OR clopentixol OR flupenthixol OR flupentixol OR depixol* OR fluanxol* #11 clothiapine OR metylperon OR melperon OR droperidol OR Droleptan* OR Dridol* OR Inapsine* OR Xomolix* #12 pipamperone OR Dipiperon* OR benperidol OR Anquil* OR bromperidol OR Bromidol* OR fluspirilene OR Redeptin* OR Imap* #13 pimozide OR orap* OR penfluridol OR Semap* OR Micefal* #14 sulpiride OR veralipride OR Agreal* OR Agradil* OR levosulpiride OR sultopride	Jun 2012: 13 Nov 2012: 2 (plus suppl search hits) Mar 2017: 105 Jan 2018: 96

	#15 Barnetil* OR Barnotil* OR Topral* #16 aripiprazole OR Abilify* OR Aripiprex* OR clozapine OR Clozaril* OR Azaleptin* OR Leponex* OR Fazaclo* OR Froidir* OR Denzapine* OR Zaponex* OR Klozapol* #17 quetiapine OR Seroquel* OR Ketipinor* #18 thioridazine OR Mellaril* OR Novoridazine* OR Thioril* #19 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18) #20 Dement* #21 Deliri* #22 alzheimer* #23 ”organic brain disease“ OR ”organic brain syndrome“ #24 creutzfeldt OR jcd OR cjd #25 huntington* #26 binswanger* #27 korsako* #28 ”parkinson* disease dementia*“ OR PDD #29 ”lew* bod*“ OR DLB OR LDB OR LBD #30 MeSH descriptor Dementia explode all trees #31 (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30) #32 (#19 AND #31)	
9. Clinicaltrials.gov (www.clinicaltrials.gov) [Date of most recent search: 10 January 2018]	Search 1: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop | dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | antipsychotic OR neuroleptic OR risperidone OR olanzapine OR haloperidol OR prothipendyl OR clopenthixol Search 2: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop | dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | clothiapine OR droperi-	Jun 2012: 2 + 0 + 2 = 4 Nov 2012: 0 (plus suppl search hits) Mar 2017: 1 Jan 2018: 0

(Continued)

	dol OR pipamperone OR benperidol OR bromperidol OR fluspirilene OR pimozide Search 3: Advanced search: discontinue OR withdraw OR cessation OR reduce or reducing OR reduction OR taper OR stop | dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | penfluridol OR sulpiride OR veralipride OR levosulpiride OR sultopride OR aripiprazole OR clozapine OR quetiapine OR thioridazine	
10. ICTRP Search Portal (apps.who.int/ trialsearch) (includes: Australian New Zealand Clinical Trials Registry; Clinical-Trilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; Netherlands National Trial Register) [Date of most recent search: 10 January 2018]	Search 1: Advanced search: dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | antipsychotic OR neuroleptic OR risperidone OR olanzapine OR haloperidol OR prothipendyl OR clopenthixol Search 2: Advanced search: dementia OR alzheimer OR alzhimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | clothiapine OR droperidol OR pipamperone OR benperidol OR bromperidol OR fluspirilene OR pimozide Search 3: Advanced search: dementia OR alzheimer OR alzheimers OR alzheimer's OR lewy OR DLB OR AD OR LBD | penfluridol OR sulpiride OR veralipride OR levosulpiride OR sultopride OR aripiprazole OR clozapine OR quetiapine OR thioridazine	Jun 2012: 7 + 1 + 4 = 13 Nov 2012: 0 (plus suppl search hits) Mar 2017: 20 Jan 2018: 3
TOTAL before de-duplication and first-assessment		Jun 2012: 454 Nov 2012: 436 (plus Nov suppl search hits) Mar 2017: 1540 Jan 2018: 424
TOTAL after de-duplication and first-assessment by CDCIG Information specialists based on tiles and abstarcts		Jun 2012: 11 Nov 2012: 20 Mar 2017: 75 Jan 2018: 26
Supplementary search of additional antipsychotics not covered in previous searches (all dates)		
MEDLINE In-process and other non-indexed citations and MEDLINE 1950 to present (Ovid SP)	1. exp Dementia/ 2. Delirium/ 3. Wernicke Encephalopathy/ 4. Delirium, Dementia, Amnestic, Cognitive Disorders/	194

(Continued)

	5. dement*.mp. 6. alzheimer*.mp. 7. (lewy* adj2 bod*).mp. 8. deliri*.mp. 9. (chronic adj2 cerebrovascular).mp. 10. ("organic brain disease" or "organic brain syndrome").mp 11. ("normal pressure hydrocephalus" and "shunt*").mp. 12. "benign senescent forgetfulness".mp. 13. (cerebr* adj2 deteriorat*).mp. 14. (cerebral* adj2 insufficient*).mp. 15. (pick* adj2 disease).mp. 16. (creutzfeldt or jcd or cjd).mp. 17. huntington*.mp. 18. binswanger*.mp. 19. korsako*.mp. 20. or/1-19 21. amisulpiride.ti,ab. 22. Chlorpromazine/ 23. chlorpromazine.ti,ab. 24. Promazine/ 25. promazine.ti,ab. 26. Trifluoperazine/ 27. trifluoperazine.ti,ab. 28. Prochlorperazine/ 29. prochlorperazine.ti,ab. 30. or/21-29 31. 20 and 30 32. randomized controlled trial.pt. 33. controlled clinical trial.pt. 34. randomized.ab. 35. placebo.ab. 36. drug therapy.fs. 37. randomly.ab. 38. trial.ab. 39. groups.ab. 40. or/32-39 41. 31 and 40	
Embase 1980 to 2012 August 03 (Ovid SP)	1. exp dementia/ 2. Lewy body/ 3. delirium/ 4. Wernicke encephalopathy/ 5. cognitive defect/ 6. dement*.mp. 7. alzheimer*.mp. 8. (lewy* adj2 bod*).mp. 9. deliri*.mp.	425

(Continued)

| | 10. (chronic adj2 cerebrovascular).mp.
11. (”organic brain disease“ or ”organic brain syndrome“).mp
12. ”supranuclear palsy“.mp.
13. (”normal pressure hydrocephalus“ and ”shunt*“).mp.
14. ”benign senescent forgetfulness“.mp.
15. (cerebr* adj2 deteriorat*).mp.
16. (cerebral* adj2 insufficient*).mp.
17. (pick* adj2 disease).mp.
18. (creutzfeldt or jcd or cjd).mp.
19. huntington*.mp.
20. binswanger*.mp.
21. korsako*.mp.
22. CADASIL.mp.
23. or/1-22
24. amisulpride/
25. amisulpiride.ti,ab.
26. chlorpromazine/
27. Chlorpromazine.ti,ab.
28. promazine/
29. promazine.ti,ab.
30. trifluoperazine/
31. trifluoperazine.ti,ab.
32. prochlorperazine/
33. prochlorperazine.ti,ab.
34. or/24-33
35. 23 and 34
36. randomized controlled trial/
37. controlled clinical trial/
38. randomi?ed.ab.
39. placebo.ab.
40. randomly.ab.
41. trial.ab.
42. groups.ab.
43. (”double-blind*“ or ”single-blind*“).ti,ab.
44. or/36-43
45. 35 and 44 | |
| PsycINFO
1806 to July week 5 2012 (Ovid SP) | 1. exp Dementia/
2. exp Delirium/
3. exp Huntingtons Disease/
4. exp Kluver Bucy Syndrome/
5. exp Wernickes Syndrome/
6. exp Cognitive Impairment/
7. dement*.mp.
8. alzheimer*.mp.
9. (lewy* adj2 bod*).mp. | 27 |

	10. deliri*.mp. 11. (chronic adj2 cerebrovascular).mp. 12. ("organic brain disease" or "organic brain syndrome").mp 13. "supranuclear palsy".mp. 14. ("normal pressure hydrocephalus" and "shunt*").mp. 15. "benign senescent forgetfulness".mp. 16. (cerebr* adj2 deteriorat*).mp. 17. (cerebral* adj2 insufficient*).mp. 18. (pick* adj2 disease).mp. 19. (creutzfeldt or jcd or cjd).mp. 20. huntington*.mp. 21. binswanger*.mp. 22. korsako*.mp. 23. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp 24. or/1-23 25. amisulpiride.ti,ab. 26. Chlorpromazine/ 27. chlorpromazine.ti,ab. 28. Promazine/ 29. promazine.ti,ab. 30. Trifluoperazine/ 31. trifluoperazine.ti,ab. 32. Prochlorperazine/ 33. prochlorperazine.ti,ab. 34. or/25-33 35. 24 and 34 36. randomized.ab. 37. placebo.ab. 38. randomly.ab. 39. trial.ab. 40. groups.ab. 41. "control group".ab. 42. ("double-blind*" or "single-blind*").ti,ab. 43. exp Clinical Trials/ 44. or/36-43 45. 35 and 44	
Total for supplementary searches	646	
Total for pre-publication and supplementary search	1100	
Total post first assess and de-duplication	33	

Appendix 4. Abbreviations

ADAS	Alzheimer's Disease Assessment Scale (ADAS)
AIMS	Abnormal Involuntary Movement Scale
BADLS	Bristol Activities of Daily Living Scale
BCRS	Brief Cognitive Rating Scale
BDS	Blessed Dementia Scale
BEHAVE-AD	Behavioural Pathology in Alzheimer's disease Rating Scale
BFAS	Blessed Functional Activity Scale
BPRS	Brief Psychiatric Rating Scale
CAS	Cognitive Assessment Scale
CDR	Clinical Dementia Rating Scale
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CGI-C	Clinical Global Impression-Change
CMAI	Cohen-Mansfield Agitation inventory
CUSPAD	Columbia University Scale for Psychopathology in Alzheimer's Disease
DCM	Dementia Care Mapping
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3th Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ESRS	Extrapyramidal Symptom Rating Scale
FAS	F-A-S scale, assessing phonemic verbal fluency
FAST	Functional Assessment Staging
FDA	Food and Drug Administration
ICD-9	International Statistical Classification of Diseases and Related Health Problems, Ninth Revision
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

LPRS	London Psychogeriatric Rating Scale Score
MDRS	Mattis Dementia Rating Scale
mITT	modified intention-to-treat
MMSE	Mini-Mental State Examination
M-UPDRS	Modified Unified Parkinson's Disease Rating Scale
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory Score
NPS	Neuropsychiatric symptoms
PAB	Physical Aggressive Behaviour
PSMS	Physical Self-Maintenance Scale
QoL	Quality of life
ROAS	Retrospective Overt Aggression scale
RTD	Rockland Tardive Dyskinesia
SCAGS	Sandoz Clinical Assessment Geriatric Scale
SIB	Severe Impairment Battery
SMMSE	Standardised Mini-Mental State Examination
STALD	Sheffield Test for Acquired Language Disorder = STALD receptive and STALD expressive skill
TESS	Treatment Emergent Symptom Scale
UPDRS	Unified Parkinson's Disease Rating Scale

WHAT'S NEW

Last assessed as up-to-date: 10 January 2018.

Date	Event	Description
11 January 2018	New citation required but conclusions have not changed	One new study was added. Background and methods were updated in line with MECIR standards, GRADE assessment incorporated. Conclusions unchanged. New lead author
10 January 2018	New search has been performed	Top up searches were performed for this review on 3 March 2017 and 11 January 2018. One new study was identified for inclusion in the review

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 3, 2013

Date	Event	Description
28 March 2013	Amended	Text errors and author affiliations corrected

CONTRIBUTIONS OF AUTHORS

2018 update

EVL: lead author for the review; searched for and selected trials, obtained copies of trial reports and correspondence, 'risk of bias' table, entry of data into RevMan and into GRADEpro, did grading, interpretation of data analyses and drafting review.
MP: selection of included studies and interpretation of data analyses, contributed to the text.
MVD: selection of included studies, interpretation of data analyses, grading and 'risk of bias' table, contributed to the text and text editing.
ADS: interpretation data analyses and grading, contributed to the text.
RVDS: interpretation of data analyses, contributed to the text.
TD: performed previous work that was used in the current review: obtaining copies of trial reports, extraction of data and interpretation of data analyses. Contributed to the text.
TC: arbiter in the selection of trials, interpretation of data analyses and grading, contributed to the text.

Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia (Review)

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DECLARATIONS OF INTEREST

Ellen Van Leeuwen: none known

Mirko Petrovic: none known

Mieke L van Driel: none known

An IM De Sutter: none known

Robert Vander Stichele: none known

Tom Declercq: none known

Thierry Christiaens: none known

SOURCES OF SUPPORT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes between the 2009 protocol and the 2013 review

Of the nine included studies, only Ruths 2008 established the dementia diagnosis according to DSM-IV or ICD-10. Findlay 1989 used ICD-9 criteria. Devanand 2011 and Devanand 2012 used the clinical diagnoses of dementia by DSM-IV criteria and probable Alzheimer's disease by NINCDS/ADRDA criteria. All other studies included older participants with dementia diagnosed in another way: Ballard 2008 and Ballard 2004 used new NINCDS/ADRDA criteria for possible or probable Alzheimer's disease, van Reekum 2002 and Bridges-Parlet 1997 included participants with dementia without any specification (diagnostic criteria unclear). The author of Cohen-Mansfield 1999 stated in her email (Declerck 2009a [pers comm]) that "she was quite sure all participants had dementia". All studies included, since they all studied participants with dementia. Devanand 2011 and Devanand 2012 included participants aged 50 to 95 years. The Ballard 2008 and Devanand 2012 trials did not report schizophrenia in the exclusion criteria, therefore it may be possible that some participants with dementia and schizophrenia are included in these trials.

Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia (Review)

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Changes between the 2009 protocol and this update

Ellen Van Leeuwen joined the review author team in 2017.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects; *therapeutic use]; Dementia [*psychology]; Mental Disorders [*drug therapy]; Psychomotor Agitation [*drug therapy]; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Aged; Humans