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Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia (Review)

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TABLE OF CONTENTS

[Intervention Review]

Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia

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ABSTRACT

Background

Antipsychotic agents are often used to treat neuropsychiatric symptoms (NPS) in dementia, although the literature is sceptical about their long-term use for this indication. Their effectiveness is limited and there is concern about adverse effects, including higher mortality with long-term use. When behavioural strategies have failed and drug therapy is instituted, regular attempts to withdraw these drugs are recommended. Physicians, nurses and families of older people with dementia are often reluctant to try to stop antipsychotics, fearing deterioration of NPS. Strategies to reduce antipsychotic use have been proposed, but a systematic review of interventions aimed at withdrawal of antipsychotic agents in older people with dementia has not yet been performed.

Objectives

To evaluate whether withdrawal of antipsychotic agents is successful in older people with dementia in community 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 withdrawal of antipsychotic agents on behaviour.

Search methods

ALOIS, the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS, clinical trials registries and grey literature sources were searched on 23 November 2012. The search included the following terms: antipsychotic* or neuroleptic* or phenothiazines or butyrophenones or risperidone or olanzapine or haloperidol or prothipendyl or methotrimeprazine or clopenthixol or flupenthixol or clothiapine or metylperon or droperidol or pipamperone or benperidol or bromperidol or fluspirilene or pimozide or penfluridol or sulpiride or veralipride or levosulpiride or sultopride or aripiprazole or clozapine or quetiapine or thioridazine combined with terms such as discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*.

ALOIS contains records from all major healthcare databases (*The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS), as well as from many clinical trials registries and grey literature sources.

Selection criteria

Randomised, placebo-controlled trials comparing an antipsychotic withdrawal strategy to continuation of antipsychotics in people with dementia.

Data collection and analysis

Review authors independently assessed trials for inclusion, rated their risk of bias and extracted data.

Main results

We included nine trials with 606 randomised participants. Seven trials were conducted in nursing homes, one trial in an outpatient setting and one in both settings. In these trials, different types of antipsychotics prescribed at different doses were withdrawn. Both abrupt and gradual withdrawal schedules were used. The risk of bias of the included studies was generally low regarding blinding and outcome reporting and unclear for randomisation procedures and recruitment of participants.

There was a wide variety of outcome measures. Our primary efficacy outcomes were success of withdrawal (i.e. remaining in study off antipsychotics) and NPS. Eight of nine trials reported no overall significant difference between groups on the primary outcomes, although in one pilot study of people with psychosis and agitation that had responded to haloperidol, time to relapse was significantly shorter in the discontinuation group (Chi^2 = 4.1, P value = 0.04). The ninth trial included people with psychosis or agitation who had responded well to risperidone therapy for four to eight months and reported that discontinuation led to an increased risk of relapse, that is, increase in the Neuropsychiatric Inventory (NPI)-core score of 30% or greater (P value = 0.004, hazard ratio (HR) 1.94, 95% confidence interval (CI) 1.09 to 3.45 at four months). The only outcome that could be pooled was the full NPI-score, used in two studies. For this outcome there was no significant difference between people withdrawn from and those continuing on antipsychotics at three months (mean difference (MD) -1.49, 95% CI -5.39 to 2.40). These two studies reported subgroup analyses according to baseline NPI-score (14 or less versus > 14). In one study, those with milder symptoms at baseline were significantly less agitated at three months in the discontinuation group (NPI-agitation, Mann-Whitney U test z = 2.4, P value = 0.018). In both studies, there was evidence of significant behavioural deterioration in people with more severe baseline NPS who were withdrawn from antipsychotics (Chi^2 = 6.8; P value = 0.009 for the marked symptom score in one study).

Individual studies did not report significant differences between groups on any other outcome except one trial that found a significant difference in a measure of verbal fluency, favouring discontinuation. Most trials lacked power to detect clinically important differences between groups.

Adverse events were not systematically assessed. In one trial there was a non-significant increase in mortality in people who continued antipsychotic treatment (5% to 8% greater than placebo, depending on the population analysed, measured at 12 months). This trend became significant three years after randomisation, but due to dropout and uncertainty about the use of antipsychotics in this follow-up period this result should be interpreted with caution.

Authors' conclusions

Our findings suggest that many older people with Alzheimer's dementia and NPS can be withdrawn from chronic antipsychotic medication without detrimental effects on their behaviour. It remains uncertain whether withdrawal is beneficial for cognition or psychomotor status, but the results of this review suggest that discontinuation programmes could be incorporated into routine practice. However, two studies of people whose agitation or psychosis had previously responded well to antipsychotic treatment found an increased risk of relapse or shorter time to relapse after discontinuation. Two other studies suggest that people with more severe NPS at baseline could benefit from continuing their antipsychotic medication. In these people, withdrawal might not be recommended.

PLAIN LANGUAGE SUMMARY

Withdrawal of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia

People with dementia often have behavioural problems that can be difficult for carers to manage. Antipsychotic drugs are often prescribed to control symptoms and assist with controlling difficult behaviour. Many people with dementia continue to take these drugs over long periods of time. This review investigates whether withdrawal of long-term antipsychotic treatment is feasible in older

people with dementia suffering from behavioural symptoms (often called neuropsychiatric symptoms or NPS). These include agitation, aggression, hallucinations, anxiety, apathy, depression, delusions (beliefs that cannot be true), wandering, repeating of words or sounds, and shouting. Nine studies with 606 participants provided data for the review. Most of the participants were residents in nursing homes, but some were outpatients. The studies differed considerably in participants, methods and outcomes so that is was not possible to combine most of the data numerically.

The evidence suggests that older nursing home residents or outpatients with dementia can be withdrawn from long-term antipsychotics without detrimental effects on their behaviour. Caution is required in older nursing home residents with more severe NPS, as two studies suggest these peoples' symptoms might be worse if their antipsychotic medication is withdrawn. Moreover, one study suggested that older people with dementia and psychosis or agitation and a good response to their antipsychotic treatment for several months could relapse after discontinuation of their antipsychotic medication. We do not know if there are beneficial effects of withdrawal on intellectual processes, quality of life or ability to carry out daily tasks, or if the risk of harmful events is reduced by drug withdrawal. One study suggests that older people with dementia who continue to take antipsychotics might die earlier.

We recommend that programmes that aim to withdraw older nursing home residents from long-term antipsychotics should be incorporated into routine clinical practice, especially if the NPS are not severe. More research is needed to identify people for whom withdrawal is not indicated and risk of relapse should be weighed against the risk of adverse events with long-term antipsychotic treatment.

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 the next 10 years (Ferri 2005). Up to 50% of older individuals aged 85 years and above have dementia, with Alzheimer's dementia (AD), vascular dementia and dementia with Lewy bodies being the most frequent diagnoses.

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, hallucinations, anxiety, apathy, depression, delusions, 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. Prevalences of each type of NPS vary 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). There are several clusters of NPS according to the dominant symptom and different clusters have been described. Petrovic reports four behavioural syndromes: a cluster with predominantly psychotic symptoms (hallucinations, irritability, agitation and anxiety); a cluster with predominantly mood disorders (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) (Petrovic 2007). Each cluster could reflect a different prevalence, course over time, biological correlate, psychosocial determinant and treatment, but there probably is overlap between different clusters. In the US the cluster with predominantly psychotic symptoms, including hallucinations and delusions, is considered to be robust enough for the Food and Drug Administration (FDA) to recognise it as an indication for drug treatment (Ballard 2006).

NPS lead to carer stress and depression and can cause considerable emotional discomfort. In people with dementia, NPS are associated with higher mortality, 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). Therefore, interventions aimed at treating NPS could have an important impact on people with dementia, carers and society (Sink 2005).

Although multiple classes of drugs, including antipsychotic or neuroleptic agents, are used to treat NPS, there is no strong evidence to support the choice of drugs for different clusters of NPS. NPS have a fluctuating nature and high placebo response rates have been reported. Furthermore, most trials investigating the efficacy of drug treatment are only short-term. Therefore, treatment is often based on expert opinion, consensus guidelines or local prescribing habits (Finkel 1996; IPA 2003). An individual tailored approach may offer more and better non-pharmacological and pharmacological treatment opportunities (Robert 2005).

Numerous authors (Ballard 2010; Gauthier 2010), as well as good

practice guidelines (NICE 2006), suggest that non-pharmacological treatment of NPS in people with dementia should be the first choice. Clinical trials show non-pharmacological treatments, such as psychological and training interventions, are effective in reducing NPS in people with dementia (Deudon 2009).

The effect of pharmacological 'dementia treatments' on NPS has been studied in different trials. A review of the effect of cholinesterase inhibitors on NPS in dementia concluded that the evidence is equivocal and unconvincing (Sink 2005). Although some suggest cholinesterase inhibitors may be useful for symptoms, such as apathy and psychosis, initial reports that these medications may reduce agitation were not confirmed by a large non-industry-funded randomised controlled trial (RCT) (Howard 2007). Post-hoc analysis of trials of memantine, a N-methyl D-aspartate antagonist, suggests a potential effect on agitation and aggression (Gauthier 2005). Ongoing RCTs in Canada and in the UK will hopefully clarify the role of memantine in the treatment of agitation/aggression in AD and vascular dementia (Ballard 2010). Evidence for other drugs, such as carbamazepine and antidepressants in managing behavioural and psychological symptoms of dementia, is very limited. 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). There is also evidence that atypical or second-generation antipsychotic agents can effectively treat agitation, aggression or psychotic symptoms when non-pharmacological, that is, behavioural, interventions have failed (Ballard 2006).

A major concern of antipsychotic treatment for behavioural symptoms in people with dementia is the increased risk of mortality and stroke (Schneider 2005; Schneider 2006). Product side effect and hazard warnings have been issued for atypical antipsychotics (FDA 2005; FDA 2008), and also for the older typical or first-generation antipsychotics in the treatment of psychotic symptoms in older people with dementia. Meanwhile in the UK, Banerjee concluded it was "time for action" in his report to the Minister of State (Banerjee 2009). His review of the literature 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 a significant increase in absolute mortality risk of approximately 1% (Banerjee 2009). As the literature suggests that prescribing of antipsychotics in dementia continues beyond 6 to 12 weeks, the harm of continued antipsychotic treatment in dementia is likely to be substantial. Moreover, Huybrechts and co-workers report that in their population cohort study the risk of mortality in people taking antipsychotics is generally increased with higher doses and seems to be different for each molecule (in their study it was highest for haloperidol) (Huybrechts 2012).

In spite of this evidence, antipsychotic agents remain widely used as the first-line management of NPS in people with dementia (Briesacher 2005). According to a retrospective analysis in the US, approximately 27.6% of all Medicare beneficiaries in nursing homes received at least one prescription for antipsychotic drugs during 2000 to 2001. Most of the atypical antipsychotics were not prescribed in accordance with guidelines and the administered doses and indications were not supported by strong clinical evidence. In 2001, antipsychotics were ranked highest on the list of expenditure for Medicaid programmes, the main provider of medications prescribed in nursing homes in the US (Briesacher 2005).

Unlike the US, other countries do not have legislation on the use of chemical restraints for people with dementia and NPS. In a survey of medication use in Belgian nursing homes, the list of health insurance drug expenditure is headed by antipsychotics, antithrombotic agents and antidepressants. In terms of health costs, antipsychotics are the second largest group of prescribed drugs in older people living in Belgian nursing homes. Most frequently prescribed are atypical antipsychotics, with risperidone and olanzapine at the top of the list (Azermai 2011; Vander Stichele 2006). Considering the lack of efficacy in chronic use coupled with concerns for safety and high health expenditure, the use of antipsychotics for individuals in nursing homes should be limited in time (O'Brien 2008). In the UK, Banerjee recommended using antipsychotics only "when they really need it" and more attention should go to training and non-pharmacological interventions (Banerjee 2009). Withdrawal seems a rational management option when the person has stabilised. Data on the clinical effect of antipsychotic withdrawal remain limited and antipsychotic withdrawal symptoms/syndrome, although rare, can be very severe (Mortimer 2005). However, Ballard has shown that withdrawal from antipsychotics can be safe in people with dementia who have taken antipsychotics for prolonged periods, especially when symptoms have largely resolved (Ballard 2008).

Description of the intervention

Withdrawal from antipsychotic agents can be either abrupt (immediate cessation of the active medication) or tapered (gradual withdrawal according to a predefined dosing schedule or following clinical response).

In this review, we assemble and appraise 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 in older people, often frail, people with dementia and NPS might theoretically improve cognitive function, quality of life (QoL) for people with dementia and carers, and decrease mortality and adverse events (e.g. falls and extrapyramidal symptoms). However, drug withdrawal might

also cause a recurrence or worsening of the original NPS with a negative impact on the QoL for people with dementia and their carers and it might 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 such symptoms, are sometimes understandably reluctant to consider withdrawal of the drug. However, the episodic nature of such symptoms and the harms associated with antipsychotic use is less well appreciated. A systematic review of the risks and benefits of antipsychotic withdrawal and of the feasibility of maintaining people off antipsychotics is therefore needed.

OBJECTIVES

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.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant RCTs. Withdrawal trials that were not placebo-controlled were only included if the outcome assessors were blinded. No language restrictions were applied.

Types of participants

Older people with dementia under primary care or living in nursing homes and taking an antipsychotic drug.

Older people are defined as 65 years or older without age limit.

Dementia is 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 were asked to provide further information. All grades of dementia severity were included. People with schizophrenia were excluded if this was reported in the trial. By accepting all types and grades of dementia severity, regardless of the method of diagnosis, we are reflecting the current situation in practice in which many demented residents in nursing homes are not formally diagnosed. We believe this way of including people will make the review as widely applicable as possible.

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

Withdrawal of antipsychotic drugs prescribed chronically for behavioural and NPS in older people with dementia. Chronic 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 above 'new' or 'second-generation antipsychotics'. The antipsychotic agents are listed according to the Anatomical Therapeutic Chemical (ATC) classification. Names of drug classes are listed in Table 1, names of individual drug are listed in Table 2, and atypical antipsychotic agents are labelled with an asterisk. The antipsychotic agent should be used in a stable dose, and within the therapeutic range as mentioned in the attached drug information insert. Defined daily doses (per os) as mentioned in the ATC classification are also listed in Table 2. Chlorpromazine is considered 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 in Ballard The DART-AD Trial (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

1.1. Success of withdrawal from antipsychotics over short-term (four weeks or less) and long-term (more than four weeks) follow-up. Success rate is defined as the ability to complete the study, that is, no dropout of the trial due to worsening of NPS, or no relapse to antipsychotic drug use during the trial.

1.2. Behavioural and psychological symptoms (especially agitation, aggression and psychotic symptoms) of people continuing on antipsychotics versus people withdrawn from antipsychotics

measured with appropriate scales (e.g. Neuropsychiatric Inventory (NPI) score, Neuropsychiatric Inventory Questionnaire score (NPI-Q) score), and compared to baseline.

1.3. Presence or absence of withdrawal symptoms or withdrawal syndrome in people withdrawn from antipsychotics in the first four weeks after withdrawal.

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.

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

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

1.4. Adverse events of antipsychotics (e.g. falls, extrapyramidal symptoms using the Extrapyramidal Symptom Rating Scale (ESRS), cardiovascular events and diabetes) in people withdrawn from antipsychotics versus people continuing antipsychotics.

Secondary outcomes

2.1. Cognitive function (e.g. short-term memory) of people continuing on antipsychotics versus people withdrawn from antipsychotics measured with appropriate scales (Severe Impairment Battery (SIB) score, Standardised Mini-Mental State Examination (SMMSE)) and compared to baseline.

2.2. QoL of participants, carers, families, or a combination continuing on antipsychotics versus people withdrawn from antipsychotics measured with appropriate scales (e.g. Dementia Care Mapping) and compared to baseline.

2.3. Time, in days, until repeat prescription of any psychotropic or any antipsychotic agent in people withdrawn from antipsychotics versus people continuing on antipsychotics.

2.4. Use of physical restraint in people withdrawn from antipsychotics versus people continuing on antipsychotics compared with baseline.

2.5. Mortality in people withdrawn from antipsychotics versus people continuing on antipsychotics.

2.6. Other secondary outcomes (e.g. global functioning, sleep or language) measured with appropriate scales and compared to baseline.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's Specialized Register, on 9 February 2009 (initial search), 11 March 2011 (updated search) and 1 June and 23 November (pre-publication searches). After external review, we did a supplementary search of additional antipsychotics not covered in previous searches in August and November 2012 (supplementary searches).

ALOIS is maintained by the Trials Search Co-ordinator of the Dementia Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. The studies are identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACs;
2. monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the WHO portal (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, plus others);
3. quarterly search of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL);
4. six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the 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. The search strategies used can be seen in Appendix 1, Appendix 2 and Appendix 3.

Appendix 4 gives a full list of abbreviations used in this review.

Data collection and analysis

Selection of studies

1. Searches and screening of the identified studies were performed independently by two review authors (TD and MP).
2. All trials were scrutinised for relevance and pre-defined inclusion criteria. Trials that did not fulfil the criteria were excluded.
3. Differences between review authors were resolved by consensus and by consulting a third review author (TC).

Data extraction and management

Data extraction was performed by two independent review authors (TD, MA). Disagreement was resolved by an external expert (Ellen De Schepper, biomedical statistician).
The summary statistics required for each trial and outcome for continuous data are the mean change from baseline, the standard error of the mean change, and the number of participants for each treatment group at each assessment. The baseline assessment is defined as the latest available assessment prior to randomisation, but no longer than two weeks before randomisation. Where changes from baseline were not reported, the mean, standard deviation (SD), and the number of people in each treatment group at each time point were extracted if available.
For binary data, the number in each treatment group and the numbers experiencing the outcome of interest were sought.
The outcomes measured in dementia trials often arise from ordinal rating scales. Where ordinal rating scales used in the trials had a reasonable large number of categories (more than 10), the data were treated as continuous outcomes arising from a normal distribution, where necessary using a Turnstone Transformation.

For each outcome measure, data were sought on every person assessed. To allow an intention-to-treat (ITT) analysis, the data were sought irrespective of compliance, whether or not the person was subsequently deemed ineligible, or otherwise excluded from treatment or follow-up. If ITT data were not available in the publications, 'on-treatment', or the data of those who completed the trial were sought and indicated as such.

When studies included an open period after the main comparative phase, data from non-randomised follow-on periods were not used.
Additional data and characteristics of the participants extracted from the individual studies were listed as co-variables:

- 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);
- sex of participant;
- age of participant by age groups (years): 65 to 69; 70 to 79; 80 to 89; 90 and older.

Assessment of risk of bias in included studies

The risk of bias in each of the trials was assessed by using the following criteria of internal validity: randomisation (sequence allocation), allocation concealment, blinding of participant and outcome assessor, adequate reporting of and dealing with withdrawals and dropouts, selective outcome reporting and other risks of bias. The guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* were used (Higgins 2011).
Two review authors (TD, MA) independently assessed the risk of bias of the included studies.
Disagreement was resolved by consulting with two other review authors (MP, TC).

Measures of treatment effect

Meta-analysis requires the combination of data from trials that may not use the same rating scale to assess an outcome. The measure of the treatment difference for any continuous outcome is the weighted mean difference when the pooled trials use the same rating scale or test. The standardised mean difference, which is the absolute mean difference divided by the pooled SD, was calculated when different rating scales or tests were used.

For binary outcomes, such as improvement or no improvement, the odds ratio was used to measure treatment effect.
Peto odds ratios were calculated using RevMan 5 Software (RevMan 2011). 95% Confidence intervals were calculated for each of the pooled estimates.

Unit of analysis issues

We considered whether in each study, groups of individuals were randomised together (in clusters) to the same intervention, whether individuals underwent more than one intervention, or whether there were multiple observations for the same outcome.

Dealing with missing data

We describe if data were missing from the published report.
We contacted the original investigators to request missing data. If these data remained unavailable we analysed the available data using an ITT analysis.
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 is 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

Studies were analysed and presented separately. Meta-analysis was only performed when studies were sufficiently homogeneous in terms of participants, interventions and outcomes. Both clinical

(face value) heterogeneity and statistical heterogeneity were considered, the latter by means of a Higgins I^2 test. An I^2 value of 50% or higher was considered as significant heterogeneity.

Assessment of reporting biases

In order to minimise the risk of publication bias, a comprehensive search was performed in multiple databases, including searching for unpublished studies. The existence of publication bias was not explored by means of a graphical funnel plot analysis as an insufficient number of studies was available (< 10 studies).

Data synthesis

If trials were considered too clinically heterogeneous at face value the results were not pooled in meta-analysis.

The duration of follow-up in trials varied considerably. If the range of follow-up was considered too large to pool results into one meta-analysis, the data were divided into smaller time periods and a separate meta-analysis was conducted for each period. Some trials contributed data to more than one time period if multiple assessments were made.

The overall estimate was calculated using a fixed-effect model in the absence of statistical heterogeneity. In the presence of substantial statistical heterogeneity, a random-effects model was used (Higgins 2011). Data are reported in the table of comparisons. A complete list of outcomes can be found in the table of comparisons.

Further analyses included examination of dropout rates.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed for relevant and clinically meaningful subgroups when sufficient data were available (i.e. more than one study), such as type of intervention, severity of dementia or NPS, setting, gender of participant and type of antipsychotic agent.

Sensitivity analysis

When evidence of small study effects was found, authors considered sensitivity analyses according to Copas examining how the results of the possible meta-analysis change under different assumptions relating to the reasons for these effects (Higgins 2011).

RESULTS

Description of studies

Nine studies met the inclusion criteria. The characteristics of all included studies are described in detail in the Characteristics of included studies tables.

Results of the search

From the 529 hits found in 17 different databases through the initial electronic search from 9 February 2009, 309 references of published studies and four references of ongoing studies were retrieved. After screening (by TD and MP), 22 references of published studies were selected as potentially eligible. These were found to refer to seven unique studies. Bridges-Parlet 1996 was retrieved as a dissertation that was subsequently published as Bridges-Parlet 1997; Cohen-Mansfield 1996 was the conference proceedings of Cohen-Mansfield 1999; and Ballard 2000, Ballard 2003b, Fossey and Ballard 2000 and Ballard 2006 were all references related to the registration of Ballard 2004. Another reference (Onyike 2008) was a comment on Ballard The DART-AD Trial and was therefore not considered for inclusion. Findlay 1989 was identified from reference lists as the seventh study eligible for inclusion. One potentially relevant to date unpublished study (Engedal) was also identified and added to the list of ongoing studies to be included in future updates of this review (Appendix 1; Appendix 2).

The updated search of 11 March 2011 retrieved 776 hits of which the review authors (TD and MP) assessed 70 thoroughly. No new trials were identified for inclusion or exclusion.

The pre-publication search of 1 June 2012 retrieved 454 hits of which 11 were further assessed: the review authors (TD and MP) identified one new pilot study for the ongoing Devanand ADAD-Trial, which was included in this review (Devanand 2011). In addition, in April 2012 the study design of the Devanand ADAD 2012 was published and this reference added to the other references section.

The search of 13 August 2012 revealed one additional study that was potentially eligible for inclusion (Horwitz 1995). However this study was not a clinical trial and therefore was excluded. In November 2012, the second pre-publication search revealed 19 new hits, from which one study was identified and included (the Devanand ADAD 2012 trial).

Included studies

Two review authors (TD, MP) independently selected nine different trials from 11 papers: they found two papers reporting the Ballard The DART-AD Trial and one paper (Ruths 2004) reporting a subgroup analysis of Ruths The BEDNURS Study.

The included trials were very different 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 time of assessment. Only two studies (Ballard The DART-AD Trial; Ballard 2004) used the same main

outcome (i.e. the NPI -score), and provided sufficient information to allow pooling of data. Ruths The BEDNURS Study used the NPI-Q as main outcome, which is a short version of the NPI. Devanand ADAD 2012 reported relapse defined as an increase in the NPI core score (i.e. the sum of the sub-scales for agitation-aggression, hallucinations, and delusions on the NPI-score), and a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression of Change (CGI-C) scale for overall psychosis or agitation. Therefore data of these two trials (Devanand ADAD 2012; Ruths The BEDNURS Study) could not be pooled with data of the former two Ballard trials. The authors of Bridges-Parlet 1997, Cohen-Mansfield 1999, Findlay 1989 and van Reekum 2002 responded that they were unable to provide additional data.

Setting

Seven studies include people in nursing homes. One pilot study included outpatients with AD and psychosis, agitation or aggression (Devanand 2011). Devanand ADAD 2012 included outpatients or residents of assisted-living facilities or nursing homes with AD and psychosis, agitation, or aggression.

Case definition of dementia

All studies used different methods (e.g. Diagnostic and Statistical Manual of Mental Disorders - 3rd Edition Revised (DSM IIIR), Diagnostic and Statistical Manual of Mental Disorders - 4th Edition (DSM IV)) to diagnose dementia, including AD.

- Ballard 2004 and Ballard The DART-AD Trial included only people with AD that 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 AD.
- Bridges-Parlet 1997 included residents with a diagnosis of dementia and subjects with a history of physical aggressive behaviour (PAB) according to the nursing home staff.
- Cohen-Mansfield 1999 had no explicit diagnostic standard for dementia because the study included nursing home residents older than 70 years receiving haloperidol, thioridazine and lorazepam. The first author confirmed by e-mail that the residents participating in her study met the inclusion criteria for this review (suffering from dementia).
- Devanand 2011 included outpatients with probable AD using the DSM-IV and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.
- Devanand ADAD 2012 included outpatients or residents of assisted-living facilities or nursing homes who met the criteria for dementia using the DSM-IV, and the criteria for probable AD of the NINCDS-ADRDA.
- Findlay 1989 included exclusively women with AD in accordance with the International Classification of Diseases (ICD)-9 criteria, assessed by a consultant psychiatrist and based on the medical history.
- van Reekum 2002 included people with all forms of dementia based on chart review.
- Ruths and co-workers included people with a dementia diagnosis according to the clinical criteria of ICD, 10th Revision (Ruths The BEDNURS Study).

Severity of dementia

In three studies, participants were described as having mild-to-moderate or severe dementia, based on MMSE scores.

- In the Ballard 2004 study participants had a Clinical Dementia Rating (CDR) Scale severity of stage 1 or greater.
- Participants in the Ballard The DART-AD Trial had either an MMSE score > 6 or a Severe Battery Impairment score > 30.
- Ruths The BEDNURS Study included all participants regardless individual symptoms (absent = 0, mild = 1, moderate = 2, severe = 3), providing a NPI-Q sum score ranging from 0 to 36.

In the other studies, no clear cut-off values were reported to indicate the difference in degree/severity of dementia. However, assessment of cognitive status occurred in most studies using the MMSE.

- Bridges-Parlet 1997 did not report the severity of dementia. At baseline cognitive status was assessed using the MMSE. Participants were selected by nurse supervisors who identified physically aggressive people with dementia treated with antipsychotics.
- In the study by Cohen-Mansfield 1999, the Brief Cognitive Rating Scale (BCRS) was used at baseline to determine participants' stage of dementia, to characterise the study population and to stratify groups according to cognitive function (1 to 3 versus 4 to 7 on the BCRS).
- In the Devanand 2011 pilot trial the eligible MMSE score was 5 to 26. Participants also needed to have signs of psychosis or agitation, or both, to be included in the study. Psychosis was identified by 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 was measured on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavioural Rating Scale for Dementia (score of greater than 3 and present 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 ADAD 2012 had a score of 5 to 26 on the MMSE in the case of outpatients and a score of 2 to 26 in the case of nursing home residents. In addition participants had a score on the NPI of 4 or more at both screening and

baseline on the delusions or hallucinations sub-scale (psychosis score) or the agitation-aggression sub-scale (agitation score).

- The study of Findlay 1989 was limited to AD without further specification.

Antipsychotic treatments to be withdrawn

All studies used different antipsychotics in different dosages. Antipsychotics used were thioridazine, chlorpromazine, haloperidol, trifluoperazine (classified as 'typical antipsychotics') and risperidone or olanzapine (classified as 'atypical antipsychotics'). Antipsychotic dosage varied across the studies. Three studies used an abrupt withdrawal schedule (Ballard 2004; Ballard The DART-AD Trial; Ruths The BEDNURS Study). Two studies (Bridges-Parlet 1997; Devanand ADAD 2012) withdrew most participants abruptly from antipsychotic drugs, but tapering still occurred when the baseline dose exceeded the equivalent of 50 mg of chlorpromazine by dropping the baseline antipsychotic dose in half during week one and discontinuing the antipsychotic agent completely at the beginning of week two (Bridges-Parlet 1997) or when the baseline dose was 2 mg risperidone or more daily by one-week tapering 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) (Devanand ADAD 2012).The other studies used a tapering schedule.

- In the Ballard The DART-AD Trial, a majority of participants were taking risperidone or haloperidol at variable dosages: participants were taking at least 10-mg chlorpromazine equivalents (CPZe) of a typical neuroleptic or at least 0.5 mg daily of risperidone. Dosages were defined as high versus low versus 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.

- In Ballard 2004, a majority of participants 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 were taking 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 period. 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 both antipsychotics (haloperidol and thioridazine), and lorazepam, which is a benzodiazepine. Because of this dual drug cross-over design, it will be difficult to interpret the results of this study.
- In Devanand 2011, outpatients with AD and symptoms of psychosis or agitation 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 or agitation, a sum score of 6 or less on these three items (range 0 to 18), and minimal or greater improvement on the CGI-C score (rated only for symptoms of psychosis or agitation). Doses of haloperidol used in phase B varied (4 mg daily, 2 to 3 mg daily, 0.5 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 to 3 mg daily switched to 1 mg daily for two weeks and then to placebo, and participants who received 0.5 or 1 mg daily were switched directly to placebo without a tapering period).
- In the Devanand ADAD 2012, phase A participants were given flexible-dose risperidone for 16 weeks: risperidone therapy was initiated at a dose of 0.25 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 and 100 mg thioridazine for at least two months.
- van Reekum 2002 did not define antipsychotic drug classes and included residents that used typical or atypical antipsychotics for at least six months. In this study, all subjects received a standard order for lorazepam (0.5 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 The BEDNURS Study, participants were taking risperidone 1.0 mg (median; range 0.5 to 2.0 mg), olanzapine 5.0 mg (2.5 to 5.0 mg), and haloperidol 1.0 mg (0.5 to 1.5 mg).

Excluded participants

See Characteristics of included studies table.

Outcome measurements

Outcome measures were very different across included studies and therefore difficult to compare. Ballard 2004, Ballard The DART-AD Trial and Ruths The BEDNURS Study reported outcomes in mean differences with SDs. Bridges-Parlet 1997, Cohen-Mansfield 1999, Devanand 2011, Devanand ADAD 2012 and van Reekum 2002 reported outcomes as means, but only Bridges-Parlet 1997, Devanand 2011 and Devanand ADAD 2012 reported SDs as well. Findlay 1989 reported outcomes as means with a range (number of observations).

1. Primary outcomes

1.1. Success of withdrawal from antipsychotics in the short term (four weeks or less) and long term (more than four weeks)

Success rate is defined as ability to complete the study (i.e. no withdrawal due to worsening of NPS, or no relapse to antipsychotic drug use during the trial).

- Ballard 2004 and Ballard The DART-AD Trial reported participant flow in the Results section, giving reason of withdrawal from the study, for example, withdrawal because of behavioural deterioration. Unfortunately relapse to antipsychotic drug use was not mentioned.
- Bridges-Parlet 1997 reported subjects completing the study and relapse to antipsychotic drug use after completion of the trial (long term).
- Cohen-Mansfield 1999 reported participant flow in the Results section, giving reasons why participants discontinued in the study before completion.
- Devanand 2011: phase B reported relapse using criteria of 50% worsening of the three target symptoms of psychosis and aggression, and a severity score $\geq$ 6 on these three items (range 0 to 18), and minimal or greater worsening on the CGI-C (rated for psychosis and agitation). Time to relapse was also measured in Devanand 2011 phase B.
- Devanand ADAD 2012: phase B reported relapse using criteria of 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 6 (much worse) or 7 (very much worse) on the CGI-C scale.

The NPI-core score is the sum of the sub-scale 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 or agitation.

- Findlay 1989 did not report withdrawals 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 The BEDNURS Study mentioned relapses of antipsychotic drug use after withdrawal from antipsychotics.

1.2. Behavioural and psychological symptoms measured with appropriate scales

1.2.1. Neuropsychiatric Inventory (NPI) Scale

The NPI covers 12 domains of behavioural and neurovegetative symptoms to assess outcome. Each sub-score 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 score has been established to be a useful instrument for characterising the psychopathology of dementia syndromes, investigating the neurobiology of brain disorders with neuropsychiatric manifestations, distinguishing among different dementia syndromes and assessing the efficacy of treatment. The total NPI score is the major primary outcome of this review and is the only one that can be pooled because all other outcome measures were only reported in individual studies.

The NPI-Q (Neuropsychiatric Inventory Questionnaire) assesses only the severity of each of the same 12 domains of the NPI (theoretically maximum of 36, range 0 to 36) and can be considered as a shorter version of the NPI.

Nevertheless, by assessing a spectrum of various symptoms, the NPI or NPI-Q score is not specifically evaluating the cluster with predominantly psychotic symptoms (hallucinations, irritability, agitation and anxiety). Two trials using the NPI or NPI-Q score as a primary outcome performed NPI-sub-score analysis, for example assessing agitation (Ruths The BEDNURS Study assessed agitation as a sub-score of the NPI-Q and Ballard 2004 assessed agitation as a sub-score of NPI total score). Only one trial Devanand ADAD 2012 reported the effect on the NPI core score, that is, the sum of the sub-scale NPI scores for agitation-aggression, hallucinations, and delusions, which are symptoms believed to be part of a cluster with significant clinical importance.

Two studies that used the NPI-score to assess NPS will be pooled (Ballard 2004; Ballard The DART-AD Trial). The van Reekum 2002 study could not be pooled because it used the NPI as outcome measure, but unfortunately did not report this outcome in the paper. Data from Ruths The BEDNURS Study could not be pooled either because NPI-Q was used as outcome.

1.2.2. Other scales that assess behavioural and psychological symptoms

- Bridges-Parlet 1997 used PAB as main outcome measure. The PAB scale assesses aggressive behaviour identified by type (coded by a bar-code system). Five different types of behaviour were identified: hitting, biting, scratching, kicking and pushing. Verbal aggressiveness was defined as an instance of speaking in an angry tone of voice, swearing or yelling in anger. Bridges-Parlet 1997 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 as primary outcome:
    - 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 CMAI. This nurses' rating 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 (Retrospective Overt Aggression scale) but scores were not reported.

1.3. Presence or absence of withdrawal symptoms

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

1.4. Adverse events

Adverse events related to antipsychotic use, such as falls, extrapyramidal symptoms, cognitive dysfunction, metabolic changes (including weight gain and diabetes), cardiovascular events and other are not systematically reported in the included studies.

- Ballard The DART-AD Trial measured parkinsonism using the M-UPDRS (Modified Unified Parkinson's Disease Rating Scale).
- Bridges-Parlet 1997 gave some attention to the 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 the Abnormal Involuntary Movement Scale (AIMS): assessment of neurological and physical side effects associated with psychotropic medication (nine items: e.g. movement of the face and the oral cavity, of the 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 by the Treatment Emergent Symptom Scale (TESS), extrapyramidal signs by the Unified Parkinson's Disease Rating Scale (UPDRS) and tardive dyskinesia by the Rockland TD scale.
- Devanand ADAD 2012 assessed extrapyramidal signs using the Simpson-Angus scale (ranges from 0 to 40, with higher scores indicating more extrapyramidal signs); tardive dyskinesia, with the use of the AIMS (ranges from 0 to 35, with higher scores indicating more severe symptoms) and general somatic symptoms developing during treatment, as assessed with the use of the TESS (ranges from 0 to 26, with higher scores indicating more somatic symptoms).
- Findlay 1989 provided some additional information on blood pressure, heart rate, mobility, and balance and sensory measures.
- van Reekum 2002 assessed extrapyramidal signs using ESRS, but does not report these outcomes in the paper.

2. Secondary outcomes

2.1. Cognitive function assessed by appropriate scales

- In the Ballard The DART-AD Trial, cognition was measured using the SMMSE and the SIB, which was the main outcome in this trial.
- Cohen-Mansfield 1999 assessed cognitive functioning using the MMSE scale.
- Devanand 2011 and Devanand ADAD 2012 also assessed cognitive functioning using the MMSE (Devanand 2011). Devanand ADAD 2012 also used the Alzheimer's Disease Assessment Scale (ADAS)-cognitive score (ranges from 0 to 70, with higher scores indicating worse cognition).
- Findlay 1989 used mixed cognitive/behavioural outcome measures assessed by different scales: the Cognitive Assessment Scale (CAS) scored by a psychiatrist, and a psychiatric assessment using the Sandoz Clinical Assessment Geriatric Scale (SCAGS), and the London Psychogeriatric Rating Scale (LPRS) score.
- van Reekum 2002 assessed cognitive outcome with the MMSE and the Mattis Dementia Rating Scale (MDRS), but did not report these outcomes in the paper.

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

Only Ballard 2004 scored QoL using the Dementia Care Mapping (DCM) as a measure of well-being of participants.

2.3. Time, in days, until repeat prescription of any psychotropic agent with exception of antipsychotics was not reported systematically

Only Ruths The BEDNURS Study reported medication changes in a subgroup analysis.

2.4. Use of physical restraint

Only Bridges-Parlet 1997 reported use of physical restraint.

2.5. Mortality

Ballard The DART-AD Trial and Devanand ADAD 2012 were the only studies reporting mortality. Mortality data in one of the two Ballard The DART-AD Trial papers were assessed at 12, 24 and 36 months' follow-up after randomisation (outcome data analysed by ITT-analysis or mITT-analysis). Devanand ADAD 2012 assessed mortality at 16 weeks (four months) and 32 weeks (eight months).

2.6. Other secondary outcomes

2.6.1. Global functioning

- Ballard The DART-AD Trial reported global functioning with the BADLS (Bristol Activities of Daily Living Scale), FAST (Functional Assessment Staging) and CGI-C scales.
- Cohen-Mansfield 1999 reported resident functioning and global impressions of functioning as secondary outcomes using different scales, such as the CGI-C scale.
- Devanand 2011 assessed impairment in activities of daily living using the modified Blessed Functional Activity Scale (BFAS).
- Devanand ADAD 2012 assessed physical function with the use of the Physical Self-Maintenance Scale (PSMS; ranges from 1 to 30, with higher scores indicating worse functioning).
- van Reekum 2002 assessed functional outcome with the Blessed Dementia Scale (BDS), but did not report these outcomes in the paper.

2.6.2. Frontal executive function

- In the Ballard The DART-AD Trial, frontal executive function was measured by the FAS verbal fluency test, assessing phonemic verbal fluency.

2.6.3. Sleep

- Ruths The BEDNURS Study (sub-study Ruths 2004) and Bridges-Parlet 1997 reported the effect on sleep.
- Cohen-Mansfield 1999 reported the effect on sleep and activity level ratings (daytime sleep, time to fall asleep and activity level).

2.6.4. Language

- Ballard The DART-AD Trial reported language by using different scales (Sheffield Test for Acquired Language Disorder (STALD receptive and STALD expressive skill)).

3. Co-variables

- Only Ballard The DART-AD Trial conducted a post hoc sub-analysis per type of antipsychotic drug (i.e. typical versus atypical).

Time of assessment of outcome measurements

Most outcomes are assessed in different studies at different times and therefore difficult to pool.

- Ballard 2004 assessed outcomes at three months.
- Ballard The DART-AD Trial assessed outcomes in a first paper at 1, 3, 6 and 12 months: only the data assessed at six months were reported. In a second paper Ballard assessed the outcome mortality at 12, 24 and 36 months (outcome data analysed by ITT analysis).

In order to pool the NPI score in a correct way we asked Clive Ballard to provide data from the DART-AD study assessed at three months. 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 reported outcomes at four times of assessment: one week after start of dosage tapering (week one), phase 1 tapering (week three), phase 1 end point (week 10), phase 2 tapering (week 13), and phase 2 end point (week 20).
- Devanand 2011 assessed outcomes in phase B at 0, 2, 4, 8, 12, 16, 20 and 24 weeks.
- Devanand ADAD 2012: phase B assessed outcomes at 16 weeks (four months) and 32 weeks (eight months).
- Findlay 1989 reported outcomes at two and four weeks.
- Ruths The BEDNURS Study assessed outcomes at four weeks (one month).
- van Reekum 2002 reported outcomes only in a figure from visit 1 (baseline) to visit 15 (six months).

Excluded studies

One trial (McLennan 1992) was excluded because it analysed the Findlay 1989 cohort for outcomes that are not relevant to our review. 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). Horwitz 1995, Wessels 2010 and Westbury 2011 were excluded because these were not randomised controlled discontinuation trials.

Risk of bias in included studies

See 'Risk of bias' table and summary of 'Risk of bias' graph (Figure 1; Figure 2).

Figure 1. Risk of bias graph for the 9 included studies.

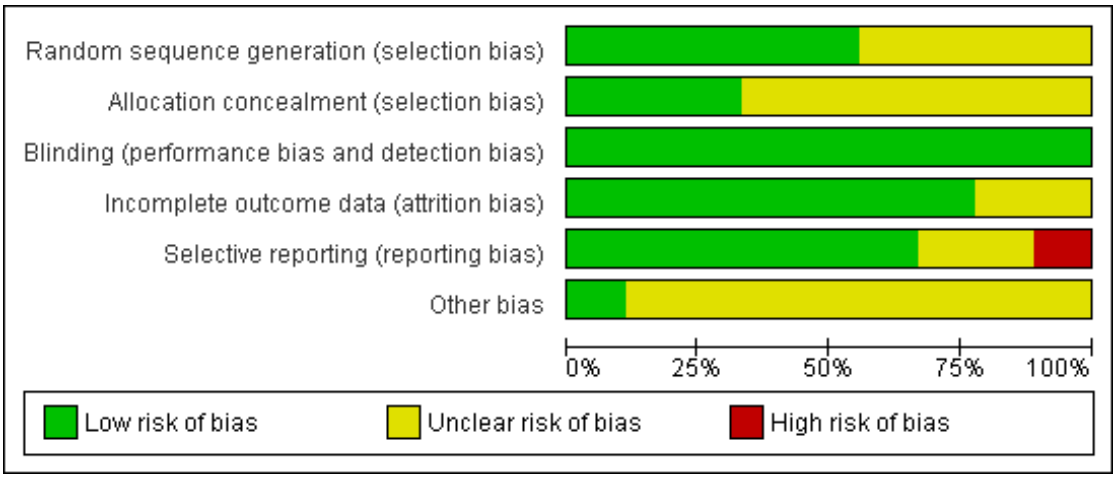
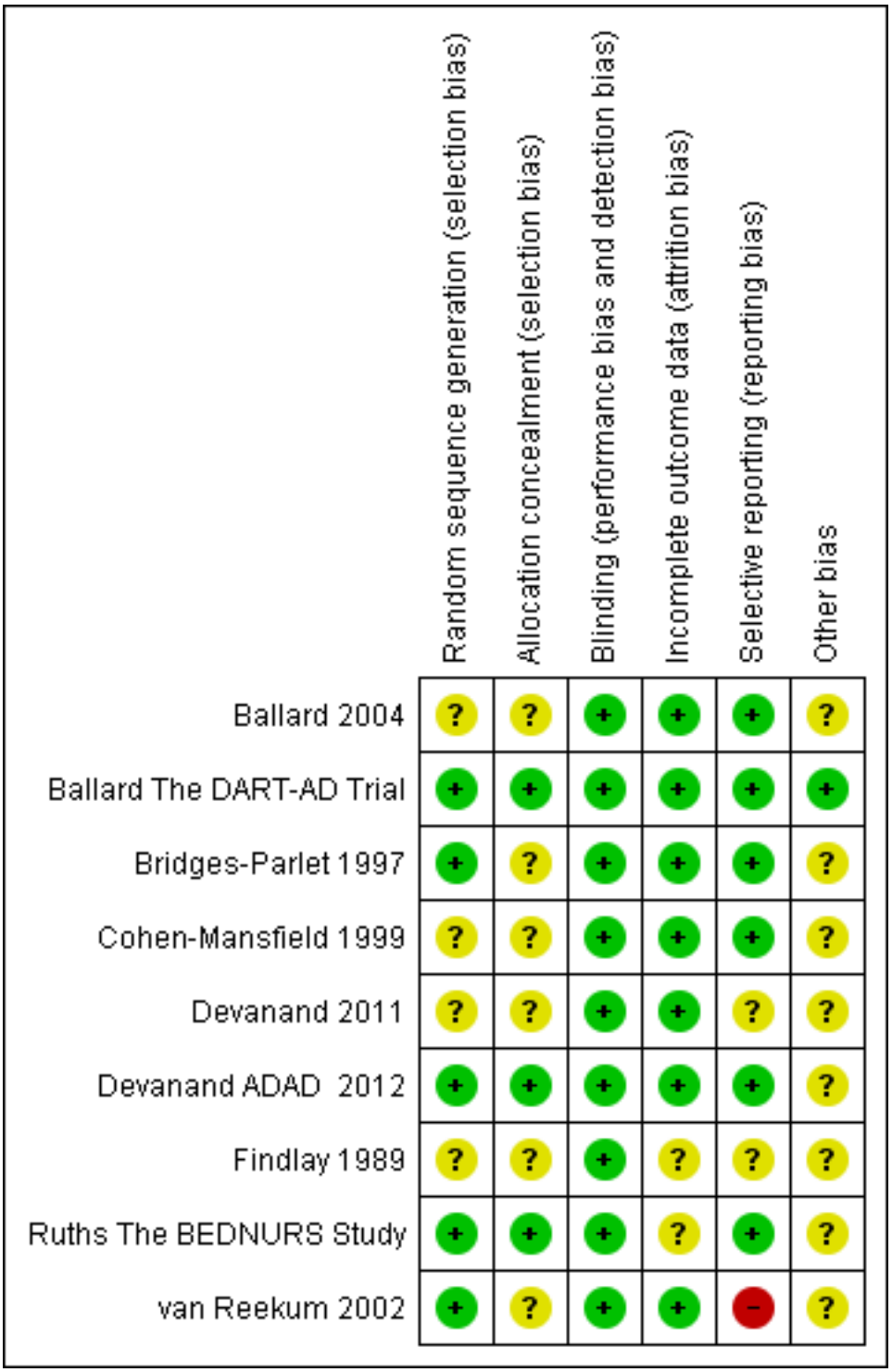


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomisation sequence generation was described and adequate in five trials (Ballard The DART-AD Trial; Bridges-Parlet 1997; Devanand ADAD 2012; Ruths The BEDNURS Study; van Reekum 2002) and unclear in the other trials.

Allocation concealment was only described sufficiently detailed to assess the risk of bias as low in three studies (Ballard The DART-AD Trial; Devanand ADAD 2012; Ruths The BEDNURS Study) and hence is classified as unclear for the other trials.

Blinding

All included studies report blinding of the participants/carers and the outcome assessors.

Incomplete outcome data

Seven of the nine trials address the issue of incomplete outcome data in their report (Ballard 2004; Ballard The DART-AD Trial; Bridges-Parlet 1997; Cohen-Mansfield 1999; Devanand 2011; Devanand ADAD 2012; van Reekum 2002).

Selective reporting

All studies seem free of selective reporting, except the studies by Devanand 2011, Findlay 1989 and van Reekum 2002. van Reekum 2002 does not report several outcomes in numbers. Findlay 1989 does not describe the primary outcome and it is unclear if a selection of outcomes was reported. In van Reekum 2002 some outcomes initially mentioned were not reported. It is not clear why the primary outcome relapse in the Devanand 2011 pilot trial was changed to the NPI sub-score, that is, the sum score of delusions, hallucinations and agitation/aggression as mentioned in the protocol (Devanand 2012a) of the subsequent Devanand ADAD 2012 trial.

Other potential sources of bias

Other potential sources of bias include uncertainty about the method of recruitment (Ballard 2004; Bridges-Parlet 1997; Findlay 1989), or the method of analysis (ITT or not) (Cohen-Mansfield 1999). It was unclear if people in the two groups were similar in the BEDNURS study (Ruths The BEDNURS Study). In the Findlay 1989 study there was a baseline imbalance in two people for one of the three scales (CAS) used to measure outcome. In Devanand 2011 and Devanand ADAD 2012, non-responders were excluded.

Effects of interventions

1. Primary outcomes

1.1. Success of antipsychotic withdrawal

In most studies reporting the withdrawal rate from the study due to behavioural deterioration there was no significant difference between the continuation and the discontinuation group (Ballard 2004; Ballard The DART-AD Trial; Bridges-Parlet 1997; Devanand 2011). Devanand 2011 mentioned a significant difference in time to relapse of behavioural problems between the two groups favouring the continuation group. Devanand ADAD 2012 found a significant increased risk of relapse in those people that responded to risperidone therapy before.

- Ballard 2004 and Ballard The DART-AD Trial reported no statistical difference in the rate of withdrawal from the study due to behavioural deterioration between the continuation and the discontinuation group.
- In the study of Bridges-Parlet 1997 the completion of the four-week trial was considered as a primary outcome. There was no significant difference in completion or early withdrawal rate from the study between continuation and discontinuation groups.
- Cohen-Mansfield 1999 reported numbers of people withdrawn from the study (e.g. because of increased agitation), without distinguishing between placebo and continuation group. Most withdrawals from the study occurred in the first part of the study (no numbers given).
- In the study of Devanand 2011, only responders to haloperidol were included in phase B and randomised again into discontinuation and continuation groups. This resulted in a trend towards significance (P value = 0.07) between groups on the outcome of relapse, and time to relapse of behavioural problems was shorter in people on placebo (discontinuation group) (P value = 0.04).
- In the Devanand ADAD 2012 trial, only responders to risperidone treatment were included in phase B and randomly assigned, in a double-blind way, to one of three regimens (group 1, 2 and 3). In the first 16 weeks (four months) after randomisation the rate of relapse was higher in the group that received placebo (group 3) than in the groups that received risperidone (groups 1 and 2) (60% (24 of 40 participants in group 3) versus 33% (23 of 70 participants in groups 1 and 2); P value = 0.004; hazard ratio with placebo 1.94, 95% CI 1.09 to 3.45, P value = 0.02). During the next 16 weeks (i.e. at eight months after randomisation), the rate of relapse was higher in

the group that switched to placebo (group 2) than in the group that continued to receive risperidone (group 1) (48% (13 of 27 participants in group 2) versus 15% (2 of 13 participants in group 1); P value = 0.02; hazard ratio 4.88, 95% CI 1.08 to 21.98; P value = 0.02).

Crude (unstratified) rates of relapse at four months were 6.5 and 3.0 per 100 patient-weeks of follow-up for discontinuation (group 3) and continuation groups (group 1 and group 2), respectively. At eight months, crude rates of relapse were 4.3 and 1.1 per 100 patient-weeks of follow-up for discontinuation (group 2) and continuation group (group 1).

- Analysis of the results from Findlay 1989 shows no difference in rates of withdrawal from the study between the discontinuation and the continuation group (no dropouts).
- van Reekum 2002 did not report a statistical difference between the two groups, although participants in the discontinuation group seemed to be slightly more likely to withdraw from the study because of worsening behaviour (no numbers reported, only descriptive figure).
- Ruths The BEDNURS Study reported in a subgroup analysis (Ruths 2004) that one participants restarted her antipsychotic medication nine days after it was discontinued in the intervention group (15 people): although not mentioned in the text, there was no indication of a significant difference between the discontinuation and continuation groups.

1.2. Behavioural and psychological symptoms

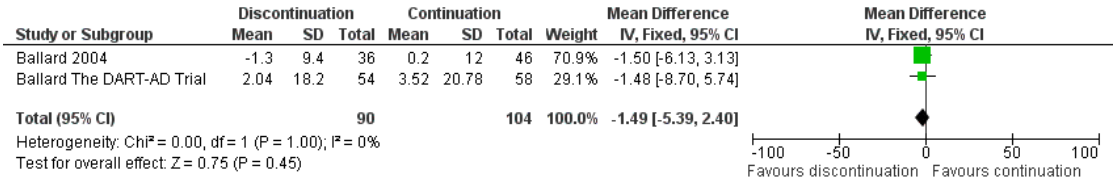
1.2.1. NPI and NPI-Q scores

- In the Ballard 2004 study there were no significant differences between groups in change on the NPI total score or the key psychiatric/behavioural factors of agitation, mood and psychosis. Results are reported for on-treatment-analysis only (i.e. all participants who completed the programme).
    - A subgroup of participants with baseline NPI scores at or below the median ($\leq$ 14) had a particularly good outcome, with a significantly greater reduction of agitation (a sub-score of the NPI) in participants receiving placebo (Mann-Whitney U test z = 2.4; P value = 0.018), while participants with higher baseline NPI scores were significantly more likely to develop marked behavioural problems if antipsychotics were discontinued (Chi^2 = 6.8; P value = 0.009). A marked behavioural problem was defined as a score of 8 or above on an individual item (information kindly given by Professor Clive Ballard by e-mail).
- In the Ballard The DART-AD Trial results were reported for the mITT analysis (i.e. only participants who had at least one dose of treatment are included in the analysis) and for the ITT populations at 6 and 12 months. There was a marginal non-significant advantage on the total NPI score for continuing antipsychotic treatment over the first six months of treatment.
    - Using a baseline NPI threshold of 14 or less, which was reported to be predictive of the outcome in the former three months antipsychotic withdrawal trial of Ballard 2004, the change in NPI did not differ between the treatment groups. Participants with baseline NPI scores above 14 had an almost 5-point non-significant advantage, if they remained on antipsychotics for six months. In this subgroup there were even more substantial advantages at 12 months for the people who continued on antipsychotics (a significant -16.9 point advantage, 95% CI -32.5 to -1.2). The authors mention that the test for interaction (although underpowered) was not significant and therefore concluded there was no evidence of interaction (Ballard The DART-AD Trial).
- In the Ruths The BEDNURS Study, NPI-Q scores are reported for all 55 participants at 1 month' follow-up. The NPI-Q scores remained stable or decreased in 42 participants (discontinuation group, 18 out of 27; continuation group 24 out of 28; P value = 0.18). Changes for individual symptoms and NPI-Q sum scores did not differ significantly between study groups. Participants with behavioural deterioration after antipsychotic cessation used higher daily drug doses at baseline (P value = 0.042).
- In Devanand ADAD 2012, total NPI scores were measured at baseline (phase A) and at time of randomisation (phase B), but no results were reported at later times of assessment. Nevertheless in this trial the total NPI score at baseline did not predict a relapse during the first 16 weeks of phase B. The NPI core score was measured at different times of assessment but not reported as such. The presence of psychosis at baseline or randomisation did not predict a relapse after discontinuation of risperidone neither.

Pooled results

Pooled results of NPI assessment are described in a forest plot (see Data and analyses and figures; Figure 3).

Figure 3. Forest plot of comparison: 1 Discontinuation versus continuation of antipsychotic medication: 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) (forest plot 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 The DART-AD Trial 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.

One forest plot was calculated: forest plot 1 (see Figure 3): behavioural assessment from Ballard 2004 (on-treatment data) and Ballard DART-AD (mITT data) at three months.

In this forest plot there was no significant pooled difference in NPI scores between the continuation and discontinuation group (mean difference -1.49, 95% CI -5.39 to 2.40).

1.2.2. Other scales that assess behavioural and psychological symptoms

- Bridges-Parlet 1997 concluded that based on the observed instances of PAB, there was no significant difference between withdrawn and not-withdrawn subjects and that withdrawal of antipsychotics in institutionalised people with dementia was successful in most but not all participants. There was also no difference in verbally aggressive behaviour between the two treatment groups in the Bridges-Parlet 1997 study.
- Cohen-Mansfield 1999 concluded that there was no impact of drug therapy discontinuation on the behaviour of residents in terms of scores on the CMAI or BPRS.
- In Devanand ADAD 2012, the CGI-C was also measured at different times of assessment, but was not reported as such in the paper.
- van Reekum 2002 concluded that the discontinuation of antipsychotics did not lead to differences in behaviour between the active treatment and control groups (BEHAVE-AD). The placebo group did have a tendency towards more aggression directed towards themselves (not significant), assessed by ROAS (data not reported in the paper) and also appeared to develop more apathy.

1.3. Withdrawal symptoms

Not reported.

1.4. Adverse events

- In Ballard The DART-AD Trial, there was a slight, non-significant advantage for the placebo group with respect to the change in severity of parkinsonism (M-UPDRS): there was a slight but non-significant difference between baseline and six months.
- Cohen-Mansfield 1999 reported no difference in adverse effects between withdrawal and continuation groups.
- In Devanand ADAD 2012, all adverse and serious adverse events were reported in a separate table in the paper and an expanded version of this table was given in the Supplementary Appendix online. A serious adverse event was an adverse event that resulted in any of the following outcomes: death (see also mortality), a life-threatening condition, hospital admission or prolongation of hospital stay, or an unexpected event leading to clinically significant disability or incapacity. The rates of adverse events (and death) after randomisation measured by different scales did not differ significantly among the continuation and discontinuation groups, although comparisons were based on small numbers of participants, especially during the final 16 weeks.
- Although there were no significant differences between groups for adverse effects, Findlay 1989 found a trend for greater reduction of adverse events in the group that stopped taking antipsychotics.
- van Reekum 2002 reported no difference in extrapyramidal symptoms between withdrawal and continuation groups.

2. Secondary outcomes

2.1. Cognition assessed by different scales

- In Ballard The DART-AD Trial, the change in SIB and SMMSE scores from baseline to six months did not differ significantly between withdrawal and continuation groups.
- Cohen-Mansfield 1999 concluded there was no difference between the continuation and discontinuation groups in cognition, measured by MMSE, although there were some numerical but not statistically significant advantages in favour of the placebo group (data reported without SD, therefore pooling was not possible).
- In Devanand 2011, the change in MMSE in phase B did not differ between the continuation and discontinuation group.
- In Devanand ADAD 2012, the change in MMSE in phase B did not differed between the continuation and discontinuation groups.
- Findlay 1989 concluded there was no significant difference in terms of cognitive function and behaviour measured by different scales over a four-week study period. However, for the assessment of cognition with the CAS the difference between the intervention and control group at baseline, could have had an effect on the result. Data were presented as means and ranges only and therefore pooling was not possible.
- van Reekum 2002 also concluded there was no difference between the continuation and discontinuation groups in cognition, measured by MMSE, without reporting any detail (no figures, no data).

2.2. Quality of life

- Ballard 2004 reported a non-significant improvement in well-being, measured by DCM, in people withdrawn from antipsychotics compared with a slight worsening in people continuing antipsychotic treatment. This difference was not significant, either in the overall cohort or in those with NPI scores above or at or below the median.

2.3. Use of physical restraint

- Bridges-Parlet 1997 reported no difference in use of physical restraints between the intervention and control groups.

2.4. Mortality

- Ballard The DART-AD Trial reported mortality data in his second paper at 12, 24 and 36 months follow-up for people randomised in the 12 months' discontinuation trial (first paper) and found a non-significant increase in mortality in people who continued antipsychotic treatment: cumulative probability of survival during 12 months 70% (95% CI 58% to 80%) compared with 77% (95% CI 64% to 85%) (mITT analysis; i.e. participants received at least one dose of treatment) in the withdrawal group. This higher but non-significant mortality in the continuation group was persistent and even more pronounced over time. After 24 months' follow-up the cumulative survival rates were 46% and 71%, respectively (significant), and at 36 months 30% versus 59% (significant). Due to dropout and uncertainty about the use of antipsychotics these figures should be interpreted with caution. The survival rates were similar in additional analyses that focused on the people who continued their allocated treatment for at least 12 months.
- On the contrary, in Devanand ADAD 2012, mortality measured at different times of assessment (16 and 32 weeks) did not differ significantly between the continuation and discontinuation groups. However, comparisons were made on small numbers of participants, especially during the final 16 weeks.

2.5. Other secondary outcomes

2.5.1. Global functioning

- In Ballard The DART-AD Trial for the BADLS, assessing function, there was no significant difference between the continue treatment and withdrawal groups. For the change in FAST and CGI-C, that measure global outcome, there was no evidence of any differences between the continue treatment and discontinuation groups.
- In Devanand 2011, there was no difference in the BFAS scores between the continuation and discontinuation group in phase B.
- van Reekum 2002 concluded that discontinuation of antipsychotics did not lead to differences in function compared with group continuing antipsychotic treatment.

2.5.2. Frontal executive function

For the FAS (used to assess verbal fluency) assessed in Ballard The DART-AD Trial there was strong evidence (i.e. a highly significant difference between the continue treatment and placebo groups) in the estimated change in FAS totals between baseline and six months: 0.6 point (SD 6.2) improvement in the placebo group compared to 3.2 points (SD 6.6) deterioration in the continue treatment group (estimated mean difference favouring discontinuation -4.5, 95% CI -7.3 to -1.7, adjusted for baseline value P value = 0.002).

2.5.3. Sleep

- Bridges-Parlet 1997 reported no difference in time sleeping between the two treatment groups.
- The Ruths The BEDNURS Study measured sleep and activity by actigraphic registrations in a subgroup of 30 people over a period of four weeks (Ruths 2004). Abrupt discontinuation of antipsychotics was associated with statistically non-significantly decreased average sleep efficiency from 86% to 75% (i.e. 54 minutes less sleep; P value = 0.29).

2.5.4. Language

- In the Ballard The DART-AD Trial for the STALD, assessing dysphasia, there was no significant difference between the continue treatment and placebo groups.

3. Co-variables

- In the post-hoc analysis of Ballard The DART-AD Trial there was no indication of a difference between participants taking typical or atypical antipsychotics. The majority of participants were taking risperidone or haloperidol, and the number of people taking other drugs was too small for any meaningful comparison.

4. Sensitivity analysis

A sensitivity analysis was not appropriate and therefore not performed.

DISCUSSION

Summary of main results

Overall, in seven of nine included trials, antipsychotics could be withdrawn in older people with dementia and NPS without a significant effect on most outcomes. In particular, behavioural symptoms measured by the NPI or NPI-Q were not influenced by withdrawing antipsychotic medication in most of the discussed studies (for the two pooled studies: see Data and analyses and Figure 3).

However in a small pilot study of haloperidol, discontinuation in outpatients with agitation or psychosis who had previously responded to haloperidol, there was a non-significant difference between the discontinuation and continuation groups in the proportion of participants who relapsed, favouring the continuation group (Devanand 2011). Time to relapse was significantly shorter on placebo than on haloperidol in this pilot study.

The subsequent Devanand ADAD 2012 trial reported a significant increased risk of relapse in the group of people with AD and psychosis or agitation that had responded to titrated and prolonged risperidone therapy (four to eight months) before and was discontinued from risperidone therapy afterwards. The risk of relapse was independent from baseline or randomisation total NPI score and independent from the presence of psychosis at baseline or randomisation.

On the contrary, the two Ballard trials reported significant differences in some outcomes between subgroups with high and low NPI scores at baseline. In the study by Ballard 2004, people with a baseline NPI score equal to or below the median (14) had a significantly better outcome in terms of agitation (a sub-score of the NPI) if antipsychotics were discontinued. In Ballard The DART-AD Trial, the subgroup of people with a baseline NPI score greater than 14, had more severe NPS if antipsychotics were discontinued than if they were continued; the difference was non-significant at six months, but reached significance at 12 months. In Ballard 2004, participants with a baseline NPI score greater than 14 taking placebo were also significantly more likely to develop marked behavioural disturbance than were those assigned to continue antipsychotic treatment (Chi^2 = 6.8; P value = 0.009).

There was no difference in outcomes other than behavioural symptoms.

Especially there was no difference in cognition between the discontinuation and the continuation group in all studies.

- In Ballard The DART-AD Trial there were some numerical advantages for the placebo-treated group on some scales measuring cognition. Ballard 2004 reported a non-significant improvement of well-being. In one study there was a significant difference in FAS scores, assessing frontal executive function (Ballard The DART-AD Trial).
- We could find no significant differences in adverse events between continuation and discontinuation groups.
- There was a slight, but non-significant, difference in parkinsonism between the continuing treatment and placebo groups in two studies (Ballard The DART-AD Trial; Findlay 1989).
- In Ruths The BEDNURS Study, abrupt discontinuation of antipsychotics was associated with decreased, but non-significant, average sleep efficiency.

In the two studies that reported mortality (Ballard The DART-AD Trial; Devanand ADAD 2012) there was no significant difference between the continuation and discontinuation groups.

However, in the long-term follow-up of the Ballard The DART-AD Trial, we found a statistically non-significant increase in mortality in people on prolonged antipsychotic therapy, which is alarming. According to Smith, the number needed to treat for an additional harmful outcome (NNTH) is 22 at one year and although calculated from non-significant differences it approaches numbers calculated from other studies and sources (Smith 2011). The mortality differences appear to persist in the long term and are statistically significant after 24 or 36 months, but the numbers at these time points are small and data on treatment during the follow-up years after the study are lacking. Nevertheless, these follow-up data point to a clear hazard with long-term antipsychotic treatment in people with dementia and suggest that such treatment might contribute to a considerable number of avoidable deaths in this group of vulnerable people.

Overall completeness and applicability of evidence

We found few studies on this topic with good overall methodological quality. Two studies were identified as having a potential

risk of reporting bias although most of the results they reported were negative, suggesting that they were not tending to favour the reporting of positive results (see 'Risk of bias' graph, Figure 1). All included studies had problems including enough frail older people (a group with high mortality) and as a result the statistical power of the studies was low and very few outcomes showed statistically significant differences between the groups. As it was not possible to pool data for most outcomes, the potential benefits of a meta-analysis could not be realised. Therefore, 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, especially regarding people with more severe types of dementia and regarding people with psychosis or agitation that responded well to prolonged antipsychotic therapy.

Furthermore, most of the available evidence only applies to nursing home residents, long-stay psychogeriatric wards or geriatric chronic floors (i.e. hospital setting). Only one small pilot study and its larger subsequent trial included people living in the community (outpatients).

It is possible that the profile of the original symptoms (i.e. the specific cluster of NPS) for which the antipsychotics were prescribed influences the assessed outcome. Therefore, it would be useful to know why the antipsychotics were prescribed. Devanand 2011 tried to overcome this problem by including only people with psychosis or agitation that had responded to haloperidol treatment. In his pilot study, there was a tendency towards a higher (although not statistically significant) relapse rate for psychosis and agitation in the discontinuation group, and time to relapse was shorter in the discontinuation group. These findings were confirmed in the subsequent Devanand ADAD 2012: on the contrary to all other trials, Devanand and co-workers reported a statistically significant increased risk of relapse in people with AD who had psychosis or agitation that had responded to prolonged risperidone therapy, regardless the severity of total NPI score or the presence of psychosis at baseline or randomisation.

Adverse events, withdrawal symptoms, initiation of other psychoactive medication after withdrawal and baseline antipsychotic dose are not systematically reported. Consequently, the effect of these co-variates on clinical outcomes is unknown. Also, based on the available evidence it is not possible to choose between a tapered withdrawal schedule and an abrupt withdrawal programme.

The evidence identified here concerned only antipsychotics as a pharmacological treatment of older people with dementia and NPS and the results cannot be extrapolated to other types of potentially inappropriate and harmful drugs, such as benzodiazepines.

Quality of the evidence

The methodological quality, assessed as the risk of bias of the included studies was generally good. Ballard The DART-AD Trial was assessed as having the lowest risk of bias.

Potential biases in the review process

We pooled two studies that use the same NPI scale assessed at different times. However, these results should be interpreted with caution. Results of NPI assessment are described in one forest plot (see Figure 3).

We should be aware of the fact that assessments of the NPI (Ballard 2004; Ballard The DART-AD Trial) and NPI-Q scores (Ruths The BEDNURS Study) are not always made at the same time point. It is unclear whether this difference in time of assessment has a significant influence on the conclusions. The Ballard DART-AD study suggests that people with more severe NPS show more substantial advantages of continuing antipsychotics at 12 months compared with assessment at six months. However, Devanand ADAD 2012 found no relation between the severity of total NPI score and risk of relapse.

Agreements and disagreements with other studies or reviews

We are not aware of other systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

Older people with dementia and NPS using long-term antipsychotics can be withdrawn without detrimental effects on their behaviour. However, there is some evidence suggesting that people with more severe NPS (total NPI > 14) could benefit from continuing antipsychotic treatment. We also found that a subgroup of people with dementia and psychosis or agitation who responded well to antipsychotic medication before may relapse after discontinuation of their antipsychotic medication. It remains uncertain whether withdrawal of antipsychotics has beneficial effects on cognitive or psychomotor, or both, status.

However, we suggest that planned discontinuation programmes of antipsychotics should be incorporated into routine clinical care of older people with dementia, also because of the risk of adverse effects and the marked increase in mortality in this vulnerable group when using antipsychotics in the long term. This approach is consistent with the observation that most behavioural complications of dementia are intermittent and do not persist for longer than three months. Caution is required in residents with more severe NPS and in people with psychosis or agitation who responded well to antipsychotic medication before. In these people, withdrawal might not be recommended until further evidence becomes available.

Implications for research

Abrupt drug discontinuation may contribute to observed withdrawal effects (Ruths The BEDNURS Study), and tapering medication may produce different effects, particularly in people taking high doses of antipsychotics (Bridges-Parlet 1997). More studies focusing on the method 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 a clinically relevant, and appropriate primary outcome for studies assessing the effect of withdrawal from antipsychotics in people with dementia. It is likely that scales other than the NPI scale (e.g. the agitation NPI sub-score) will correspond better with this symptom cluster and should, therefore, be used in further trials. By including people with psychosis or agitation, the Devanand 2011 pilot trial tried to overcome that problem. The Devanand ADAD 2012 suggests that people with psychosis or agitation-aggression who responded to antipsychotic treatment for a longer time may have a significant increased risk of relapse after discontinuation their antipsychotic medication.

Studies are needed to explore the effects of withdrawal on different aspects of cognitive function and to determine whether the impact on cognition also impacts on ability to carry out daily activities.

The available studies suffer from 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 statistically significant change in cognition or well-being. However, the sample of people included in these studies reflects day-to-day reality. Conducting trials in this context of frail older people requires a delicate balance between methodological rigor and feasibility.

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 of discontinuation of antipsychotics depend on the agent (e.g. haloperidol in the Devanand 2011 pilot trial) and on drug interactions/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 chronic antipsychotic 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 reports that in the Ballard The DART-AD Trial consent was withdrawn in 16% of the eligible cases before blinding, either by the participant, the family practitioner or the family (Smith 2011). In addition, Cohen-Mansfield 1999 report 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.

The findings of this Cochrane review reinforce 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 in order 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	Double-blind, placebo-controlled study
Participants	100 older people (aged > 65 years) care-facility residents in the UK with probable or possible AD, no severe behavioural disturbances, taking neuroleptics for longer than 3 months were included. All participants having severe behavioural symptoms, i.e. individual scores > 7 on 1 of the 12 items of the NPI-scale at the time of evaluation were excluded
Interventions	Abrupt discontinuation of antipsychotics
Outcomes	Changes in behavioural and psychiatric symptoms measured by the NPI, quality of life measured by well-being using DCM
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were then randomized to neuroleptic (N=54) or placebo (N=46)" Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	"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 randomization in a twice-daily regimen, allocating to each participant the closest dose to their pre-existing prescription from the doses encapsulated" "...the centre coordinator, blinded to neuroleptic status..." Encapsulation of the administered drugs ensured blinding of participants and doctors/nurses, but blinding of outcome assessors is not described

Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	"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 people developing marked behavioural symptoms are described and compared between groups using the chi-square test" "Fourteen patients (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 N=3 (6%), placebo N=3 (7%)), protocol violation (active N=2(4%), placebo N=1(2%)) or withdrawal of consent (active N=3(6%), placebo N=2(4%))" "Eighty-two (82%) of the patients 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	NPI and well-being scale reported, but MMSE only assessed at start of study
Other bias	Unclear risk	Not clear how participants were recruited

Ballard The DART-AD Trial

Methods	Randomised, blinded, placebo-controlled parallel 2-group treatment discontinuation study
Participants	165 institutionalised people in the UK currently prescribed neuroleptics thioridazine, chlorpromazine, haloperidol, trifluoperazine or risperidone for behavioural or psychiatric disturbance in dementia for at least 3 months were included. The following people were excluded: those who were unable to complete primary outcome measures at baseline assessment; if a clinician responsible for care or study clinician considered the person suffered from any physical condition that would make participation in the trial distressing or likely to increase suffering; if the person was currently taking thioridazine and showing a prolonged QTc on electrocardiogram; if the person was likely to be unable to take capsules
Interventions	Abrupt discontinuation of neuroleptics

Outcomes	Primary outcome: total SIB score NPS were evaluated by the NPI
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"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	"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 (performance bias and detection bias) All outcomes	Low risk	The clinicians, those administering the trial medication, the carers, the relatives, the participants themselves, and those assessing the outcomes were all blinded to treatment allocation
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	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

Ballard The DART-AD Trial (*Continued*)

		was limited to those people 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	All intended primary and secondary outcomes are reported in the first and the follow-up study
Other bias	Low risk	There are limiting factors to consider the interpretation of this excellent trial First, recruitment focused on people 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)

Bridges-Parlet 1997

Methods	Double-blind, baseline-treatment-controlled pilot study
Participants	36 nursing home residents in the US with a diagnosis of dementia and a history of physically aggressive behaviour taking for 3 months prior to the study a stable dose of any neuroleptic. People with primary psychiatric diagnoses, mental retardation and terminal illness or other recent acute changes were excluded
Interventions	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

Bridges-Parlet 1997 (*Continued*)

	at the beginning of week 2
Outcomes	Primary outcome measures: completion of the 4 weeks of study, change in the amount of observed physically aggressive behaviour in each week over the course of the trial Secondary outcomes were a number of other behaviours, such as verbally aggressive behaviour, walking or amount of time spent sleeping These behaviours were observed by experienced study personnel, blinded to treatment assignments and using a portable bar-code reader capable of storing several hours of observation Physically aggressive acts were identified by type, each of which was coded separately by the bar-code system. Specific types of physically aggressive behaviour included hitting, biting, scratching, kicking and pushing. The severity of a particular instance was not recorded, but if multiple instances of striking occurred, the code for the particular type of physically aggressive behaviour was recorded for each minute in which physical contact occurred. The measure of physically aggressive acts that was used as the primary outcome measure was the sum of all bar-code reader-identified instances of all five types of physically aggressive behaviour Verbal aggressiveness was defined as an instance of speaking in an angry tone of voice, swearing or yelling in anger. Individual instances were recorded in 1-minute increments, so that if a sustained period of swearing or yelling occurred, each minute in which the behaviour occurred was noted For behaviours such as walking, sitting restrained or sleeping, the observers recorded the person's current activity at least every minute. Based on this complete activity log, we were able to tabulate the total time spent in these activities The observers also kept hand-written notes of the period of observation as a back-up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"At the end of week 1, subjects were randomly assigned to either withdrawal or no withdrawal" "Assignment was based on a predetermined sequence such that three patients were assigned to withdrawal for every two not withdrawn"
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described. It may not have been blinded Participant groups were well matched for age, chlorpromazine-equivalent neuroleptic dose and physically aggressive behaviour at baseline
Blinding (performance bias and detection bias)	Low risk	"The patients were directly observed by experienced study personnel who were

Bridges-Parlet 1997 (*Continued*)

All outcomes		blinded to treatment assignments" "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" Completion of the 4-week programme was the primary outcome. 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
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	"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-code reader failed. Handwritten back-up notes were used for physically aggressive behaviour frequency"
Selective reporting (reporting bias)	Low risk	All intended outcomes reported
Other bias	Unclear risk	There may have been selective recruitment limiting the generalisability of the results "Five nursing homes referred patients to the study. Nursing supervisors identified physically aggressive patients with dementia who were currently being treated with a neuroleptic. We relied on the judgements of the nursing supervisors regarding the prior presence of physically aggressive behaviour. Other than the criteria we gave the supervisors, we did not know what criteria the nursing supervisors used to choose potential study subjects. It was beyond the resources of our project to collect data on all patients whom the nursing supervisors considered as eligible but either than rejected,

Bridges-Parlet 1997 (*Continued*)

		or who were denied permission to participate by the family. It is possible that our study patients differed in some systematic way from nonparticipating patients. Our participants may have been more suitable for withdrawal than other patients on neuroleptics"

Cohen-Mansfield 1999

Methods	Double-blind crossover study
Participants	58 nursing home residents in the US older than 70 years taking, for at least 4 weeks, haloperidol, thioridazine or lorazepam for agitation were included. Because the diagnosis of dementia was not mentioned in the paper, we emailed the first author to ask her whether the participants included suffered from dementia and her answer was positive (referring to the MMSE scores). The following people were excluded: people with concomitant administration of other antipsychotic or antianxiety drugs other than low-dose trazodone hydrochloride for sleep, life expectancy of < 3 months, psychiatric diagnosis of a major affective disorder of schizophrenia, acute infection within 10 days before entering the nursing home, expectancy of leaving the nursing home within 3 months, and uncontrolled hyperglycaemia or hypoglycaemia
Interventions	Withdrawal of antipsychotic and lorazepam use by tapering to placebo during a 3-week period. After 7 weeks of taking either placebo or medication, the group taking placebo was titrated back to the initial dose and the group taking medication was tapered to placebo
Outcomes	Primary outcomes were overall psychiatric symptoms measured by the BPRS and agitation measured by the CMAI The BPRS assessed the following symptoms: 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 affect. Each symptom was rated on a severity scale ranging from 1 (not present) to 7 (extremely severe) . The BPRS was assessed by daytime and evening nursing staff and by the unit's social worker The CMAI consists of 29 agitated behaviours, each rated on a 7-point scale of frequency (1 indicates the participant never engages in that specific behaviour, and 7 indicates the participant manifests that behaviour an average of several times an hour). The period rated was the week before administration of the CMAI, and three subtypes of agitation were used: aggressive behaviour, physically non-aggressive behaviour and verbally agitated behaviour. The CMAI was independently completed by daytime and evening shift nursing staff members most familiar with the resident, and by social workers Secondary outcomes were functioning, adverse effects and global impression scales
Notes	Copy of our mail to Prof. Dr. Cohen-Mansfield and her answer: "Dear Dr. Declercq,

	I am quite sure they all had dementia, but I do not remember whether it was an inclusion criterion. The MMSE scores also fit with a dementia diagnosis Jiska Cohen-Manfield, PhD, ABPP **From:** Tom Declercq [tomrw.declercq@ugent.be] **Sent:** Tuesday, April 21, 2009 9:34 AM **To:** Jiska Cohen-Mansfield **Subject:** Cochrane review on withdrawal of antipsychotics Dear Colleague, Professor, As first author of an ongoing Cochrane review on withdrawal of antipsychotics, I am very interested in the RCT you conducted on withdrawal of haloperidol, thioridazine and lorazepam in the nursing home (Arch Intern Med 1999). Can you please let me know if the selected patients, residents of nursing homes, had dementia as an inclusion criterion? Thank you Sincerely Tom Declercq MD Department of Primary Care Ghent University Belgium Tomrw.declercq@ugent.be"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	".....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" Method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"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

Cohen-Mansfield 1999 (*Continued*)

		were blinded to which group a participant was assigned"
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	"Twenty-three participants discontinued participation in the study before completion for the following reasons: death or dying (3), hospitalization (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 crossover stage" "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"
Selective reporting (reporting bias)	Low risk	All outcome data reported
Other bias	Unclear risk	Several different analyses were used to assess the robustness of the result. However, it is not clear if an intention-to-treat analysis was used 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

Devanand 2011

Methods	A 6-month, randomised, double-blind, placebo-controlled discontinuation trial (phase B) following response to haloperidol open treatment during 20 weeks (phase A)
Participants	78 outpatients aged 50-95 years with AD and psychosis or agitation were assessed for eligibility in phase A of the trial Exclusion criteria were: 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, tardive dyskinesia, diagnosis of a psychotic disorder antedating the onset of dementia, antipsychotic medication usage during the 4 weeks prior to study entry, and contraindication to the use of haloperidol 44 participants were included in phase A 22 responders of phase A were eligible for randomisation in phase B (21 entered Phase B and 20 had at least one follow-up visit)

Interventions	Phase A: open treatment (20 weeks): 44 outpatients with AD and psychosis or agitation receiving psychotropic medication had a 1-week washout prior to entering phase A. During phase A flexible doses of haloperidol 0.5-5 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 people randomised to placebo, there was a 2-week double-blind sequential placebo substitution tapering period to placebo. Time points of assessment during phase B were 0 (same as end of phase A), 2, 4, 8, 12, 16, 20 and 24 weeks (i.e. 6 months)
Outcomes	Phase A: the 3 most prominent target of psychosis or agitation were identified, 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 $\leq$ 6 on these 3 items (range 0-18), and minimal or greater improvement on the CGI-C score (rated only for symptoms of psychosis or agitation) Phase B: relapse (primary outcome) was 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 $\geq$ 6 on these 3 items (range 0-18), and minimal or greater worsening on the CGI-C score (rated for psychosis and agitation) Secondary outcomes were: 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 the MMSE and impairment in ADL was assessed by the modified BFAS at baseline, end-phase A and end-phase B
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	"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" No description of the blinding of random allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and carer blinding: "Haloperidol and placebo were made up in identical looking opaque white capsules" Outcome assessors seem to be adequately blinded: "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"
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	Attrition at end of phase A fully accounted for: "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: "Twenty of the 21 patients randomized in Phase B to continuation haloperidol or placebo had at least one follow-up visit after randomization 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	This pilot study report mentions the following primary outcome: "Criteria for relapse were minimum 50% worsening from the sum score of three target symptoms at end Phase A, a sum score 6 on these three items (range 0-18), and minimal or greater worsening on the CGI-C score (rated for psychosis/agitation)" The protocol (Devanand 2012a) for the subsequent study (Devanand ADAD-Trial) mentions NPI as primary outcome measure: "*Primary Efficacy Measure* is NPI sum score of delusions, hallucinations, and agitation/aggression, which are three of 12 domains in the NPI". It is not clear why the primary outcome definition was changed for the subsequent study
Other bias	Unclear risk	The discontinuation trial only included people who responded to haloperidol. Non-responders after first 12 weeks (phase A) were excluded from the discontinuation phase (B) Study supported by NIH grant but authors have financial links with several pharma-

		ceutical companies

Devanand ADAD 2012

Methods	6-month, randomised, double-blind, placebo-controlled discontinuation trial (phase B) following response to flexible dose risperidone open treatment for 16 weeks (phase A)
Participants	"Patients were recruited from memory clinics (including Alzheimer's research centers) , geriatric psychiatry clinics, and clinics at Veterans Affairs medical centers, as well as through physician referrals and advertising. Patients were eligible for participation in the study if they were outpatients or residents of assisted-living facilities or nursing homes, were 50 to 95 years of age, and 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 National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association" "In addition, eligible patients had 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) and a score of 5 to 26 on the Mini-Mental State Examination (MMSE, with scores ranging from 0 to 30 and higher scores indicating better cognition) in the case of outpatients and 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 were a history of stroke, transient ischemic attack, or uncontrolled atrial fibrillation" 253 people screened; 180 received risperidone; 110 randomised in phase B Group 1 (continue risperidone 32 people at start, 13 received risperidone at wk 16, 10 completed 48 wks without relapse) Group 2 (continue risperidone for 16 wks and then placebo, 38 people at start, 27 received placebo at wk 16, 14 completed 48 wks without relapse) Group 3 (start placebo in phase B, 40 people, 13 received placebo at wk 16, 10 completed 48 wks without relapse)
Interventions	"Patients with Alzheimer's disease and psychosis or agitation-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)" 1-week washout period for psychotropic medication "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"
Outcomes	Primary outcomes: time to relapse of psychosis ("the primary end point was the time to relapse during weeks 0 to 16 of phase B") or agitation ("the time to relapse during weeks 17 to 32 of phase B") "In *phase A*, patients were considered to have had a response if they had a reduction of 30% or more from baseline on the NPI core score (the sum of the subscale scores for agitation-aggression, hallucinations, and delusions) and a score of 1 (very much

	improved) or 2 (much improved) on the Clinical Global Impression of Change (CGI-C) scale (which ranges from 1 to 7, with higher scores indicating less improvement) for overall psychosis or agitation. In *phase B*, patients 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 6 (much worse) or 7 (very much worse) on the CGI-C. At any phase B study visit, if the criteria for relapse were met on the basis of scores on the NPI and CGI-C during the preceding 2 weeks, end-of-study procedures were completed, and the patient exited the study to receive open label treatment" 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); and 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)" Adverse events
Notes	Outcome symptoms slightly unevenly distributed in randomised groups in phase B: 9% agitation-aggression in group 1 (continue risperidone) vs 19% in group 2 (switch to placebo after 16 wks) 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)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The study statistician prepared a randomized permuted-blocks procedure, with blocks of 3 or 6, 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	"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"

Devanand ADAD 2012 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"...double-blind fashion..." "...all tablets identical in appearance" "Immediately before the end of phase A, the pharmacy dispensed prepackaged blister packs of risperidone or placebo tablets that were identical in appearance for patients eligible for randomization 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"
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	All randomised participants accounted for in the flowchart "The dropout rates did not differ significantly among the randomized groups (Fig. 1)"
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Funding sources: "...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. The first author received grants from several pharmaceutical companies (inside and outside the submitted work)

Findlay 1989

Methods	Randomised double-blind placebo-controlled trial
Participants	36 older people (aged $\geq$ 65 years) female inpatients in a long-stay psychogeriatric ward in the UK with senile dementia, Alzheimer type, receiving a stable dose of between 10 and 100 mg of thioridazine per day for at least 2 months. Males, multi-infarct dementia and antipsychotic agents other than thioridazine were excluded
Interventions	Withdrawal of thioridazine by tapering to half of the daily dose in the first week and to placebo over the next week; after 4 weeks, all participants were restored to half their original dose of thioridazine with any subsequent alterations being made by their regular

Findlay 1989 (*Continued*)

	medical attendant on an empirical base
Outcomes	Primary outcomes are cognitive function measured by the CAS and cognitive and behavioural dysfunction as measured by the SCAGS and the LPRS Secondary outcomes are systolic BP and heart rate (HR)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...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" Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	"...allocated by a random code to the active or placebo group in a double-blind manner" How blinding was ensured is not described. The randomisation process was not completely successful "The starting difference in Cognitive Assessment Scale scores between active-continued and placebo-substituted groups represents an artefact of the randomization process"
Blinding (performance bias and detection bias) All outcomes	Low risk	"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"
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Unclear risk	No information

Findlay 1989 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Primary outcome not described; it is unclear if a selection of measured outcomes was reported
Other bias	Unclear risk	The randomisation procedure unfortunately resulted in a baseline imbalance in 1 of the 3 cognitive /behavioural rating scales, i.e. the CAS. It is unclear if this has had an impact on outcomes It is not clear how participants were recruited

Ruths The BEDNURS Study

Methods	Randomised, placebo-controlled, double-blinded multicentre 4-week study
Participants	55 nursing home residents with dementia in Norway taking haloperidol, risperidone or olanzapine for nonpsychotic symptoms for at least 3 months before the study as standing medication in stable doses; older people, i.e. aged $\geq$ 65 years; dementia diagnosis according to the clinical criteria of International Classification of Diseases, 10th Revision; and residence in the facility for at least 3 months before inclusion were included. 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 were excluded
Interventions	Abrupt discontinuation of antipsychotic medication
Outcomes	Behavioural and Psychological Symptoms measured by the NPI-Q 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. 3 separate ratings were conducted for all the participants: in the second baseline week, in week 1 and in week 4 of the intervention period. 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. 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 p.m. to 7 a.m.), 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 comprising the second

Ruths The BEDNURS Study (*Continued*)

	baseline week and week 1 and week 4 of the intervention, corresponding with the timing for behavioural ratings
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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)	Low risk	"All study medications were provided by an independent pharmacy to maintain blindness, and dispensed at the same dose frequency as baseline treatment"
Blinding (performance bias and detection bias) All outcomes	Low risk	"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" "Sealed envelopes, containing details of study medication for each patient, were available for the nursing home physicians in case of serious health events" It is not clear how outcome assessment was blinded
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Unclear risk	All 55 participants were included in the analysis "Seven patients completed the study prematurely, due to unblinding for randomisation code, behavioural deterioration, restless legs or delirium"
Selective reporting (reporting bias)	Low risk	All intended outcomes reported
Other bias	Unclear risk	It is not clear if the participating nursing homes were different from non-participating

van Reekum 2002

Methods	Randomised, double-blind, placebo-controlled trial
Participants	34 residents in nursing homes and from geriatric chronic care floors of an academic health science centre in Canada, having any form of dementia, receiving antipsychotics for 6 months or longer. The following people were excluded: people with a 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	Withdrawal by tapering: dose reduction with original medication halved for the first week of the dose reduction period and the remaining dose halved for the second week
Outcomes	Behavioural outcome measures included the BEHAVE-AD, the NPI and the ROAS Cognitive functioning was assessed using the MMSE and the MDRS. The MMSE was completed on a monthly basis and the MDRS was completed at baseline and at the end of the study Functional level was assessed using the BDS, recording ADL and motivational behaviour sub-scale Extrapyramidal signs were assessed using the ESRS. The functional and extrapyramidal sign measures were completed on the same schedule as the MMSE A CGI was also completed for 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	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"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	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"During all study periods, medications, including placebo, were placed into identical capsules to maintain blindness"
Incomplete outcome data (attrition bias) NPI (Neuro Psychiatric Inventory) and DCM (Dementia Care Mapping)	Low risk	"The total number of subjects who were withdrawn from the study early was 16, with 10 in the placebo group and 6 in the active treatment group The difference in the rate of early study withdrawal was not

van Reekum 2002 (*Continued*)

		statistically significant. Subjects were withdrawn due to medical illness (3), death (3), extrapyramidal symptoms (3), and exacerbations in of behavioural problems (7, of 4 in the placebo and 3 in the active group)"
Selective reporting (reporting bias)	High risk	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 data
Other bias	Unclear risk	This study has less potential for referral bias than the Bridges-Parlet (1997) and Cohen-Mansfield (1999) study

AD: Alzheimer's disease; 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-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
Horwitz 1995	This publication is not a clinical trial, but a naturalistic study
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 NPS we are interested in
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

NPS: neuropsychiatric symptom.

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

Engedal

Trial name or title	Dementia Antipsychotics and Antidepressants Discontinuation Study DESEP
Methods	Randomised double-blind placebo-controlled trial
Participants	Nursing homes residents with Alzheimer dementia or vascular dementia given antipsychotics or antidepressants for 3 months or more
Interventions	Risperidone, escitalopram, citalopram, sertraline, paroxetine
Outcomes	Changes in Neuropsychiatric Inventory, changes in Cornell's Depression Scale, changes in Unified Parkinson's Disease Rating Scale sub-scale
Starting date	August 2008
Contact information	sverre.bergh@sykehuset.innlandet.no
Notes	

DATA AND ANALYSES

Comparison 1. Discontinuation versus continuation of antipsychotic medication: continuous data, analysis method mean difference

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Behavioural assessment by using NPI measuring NPS at 3 months (Ballard 2004 and Ballard DART-AD) (forest plot 1)	2	194	Mean Difference (IV, Fixed, 95% CI)	-1.49 [-5.39, 2.40]

Analysis 1.1. Comparison 1 Discontinuation versus continuation of antipsychotic medication: continuous data, analysis method mean difference, Outcome 1 Behavioural assessment by using NPI measuring NPS at 3 months (Ballard 2004 and Ballard DART-AD) (forest plot 1).

Review: Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia

Comparison: 1 Discontinuation versus continuation of antipsychotic medication: continuous data, analysis method mean difference

Outcome: 1 Behavioural assessment by using NPI measuring NPS at 3 months (Ballard 2004 and Ballard DART-AD) (forest plot 1)

Study or subgroup	Discontinuation N	Mean(SD)	Continuation N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ballard 2004	36	-1.3 (9.4)	46	0.2 (12)		70.9 %	-1.50 [-6.13, 3.13]
Ballard The DART-AD Trial	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

ADDITIONAL TABLES

Table 1. Antipsychotic drug classes

PHENOTHIAZINES with aliphatic side chain
PHENOTHIAZINES with piperazine structure
FENOTHIAZINES 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
FENOTHIAZINES 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.

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 (*The Cochrane Library*)	Issue 1 2009	75
ISTP Conference Proceedings portal.isiknowledge.com/portal.cgi	Up to 11 Feb 2009	105
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 trials register	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

(*Continued*)

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-present (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/	86

(*Continued*)

	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.	

(*Continued*)

	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 1980-2011 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	178

(*Continued*)

	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.	

(*Continued*)

	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.	

(*Continued*)

	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-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. 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.	110

(*Continued*)

	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.	

(*Continued*)

	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* 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"	99

(*Continued*)

	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 "pre-clinical 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-present) ; BIOSIS Previews (1926-present); MEDLINE (1950-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)	90

(*Continued*)

	#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 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)	
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 (*The Cochrane Library*) (Issue 1 of 4, Jan 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	46

(*Continued*)

	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 #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	9 + 0 + 2 = 11

(*Continued*)

	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	
10. ICTRP Search Portal (apps.who.int/trialsearch) (includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.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; The 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	13

(*Continued*)

	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	
TOTAL before de-duplication		776
TOTAL after de-duplication and first-assess		70

Appendix 3. Pre-publication searches: June 2012 and November 2012

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	Antipsychotic OR neuroleptic OR APSY	June: 58 Nov: 1
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (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.	June: 60 Nov: 28 (plus suppl search hits)

(*Continued*)

	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	

(*Continued*)

	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. (2011* or 2012*).ed. 103. 101 and 102	
3. EMBASE 1980-2011 December 29 (Ovid SP)	1. antipsychotic*.ti,ab. 2. "anti-psychotic*".ti,ab. 3. Antipsychotic Agents/ 4. neuroleptic*.ti,ab. 5. phenothiazines.ti,ab. 6. Phenothiazines/	June: 109 Nov: 35 (plus suppl search hits)

(*Continued*)

	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/ 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.	

(*Continued*)

	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	

(*Continued*)

	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-May week 1 2012 (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. 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.	June: 70 Nov: 58 (plus suppl search hits)

(*Continued*)

	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.	

(*Continued*)

	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)	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* 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	June: 71 Nov: 51 (plus suppl search hits)

(*Continued*)

	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 "pre-clinical 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	

(*Continued*)

	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-present) ; BIOSIS Previews (1926-present); MEDLINE (1950-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 levosulpiride 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=(2011-2012)	June: 56 Nov: 260 (plus suppl search hits)
7. LILACS (BIREME)	antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics [Words] and dementia OR demenc$ OR alzheimer$ [Words] and 2011 OR 2012 [Country, year publication]	June: 6 Nov: 1
8. CENTRAL (*The Cochrane Library*) (Issue 2 of 4, 2012)	#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 olan-	June: 13 Nov: 2 (plus suppl search hits)

(*Continued*)

	zapine #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 #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	

(*Continued*)

	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 2011 to 2012	
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 03/01/2011 to 06/01/2012 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 03/01/2011 to 06/01/2012 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 03/01/2011 to 06/01/2012	June: 2 + 0 + 2 = 4 Nov: 0 (plus suppl search hits)
10. ICTRP Search Portal (apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.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	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 | received from 01/03/2011 to 01/06/2012 Search 2: Advanced search: dementia OR alzheimer OR alzheimers OR alzheimer's	June: 7 + 1 + 4 = 13 Nov: 0 (plus suppl search hits)

(*Continued*)

Clinical Trials Registry; The Netherlands National Trial Register]	OR lewy OR DLB OR AD OR LBD | clothiapine OR droperidol OR pipamperone OR benperidol OR bromperidol OR fluspirilene OR pimozide | received from 01/03/2011 to 01/06/2012 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 | received from 01/03/2011 to 01/06/2012	
TOTAL before de-duplication and first-assess		June: 454 Nov: 436 (plus Nov suppl search hits)
TOTAL after de-dupe and first-assess		June: 11 Nov: 20
Supplementary search of additional antipsychotics not covered in previous searches (all dates)		
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present (Ovid SP)	1. exp Dementia/ 2. Delirium/ 3. Wernicke Encephalopathy/ 4. Delirium, Dementia, Amnestic, Cognitive Disorders/ 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/	194

(*Continued*)

	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 1980-2012 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. 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.	425

(*Continued*)

	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-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. 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/	27

(*Continued*)

	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-pub and supple search		1100
Total post first assess and de-duplication		33

Appendix 4. List of abbreviations

AD	Alzheimer's disease
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

(*Continued*)

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-IV	Diagnostic and Statistical Manual of Mental Disorders version IV
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 Classification of Diseases version 9
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

(*Continued*)

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: 6 December 2012.

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

CONTRIBUTIONS OF AUTHORS

Tom Declercq: correspondence, drafting protocol and review versions, developing the search, obtaining copies of trial reports, selection of trials for inclusion or exclusion, extraction of data, entry of data into RevMan and interpretation of data analyses.

Mirko Petrovic: developing the search, selection of trials, extraction of data and interpretation of data analyses.

Majda Azermai: extraction of data, entry of data into RevMan and interpretation of data analyses.

Robert Vander Stichele: searching for trials and interpretation of data analyses.

An De Sutter: drafting protocol and review versions, entry of data into RevMan and interpretation data analyses.

Mieke van Driel: developing the search and interpretation of data analyses and text editing, risk of bias table.

Thierry Christiaens: arbiter in the selection of trials and interpretation of data analyses.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No internal financial support received for this review, Not specified.

External sources

- No external funding support received for this review, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Of the eight included studies, only one study (Ruths The BEDNURS Study) established the dementia diagnosis according to DSM IV or ICD 10. Findlay 1989 used the ICD9 criteria. Devanand 2011 and Devanand ADAD 2012 used the clinical diagnoses of dementia by DSM-IV criteria and probable AD by NINCDS/ADRDA criteria. All other studies included older people with dementia diagnosed in another way: Ballard The DART-AD Trial and Ballard 2004 used new NINCDS/ADRDA criteria for possible or probable AD, van Reekum 2002 and Bridges-Parlet 1997 included people with dementia without any specification (diagnostic criteria unclear), Cohen-Mansfield stated in her email that "she was quite sure all participants had dementia". Nevertheless we (TD, MP and MA) decided to preserve the inclusion of all these studies since they all studied people with dementia.

Devanand 2011 and Devanand ADAD 2012 included people aged 50 to 95 years.

The Ballard The DART-AD Trial and Devanand ADAD 2012 did not report schizophrenia in the exclusion criteria, so it may be possible that some people with dementia and schizophrenia are included in these trials.

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