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Novel Antipsychotics for Agitation in Dementia: A Systematic Review

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Novel Antipsychotics for Agitation in Dementia: A Systematic Review

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March 2003

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Authorship

Keng Ho Pwee was the overall project lead, and as such was involved in all aspects of the project. He led the development of the research protocol, supervised the literature review process, reviewed the articles, selected the relevant studies for the review, assessed their quality, extracted data from the relevant studies, processed and summarized the results in the clinical draft document through to its final version and responded to the comments of the reviewers.

Vijay K. Shukla contributed to developing the idea and protocol preparation. He was also involved in the selection, quality assessment, and data extraction of studies used in the report. He also assisted the lead author with writing draft reprots, responding to the reviewers' comments and preparing the final report.

Nathan Herrmann developed the questions and the focus of the review. He also helped with the search strategy, interpreting the results and drafted and edited the final report.

Becky Skidmore was responsible for the design and execution of the literature search strategies, for writing the methods section and associated appendix on literature searching, and for verifying and formatting bibligraphic references.

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Conflicts of Interest

No conflicts were disclosed by Keng Ho Pwee, Vijay K. Shukla and Becky Skidmore.

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REPORT *IN BRIEF*

March 2003

Novel Antipsychotics for Agitation in Dementia

Technology Name

The novel antipsychotic drugs olanzapine (Zyprexa®) and risperidone (Risperdal®)

Disease/Condition

Dementia involves progressive loss of intellectual abilities such as language, comprehension, memory and learning, as well as changes in behaviour. This report focuses on agitation (restless movement with feelings of tension and irritability) occurring in those diagnosed with dementia.

Technology Description

Novel antipsychotics are a new generation of drugs developed to overcome the significant side effects associated with conventional antipsychotic drugs. Antipsychotic drugs may be used to treat dementia-associated agitation, typically after or in combination with environmental or behavioral changes. The novel antipsychotics clozapine, olanzapine, risperidone and quetiapine are available in Canada. Of these, only risperidone is approved for the treatment of behavioural disturbances in patients with dementia.

The Issue

DAA causes stress for caregivers and affects quality of life for patients. Conventional antipsychotic drugs have a number of significant side effects, such as extrapyramidal symptoms. Although the efficacy and safety of novel antipsychotic drugs may not be clear for all conditions, the number of prescriptions and indications for the use of novel antipsychotics continue to increase.

Assessment Objectives

This assessment critically examines the evidence on the efficacy and safety of novel antipsychotics as compared to placebo and as compared to conventional antipsychotics, for the management of patients with DAA.

Methodology

Published and grey literature were systematically searched. All relevant trials enrolling patients with DAA were included. A total of seven randomized controlled trials reporting on olanzapine and risperidone met the inclusion criteria for the review.

Conclusions

- The efficacy of intramuscular olanzapine for the rapid treatment of DAA was found to be comparable to that of lorazepam (a benzodiazepine), and better than that of placebo, for institutionalized elderly patients. Adverse events at 24 hours were the same for all three patient groups.
- Over the longer term (6 to 12 weeks), the evidence regarding the efficacy, measured using behavioural scales in elderly patients, of olanzapine and risperidone compared to placebo was variable: some trials showed benefit and some did not. Both drugs increased some types of side effects.
- In two 12-week trials in elderly patients with DAA, risperidone was compared to the conventional antipsychotic agent haloperidol. Efficacy was similar with both drugs. However, haloperidol increased the incidence of extrapyramidal symptoms significantly.
- DAA is a long-term condition often requiring treatment for years, yet trials have been relatively short (6 to 12 weeks).
- Health Canada has recently advised that elderly dementia patients on risperidone may have an increased risk of cerebrovascular adverse events.
- Novel antipsychotics are expensive drugs, relative to more established alternatives. Cost-effectiveness analyses may clarify relative costs and benefits.

This summary is based on a comprehensive health technology assessment report available from CCOHTA's web site (www.ccohta.ca): Pwee KH, Shukla VK, Herrmann N, Skidmore B. **Novel antipsychotics for agitation in dementia: a systematic review.**

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EXECUTIVE SUMMARY

The Issue

Dementia is characterized by cognitive impairment, but behavioral and psychological symptoms are also major causes of morbidity. These have significant implications for patients, their caregivers and the health care system. For dementia-associated agitation (DAA), when non-pharmacological management is insufficient, antipsychotics may provide first-line drug treatment. Novel antipsychotics were developed as alternatives to conventional antipsychotics to improve efficacy and decrease adverse effects for patients with schizophrenia and other psychotic disorders. In Canada, clozapine, olanzapine, risperidone and quetiapine are the currently available novel antipsychotics. At the time of the writing of this report, only risperidone was approved in Canada for the treatment of behavioral disturbances in patients with dementia.

Objectives

The purpose of this systematic review was to assess the efficacy and safety of the novel antipsychotic drugs for DAA. The novel antipsychotics for potential assessment included amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine.

Methods

A systematic review was performed of randomized clinical trials (RCTs) in which a novel antipsychotic drug was compared prospectively with placebo, with a traditional antipsychotic or with another novel antipsychotic, for treatment of patients with DAA. As part of this review, trials were assessed as to their quality using the Jadad Scale.

Results

Of the 36 potentially relevant studies identified, seven met our selection criteria. Two of these were only available as abstracts and were deemed to be of low quality; the remaining five studies were considered to be of moderate to high quality. Although there were eight novel antipsychotic drugs available for assessment, relevant articles were obtained for only two of them.

Olanzapine: Both intramuscular (IM) olanzapine (2.5 mg and 5.0 mg) and lorazepam (1.0 mg) were effective in acute (within two hours) reduction of agitation (defined as a 40% improvement in PANSS-EC score) in nursing home residents. The number-needed-to-treat (NNT) with a 95% confidence interval (95% CI) was 4 (95% CI 3; 13) for IM olanzapine 2.5 mg and 3 (95% CI 2; 8) for IM olanzapine 5.0 mg, and 3 (95% CI 2; 6) for IM lorazepam 1.0 mg. There was no significant difference between olanzapine and placebo in the incidence of adverse events within 24 hours of injection.

With regard to ongoing treatment of DAA, there was evidence from one RCT that oral olanzapine at 5 mg/day and 10 mg/day reduced agitation in nursing home recipients with dementia over six weeks of therapy. The NNTs for oral olanzapine 5 mg/day and 10 mg/day

were 3 (95% CI 2; 10) and 5 (95% CI 3; 69), respectively. Efficacy was not demonstrated for olanzapine at 15 mg/day. Somnolence and abnormal gait were significant adverse events related to olanzapine.

Risperidone: There were two RCTs involving risperidone. The RIS-US-63 study showed that, over 12 weeks of therapy, oral risperidone (1 mg/day and 2 mg/day) produced a clinical response (defined post hoc as a 50% or greater reduction in BEHAVE-AD total scores) in institutionalized elderly patients with dementia. The NNTs for oral risperidone 1 mg/day and 2 mg/day were 8 (95% CI 4; 68) and 6 (95% CI 4; 16), respectively. Efficacy was not demonstrated for risperidone 0.5 mg/day. In contrast, the RIS-INT-24 study showed no significant difference between risperidone (flexible doses from 0.5 to 4 mg/day) and placebo, using an a priori definition of clinical response as a 30% or greater reduction in the BEHAVE-AD total scores. However, significant improvements were shown in secondary outcomes such as the BEHAVE-AD aggression cluster, the CMAI aggressive score and the CGI. Pooling of the two studies found that the weighted mean difference for the change from baseline to endpoint of the BEHAVE-AD total score for risperidone compared to placebo was –1.80 (95% CI –3.22; –0.38).

Three of 30 deaths that occurred during the RIS-US-63 study were considered to possibly be drug-related. Patients on risperidone 2 mg/day had significantly more extrapyramidal symptoms (EPS) compared to the placebo group. Dose-related increases in occurrences of somnolence (drowsiness), EPS and mild peripheral edema were seen. An advisory by the Health Canada has recently been issued on the increased risk of cerebrovascular adverse events in elderly dementia patients on risperidone.

In the RCTs comparing risperidone and haloperidol, there was no significant difference in efficacy between the two drugs; however, patients on haloperidol had more frequent and severe EPS. In the RIS-INT-24 study, there was a suggestion of cognitive deterioration with haloperidol, not seen with risperidone.

Conclusions

- The efficacy of intramuscular olanzapine for the rapid treatment of DAA was found to be comparable to that of the benzodiazepine lorazepam, and better than that of placebo, for institutionalized elderly patients. Adverse events at 24 hours were the same for all three patient groups.
- Over the longer term (6 to 12 weeks), the evidence regarding the efficacy, measured using behavioural scales in elderly patients, of olanzapine and risperidone compared to placebo was variable: newer larger trials showed benefit whereas older trials did not. Both drugs increased some types of side effects.
- In two 12-week trials in elderly patients with DAA, risperidone was compared to the conventional antipsychotic agent haloperidol. Efficacy was similar with both drugs. However, haloperidol increased the incidence of extrapyramidal symptoms significantly.
- DAA is a long-term condition often requiring treatment for years, yet trials have been relatively short (6 to 12 weeks).

- Novel antipsychotics are expensive drugs, relative to more established alternatives. Cost may therefore become a factor in their uptake. Cost-effectiveness analyses may clarify relative costs and benefits.
- A large RCT comparing risperidone, olanzapine, quetiapine, citalopram (a selective serotonin reuptake inhibitor) and placebo over 36 weeks commenced in 2001: comparative evidence for these therapies should be available when the trial is completed in 2006.

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ABBREVIATIONS

ACES	Agitation-Calmness Evaluation Scale
AD	Alzheimer's disease
AIMS	Abnormal Involuntary Movement Scale
BAS	Barnes Akathisia Scale
BEHAVE-AD	Behaviour Pathology in Alzheimer's Disease Rating Scale
BPSD	behavioral and psychological symptoms of dementia
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression scale
CMAI	Cohen-Mansfield Agitation Inventory
CMMSE	Cantonese version of Mini-Mental State Examination
CVAE	cerebrovascular adverse events
DAA	Dementia-associated agitation
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision, American Psychiatric Association
ECG	electrocardiogram
EPS	extrapyramidal symptoms
ESRS	Extrapyramidal Symptom Rating Scale
FAST	Functional Assessment Staging
HTA	health technology assessment
IM	intramuscular
MMSE	Mini-Mental State Examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association
NNT	number needed to treat
NPI/NH	Neuropsychiatric Inventory-Nursing Home version
PANSS-EC	excited component of the Positive and Negative Syndrome Scale
RCT	randomized controlled trial
RR	relative risk
SAS	Simpson-Angus Scale
US	United States
WMD	weighted mean difference

1 INTRODUCTION

1.1 Clinical Background

Dementia is a mental syndrome in which there is a progressive general loss of intellectual abilities. It is characterized by memory impairment and other cognitive deficits, which may be aphasia, apraxia, agnosia[a] or disturbance in executive functioning.[1]

While the cognitive features of dementia are definitive, another important group of symptoms that places considerable strain on health care resources is the behavioral and psychological symptoms of dementia (BPSD). BPSD result in suffering, premature institutionalization, increased costs of care and significant loss in quality of life for a patient and his/her family and other caregivers.[2] BPSD were defined as *'symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia'* in an international consensus conference organised by the International Psychogeriatrics Association in 1996. The consensus conference divided BPSD into two groups: symptoms usually and mainly assessed on the basis of interviews of patients and relatives and symptoms usually identified on the basis of observation of patient behaviour. These symptoms are listed in Table 1 below.

Table 1: Behavioral and psychological symptoms of dementia divided according to symptom assessment

Symptoms assessed at patient/relative interview	**Symptoms assessed by behavioral observation or by patient/relative**
Anxiety Depressed mood Hallucinations Delusions	Aggression Screaming Restlessness Agitation Wandering Culturally-inappropriate behaviours Sexual disinhibition Hoarding Cursing Shadowing

Source: International Psychogeriatric Association web site[3]

[a] Aphasia: deterioration of language function.(DSM-IV-TR, 2000); Apraxia: impaired ability to execute motor activities despite intact motor abilities, sensory function and comprehension of the required task. (DSM-IV-TR, 2000); Agnosia: failure to recognise or identify objects despite intact sensory function (DSM-IV-TR, 2000); Executive functioning: involves the ability to think abstractly and to plan, initiate, sequence, monitor and stop complex behaviour.(DSM-IV-TR, 2000)

Of the BPSD, agitation frequently results in distress to patients and caregivers and requires intervention. The term agitation describes excessive motor activity with feelings of inner tension and is characterized by a cluster of related symptoms including anxiety and irritability, motor restlessness and abnormal vocalization. These symptoms are often associated with behaviours such as pacing, wandering, aggression, shouting and night-time disturbance.[4] Another definition of agitation specifies that it is not explained by apparent needs or confusion of the patient.[5]

Agitation in dementia may be a direct result of dementia or may arise from a variety of causes including delirium, pain or other distress/discomfort due to medical problems, medication (medication-induced, drug interaction, medication withdrawal), environmental or psychosocial stressors and neuropsychiatric syndromes (psychosis, depression, anxiety, insomnia, "sun-downing").[6] In this review, we will not be considering cases where agitation arises from a reversible cause or delirium, as management would be focused on the underlying causes in these cases.

Dementia is a disorder with diverse causes. Several kinds of dementia are recognized. The most common are dementia from Alzheimer's disease (AD) and vascular dementia. Less common causes include Parkinson's disease and other medical conditions, head trauma and substances like alcohol, toxins or drugs.[1]

1.2 Epidemiology

In a 1991 survey, the Canadian Study of Health and Aging, the prevalence of dementia in Canadians aged 65 and over was estimated at 8.0%.[7] Assuming the prevalence has remained constant, this would mean there were over 300,000 Canadians aged 65 and over with dementia in 2001 and numbers can be expected to grow as Canada's population ages. The 1991 survey estimated the overall prevalence of AD to be 5.1% and the overall prevalence of vascular dementia to be 1.5%.[7]

In relation to BPSD, different studies estimate that from 23 to 79% of patients with dementia in nursing homes manifest behaviors that are problematic for caregivers, families and themselves.[8] According to one study, 90% of patients with dementia of Alzheimer's type showed behavioral problems during the course of their illness.[9]

1.3 Management

As dementia-associated agitation (DAA) may have different aetiologies, an essential step in management is to fully assess a patient for possible causes and to address reversible factors. Various guidelines on the management of DAA generally recognize the importance of non-pharmacological treatments, either recommending they be tried first or be tried in combination with medication, if the agitation is more than mild. Non-pharmacological treatment may involve environmental and/or behavioral modifications. Pharmacological treatment is recommended for use only when other strategies fail or for first line use alone only in some cases of severe agitation.[6,10]

A number of drugs are used for the pharmacological treatment of agitation. Drugs prescribed for the treatment of behaviour disturbance in the elderly with dementia include antipsychotics/ neuroleptics, anxiolytics, serotoninergic antidepressants, and antihistamines. Antipsychotics and benzodiazepines are the most frequently used agents.

A variety of side effects, particularly extrapyramidal symptoms (EPS) like pseudoparkinson syndrome, dystonic reactions, akathisa and tardive dyskinesia, limit the use of conventional antipsychotics or neuroleptics. Side effects like sedation and postural hypotension lead to an increased risk of falls, which is of special concern as the majority of patients are elderly.

Novel antipsychotic agents have been developed to address the lack of efficacy in some patients and also the lack of effect on negative symptoms that conventional antipsychotics have in schizophrenia and other psychotic disorders. Also known as 'atypical', 'nonconventional' or 'second generation' antipsychotics, they have also been developed to have fewer adverse effects, especially EPS. These differences are mediated through dopaminergic and serotoninergic antagonism.[11]

Novel antipsychotics have a relatively high ratio of affinity at serotonin-2A receptors compared with dopamine D_2 receptors; they also have variable affinities for central muscarinic, dopamine D_1 and adrenergic receptors.[12] In contrast to this 'multireceptor' theory, it has also been suggested that a low affinity at the dopamine D_2 receptors, by itself, is sufficient to produce novel antipsychotic activity.[13]

With regard to safety, the EPS, movement disorders and adverse effects seen with typical antipsychotics can also be induced by novel antipsychotics.[14] Other documented adverse effects include metabolic effects, such as antipsychotic-induced weight gain,[15,16] associated risk of diabetes[16,17] and elevated serum triglyceride levels.[16] Cardiac arrhythmias and QT prolongation have also been reported.[18] Specific to clozapine is the serious adverse effect of agranulocytosis, necessitating regular blood monitoring when the drug is used.[19]

Table 2 lists a number of novel antipsychotics agents.

Table 2: Novel Antipsychotics (trade name in brackets)

Amisulpride (Solian®)	Risperidone (Risperdal®)
Clozapine (Clozaril®)	Sertindole (Serdolect®)
Olanzapine (Zyprexa®)	Ziprasidone (Zeldox®)
Quetiapine (Seroquel®)	Zotepine (Zoleptil®)

Source: Centre for Evidence Based Mental Health web site[20]

Novel antipsychotics have been recommended by some experts for use for both long-term and acute management of DAA in older patients.[6] In Canada, clozapine, olanzapine, risperidone and quetiapine are currently available. At the time of the writing of this report, only risperidone is approved in Canada for the treatment of behavioral disturbances in patients with dementia.[21]

1.4 Drug Utilization Trends

IMS Health continually surveys physicians and pharmacists to collect information on current patterns of drug prescribing and utilization. The Canadian office of IMS Health provided CCOHTA with the most recent data available (1996 to 2001) on the utilization of olanzapine, risperidone and quetiapine in Canada (Dorothy Rhodes, IMS Health, Point-Claire, QC: personal communication, 2002 Jan 23). The data show a marked increase in the utilization of olanzapine, risperidone and quetiapine during this period (Figure 1 and Figure 2).

Figure 1: Estimated number of prescriptions dispensed for olanzapine (OLN), risperidone (RIS) and quetiapine (QUT) in Canadian drug stores from 1996 to 2001

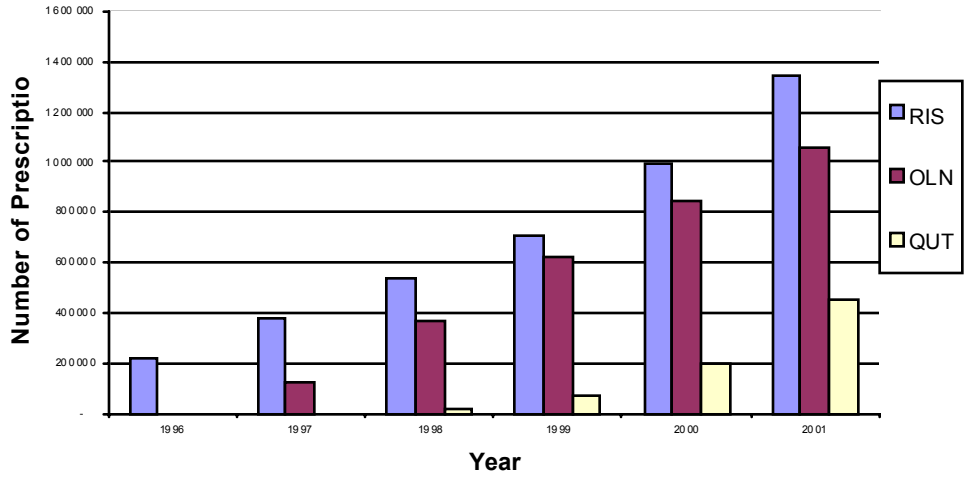
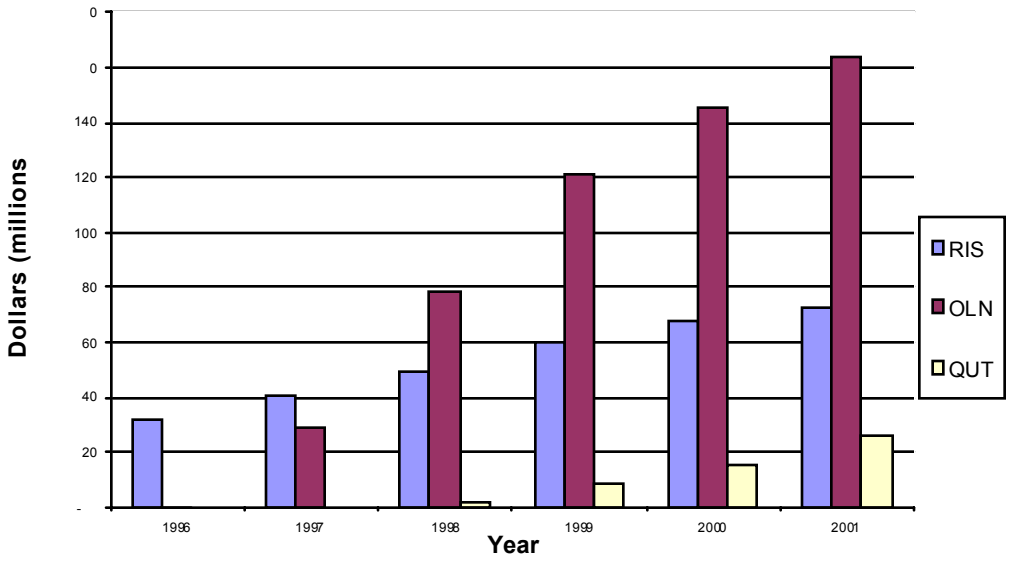


Figure 2: Canadian drug store and hospital purchases of olanzapine (OLN), risperidone (RIS) and quetiapine (QUT) from 1996 to Nov 2001



2 OBJECTIVES

The objectives of this report were to critically examine, using best evidence synthesis methodology, for patients diagnosed with DAA:

1. the evidence comparing the *efficacy* of novel antipsychotics to placebo, typical antipsychotics and other novel antipsychotics and;

2. the evidence comparing the *safety* of novel antipsychotics to placebo, typical antipsychotics and other novel antipsychotics.

3 CLINICAL EFFECTIVENESS REVIEW

3.1 Methods

3.1.1 Literature search

Published literature was identified by searching a number of databases (Appendix 1). MEDLINE®, EMBASE®, PsycINFO®, AgeLine, BIOSIS Previews®, Pascal and ToxFile were searched on the DIALOG® system, with regular alerts/updates run throughout the duration of the project on MEDLINE®, EMBASE®, and PsycINFO®. Retrieval was limited to the publication years 1985 onwards (and, where possible, the human population) with no language restrictions. The CD ROM version of The Cochrane Library was also searched and updated as new issues arrived.

Grey literature was obtained by searching the web sites of health technology assessment (HTA) and related agencies and their associated databases. Google™ and other Internet search engines were used to search for a variety of additional web-based materials and information. These searches were supplemented by hand searching the bibliographies and abstracts of selected papers and conference proceedings and through contacts with appropriate experts and agencies. In addition, manufacturers of the different novel antipsychotics were contacted for information regarding unpublished studies.

3.1.2 Selection criteria

a) Types of studies

All published and unpublished RCTs, whether of parallel or cross-over design, were to be included. Prospective cohort studies were to be included for evidence of long-term safety, if there were no RCTs investigating the issue. Studies published as abstracts were also included. There were no restrictions with respect to language of publication.

b) Types of participants

Studies of patients with DAA were included, regardless of patient age or sex.

Diagnostic criteria for dementia

Dementia is diagnosed clinically. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) lists the diagnostic criteria for dementia, subdivided by aetiology.[1] Table 3 lists the essential features (all of which must be met) for a diagnosis of dementia to be made. In the absence of these criteria, other acceptable evidence (e.g. Mini Mental State examination, psychiatric evaluation, medical evaluation, psychological evaluation) of dementia was used.

Table 3: Diagnostic criteria for dementia (all criteria to be met)

- Multiple cognitive deficits: memory impairment plus one or more of aphasia, apraxia, agnosia, disturbance in executive functioning
- Deficits impair occupational or social functioning and represent a decline from a previously higher level of functioning
- Deficits do not occur exclusively during the course of a delirium

Source: DSM-IV-TR[1]

Diagnostic criteria for agitation

The DSM-IV-TR does not provide diagnostic criteria for agitation in dementia. A commonly accepted description of agitation stated in recent British guidelines for the management of agitation in dementia is "…excessive motor activity with a feeling of inner tension, characterized by a cluster of related symptoms including anxiety and irritability, motor restlessness and abnormal vocalization. These symptoms are often associated with behaviours such as pacing, wandering, aggression, shouting, and night-time disturbances."[4] In reviewing the literature, where this definition of agitation in dementia was not used, other evidence such as descriptions of the manifestations of agitation were accepted.

A multitude of psychometric scales are available for assessing cognitive impairment, BPSD and EPS. Appendix 2 provides short descriptions of the relevant scales used in the studies included in this review.

c) Types of intervention

Trials were included if they compared any of the novel antipsychotic drugs with placebo, with classical antipsychotics or with other novel antipsychotics for the management of DAA. Trials that studied the use of novel antipsychotics for either long-term or acute management were examined.

d) Exclusion criteria

Studies were excluded in which a reversible cause of agitation, e.g. infection, drug reaction, dehydration, had not been ruled out for patients entering the trial, as were studies where delirium had not been ruled out as the cause of agitation. If this information was not available in the study, a sensitivity analysis was planned using information from such studies, if a meta-analysis of outcomes was performed.

3.1.3 Methods of the review

a) Selection of potentially relevant studies

Two reviewers independently reviewed citations and abstracts and discarded the irrelevant articles. Case reports, review articles and studies unrelated to the use of novel antipsychotics for DAA were discarded at this stage.

b) Selection of relevant articles

Potentially relevant articles were acquired from library sources. Two reviewers independently made the final selection of those to be included in the review. Disagreement regarding inclusion of any article was resolved by discussion. A third reviewer adjudicated any persisting differences.

c) Assessment of quality

The quality of reporting in the included articles was assessed using the Jadad scale, which includes appropriateness of randomization and double blinding, and a description of withdrawals and dropouts. The adequacy of allocation concealment was also assessed (Appendix 3). Two reviewers assessed quality independently. Disagreement was resolved by discussion. A third reviewer adjudicated any persisting differences.

d) Data extraction

Two reviewers independently extracted data concerning the participant characteristics, intervention details and outcome measures (See Appendix 4 for the data extraction form). Disagreement was resolved by discussion. A third reviewer adjudicated any persisting differences.

e) Statistical analysis

Pooling of results was possible in one instance. Prior to pooling, studies were reviewed for clinical heterogeneity and a chi-square Q test was performed to assess statistical heterogeneity. Analysis was carried out using Cochrane's Review Manager.[22] Intention-to-treat data were used when available. Where this was not possible, end-point data for persons completing the trials were used. Where pooling was not possible, a comprehensive qualitative synthesis was undertaken, including textual description (and tabular presentation) of study-specific characteristics, including details of study population, intervention(s) and control(s)/ comparators(s), and quality assessment.

In some instances, statistics for which standard error or standard deviation were published were converted to 95% confidence intervals for easier interpretation. Number-needed-to-treat (NNT) figures were derived where appropriate using Confidence Interval Analysis software.[23] The NNT figures were rounded off to the nearest whole number.

3.2 Results

Titles and abstracts of all citations obtained from the various data sources (bibliographic databases, Internet searches, industry, handsearches, etc.) were reviewed by both reviewers; 36 potentially relevant articles were identified (including two abstracts). Of these, seven articles were selected for potential inclusion in the systematic review by both reviewers. Figure 3 shows the steps in the selection of relevant studies. A list of excluded studies is shown in Appendix 5. There was no disagreement between the two reviewers.

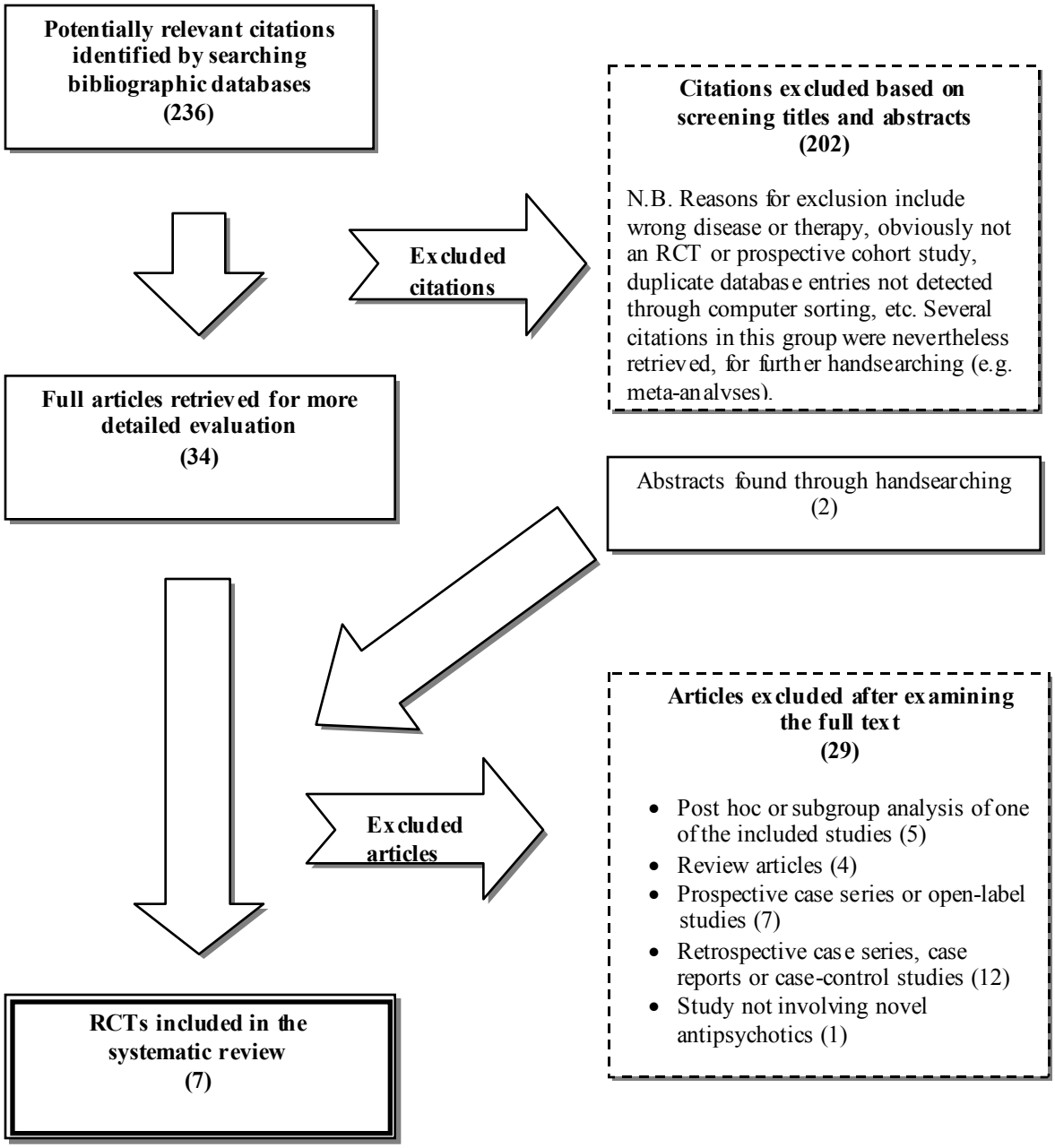
Of the seven shortlisted articles, the trials conducted by Satterlee et al.[24] and Kirwan et al.[25] were only described briefly in abstracts. More information on the study by Satterlee et al. was available in two other references.[26,27] Nevertheless, the data abstracted for these two trials were limited.

The seven shortlisted articles were all RCTs reporting on olanzapine and risperidone. No RCTs of amisulpride, clozapine, quetiapine, sertindole, ziprasidone or zotepine for DAA were identified. According to quality assessment using the Jadad scale, the studies were determined to be of moderate (quality score of 3 or 4) to high (quality score of 5) quality, except for the two abstracts, which were deemed to be of low quality (quality score of 0 to 2). The degree of agreement between the two evaluators in performance of quality assessment was 100 percent.

No prospective cohort trials meeting our inclusion criteria were identified. One prospective longitudinal study[28] was identified, comparing the nine-month cumulative incidence of tardive dyskinesia with risperidone to that with haloperidol in older patients. However, the study subjects were patients with any psychiatric diagnosis for which neuroleptic therapy was indicated, and not restricted to patients with DAA.

Table 4 provides details of the included trials. Four trials involved risperidone and three trials involved olanzapine. All the trials were funded by industry.

Figure 3: Steps in the selection of relevant RCTs



N.B. This diagram does not reflect potential references identified through handsearching or subsequent bibliographic database search updates, which were subsequently excluded.

Table 4: Characteristics of included trials of novel antipsychotics for DAA

Study *(sponsor)*	Type of Trial	Quality Assessment Score *(Jadad scale Range 0-5)*	Participants	Study Arms	Concomitant Medication Permitted	Outcomes
2001 Chan et al. Janssen Research Foundation	RCT, double-blind, parallel group	3 points (moderate quality). Allocation concealment: unclear	58 inpatients/outpatients; aged 55 or older; with dementia (AD, vascular or mixed) with behavioral disturbance (DSM-IV); score of at least 4 on one and at least 3 on another item of the CMAI; total score of at least 8 on the BEHAVE-AD.	Flexible-dose 0.5-2.0 mg/day risperidone; flexible-dose 0.5-2.0 mg/day haloperidol. Duration 12 weeks.	No particular restrictions reported. Concomitant medications included lorazepam, chlordiazepoxide, clonazepam, diazepam, chloral hydrate, benzhexol, donepezil and rivastigmine.	CMAI, BEHAVE-AD, CMSSE, AIMS, SAS, BAS, psychometric measurements, reported adverse events.
1999 De Deyn et al. (RIS-INT-24) Janssen Research Foundation	RCT, double-blind, parallel group	5 points (high quality). Allocation concealment: adequate	344 institutionalized patients; 55 years or older; with AD, vascular dementia or mixed dementia (DSM-IV); scores of ≥ 4 on FAST and ≤ 23 on MMSE; total score ≥ 8 and global rating ≥ 1 on BEHAVE-AD.	Flexible-dose 0.5-4.0 mg/day risperidone; flexible-dose 0.5-4.0 mg/day haloperidol; placebo. Duration 12 weeks.	Lorazepam, limited to 4 days per week for the first 4 weeks of double-blind treatment.	Primary outcome: BEHAVE-AD Other outcomes: CMAI; CGI; MMSE; FAST; ESRS; sedation; adverse events; vital signs; ECG

Table 4 cont'd

1999 Katz et al. (RIS-USA-63) Janssen Research Foundation	RCT, double-blind, parallel group	4 points (moderate quality). Allocation concealment: adequate	625 nursing home or chronic disease hospitalized patients; aged 55 or older; with AD, vascular dementia or a combination of both (DSM-IV); scores of ≥ 4 on FAST and ≤ 23 on MMSE; total score ≥ 8 and global rating ≥ 1 on BEHAVE-AD.	0.5 mg/day risperidone; 1.0 mg/day risperidone; 2.0 mg/day risperidone; placebo. Duration 12 weeks.	Benztropine for EPS. Lorazepam (up to 3 mg/day for up to 4 days in any 7-day period) until the end of week 4. Chloral hydrate for insomnia.	Primary outcome: BEHAVE-AD Other outcomes: CMAI; CGI; MMSE; FAST; Physical Self-Maintenance Scale; vital signs; adverse events; ECG; clinical laboratory tests; ESRS
2002 Kirwan et al. (abstract) Janssen Research Foundation	RCT, double-blind, parallel group	1 point (low quality). Allocation concealment: unclear	337 nursing home patients diagnosed with dementia (AD, vascular or mixed).	Flexible-dose 0.5-2.0 mg/day oral risperidone solution; placebo. Duration 12 weeks.	Not mentioned.	CMAI physical and verbal agression subscales, CGI
2002 Meehan et al. Eli Lilly	RCT, double-blind, parallel group	3 points (moderate quality). Allocation concealment: unclear	272 hospitalized or nursing home residents; aged 55 or older; with possible or probable AD, vascular dementia, or a combination of both (NINCDS-ADRDA or DSM-IV); scored ≥ 14 on the PANSS-EC; at least one individual PANSS item score ≥ 4; and with clinically significant agitation for which treatment with a parenteral agent was indicated.	IM olanzapine 2.5 mg; IM olanzapine 5.0 mg; IM lorazepam 1.0 mg; IM placebo. Observed 2 hr and 24 hr post first injection.	Not mentioned.	Primary outcome: change in PANSS-EC at 2 hr. Other outcomes: change in CMAI and ACES at 2 hr, change at 24 hr in PANSS-EC, BPRS total & positive symptomatology cluster, CMAI, ACES, MMSE and CGI-S.

Table 4 cont'd

1995 Satterlee et al. (abstract) Eli Lilly	RCT, double-blind, parallel group	2 points (low quality). Allocation concealment: unclear	238 outpatients aged 65 or older with psychotic and behavioral manifestations associated with AD.	Olanzapine 1 to 8 mg/day; placebo. Duration 8 weeks.	Not mentioned.	Primary outcome: safety (vital signs, treatment-emergent adverse events, EPS adverse events, SAS, BAS, AIMS, laboratory measures (incl. prolactin), ECG). Secondary outcome: efficacy (BEHAVE-AD)
2000 Street et al. Eli Lilly	RCT, double-blind, parallel group	5 points (high quality). Allocation concealment: unclear	206 elderly nursing home patients; possible or probable AD (NINCDS-ADRDA); score of ≥ 3 on any of the Agitation/ Agression, Hallucinations, or Delusions items of the NPI/NH.	Olanzapine 5 mg/day; olanzapine 10 mg/day; olanzapine 15 mg/day; placebo. Duration 6 weeks.	Benzodiazepines allowed as rescue medication but could not exceed 4 mg/day of lorazepam equivalents for a total of 21 days during active treatment.	Primary outcome: change in sum of NPI/NH item scores for the core symptoms: Agitation/Agression, Hallucinations and Delusions Seconday outcome: change in NPI/NH total, Hallucinations and Delusions total (Psychosis total), individual items, Occupational Disruptiveness score derived from the Agitation/Agression, Hallucinations, and Delusions items, BPRS total and subscale, MMSE, SAS, BAS, AIMS, vital signs, ECG, clinical laboratory testing.

ACES = Agitation-Calmness Evaluation Scale; AIMS = Abnormal Involuntary Movement Scale; BAS = Barnes Akathisia Scale; BEHAVE-AD = Behaviour Pathology in Alzheimer's Disease Rating Scale; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; CMAI = Cohen-Mansfield Agitation Inventory; CMMSE = Cantonese version of Mini-Mental State Examination; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision, American Psychiatric Association; ECG = electrocardiogram; EPS = extrapyramidal symptoms; ESRS = Extrapyramidal Symptom Rating Scale; FAST = Functional Assessment Staging; MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; NPI/NH = Neuropsychiatric Inventory-Nursing Home version; PANSS-EC = Excited Component of the Positive and Negative Syndrome Scale;
RCT = randomised controlled trial; SAS = Simpson-Angus Scale

3.2.1 Novel antipsychotic drugs for rapid management of DAA

One RCT enrolling 272 hospitalized patients and nursing home residents examined the use of olanzapine for rapid management of DAA, comparing it with lorazepam (a benzodiazepine) and placebo.[29]

The trial by Meehan et al.[29]
The study by Meehan et al.[29] assessed the efficacy and safety of IM olanzapine (2.5 mg and 5.0 mg) compared with IM placebo and IM lorazepam 1.0 mg, in improving the severity of agitation two hours after the first injection. Further assessment of patients was carried out at 4, 6 and 24 hours. Patients were given second and third injections (at the same dosage and then half dosage in the respective active-treatment groups) if it was deemed necessary. Patients in the placebo arm were given IM olanzapine for their third injection, but their endpoint scores for analysis were those observed prior to the third injection.

Efficacy two hours post first injection: The primary measure of efficacy in this study was the mean change in PANSS-EC score from baseline two hours after the first injection. The mean changes were –7.86 (95% CI –9.3; –6.4) in the olanzapine 2.5 mg group, –8.67 (95% CI –10.4; –7.0) in the olanzapine 5.0 mg group, –8.49 (95% CI –10.1; –6.9) in the lorazepam 1.0 mg group and –5.27 (95% CI –6.9; –3.6) in the placebo group. Analysis of variance in these scores demonstrated that olanzapine 5.0 mg ($p < 0.01$), olanzapine 2.5 mg ($p < 0.05$) and lorazepam 1 mg ($p < 0.01$) significantly improved PANSS-EC scores compared to placebo. Differences among the three active-treatment groups were not significant at any time point within the first two hours. A similar pattern was observed in the secondary measures of agitation (changes in mean scores on CMAI and ACES) at two hours. However, the olanzapine 2.5 mg group did not show a significant difference from the placebo group on the CMAI score. It should be noted that the analysis of variance was carried out without correction for multiple comparisons and the figures were interpreted accordingly.

A clinical response, defined a priori as ≥ 40% improvement from baseline in PANSS-EC score, was seen in 44 of the 66 patients in the olanzapine 5.0 mg group (66.7%; Fisher's exact test, $p<0.001$ relative to placebo); 44 of the 71 patients in the olanzapine 2.5 mg group (62.0%; Fisher's exact test, $p=0.006$ relative to placebo); 49 of the 68 patients in the lorazepam 1.0 mg group (72.1%; Fisher's exact test, $p<0.001$ relative to placebo); and 25 of the 67 patients in the placebo group (37.3%). All three active-treatment groups had significantly higher responses relative to placebo. Differences among the active-treatment groups were not significant.

Based on the above figures, the NNT for clinical response (number of patients that need to be treated to see a clinical response in one patient) was 4 (95% CI 3; 13) for the olanzapine 2.5 mg/day group, 3 (95% CI 2; 8) for the olanzapine 5.0 mg/day group, and 3 (95% CI 2; 6) for the lorazepam 1.0 mg group.

Efficacy 24 hours post first injection: A dosing regimen of optional second and third injections, together with analysis of outcomes on a last-observation-carried-forward basis, implies that results after the first two hours need to be interpreted with caution. It is possible that assessments happen to be made soon after a subsequent injection, resulting in a 'boost' to the observed scores. Although the numbers of patients requiring a third injection are supplied, there is no information on when the injections were given. Having the placebo group patients 'cross over' with their third injection further reduces the comparability of the study arms.

At 24 hours after the first injection, changes from baseline had lessened in all four study arms relative to the two hour time point on all three measures of agitation (PANSS-EC, CMAI, ACES). The changes from baseline in the CMAI for all active-treatment groups did not significantly differ from placebo. The changes from baseline in the ACES were still significantly different in the olanzapine 5.0 mg and lorazepam 1.0 mg groups compared with placebo, but not in the olanzapine 2.5 mg group. The changes from baseline in the PANSS-EC were still significantly different in both olanzapine groups compared with placebo, but not in the lorazepam group.

Measures of harm/safety: No patient withdrew from the study due to an adverse event. (There were, however, withdrawals due to lack of efficacy and these were approximately equal among the treatment groups.) Changes from baseline to endpoint in the extrapyramidal scores on the SAS in the active-treatment groups did not differ significantly from the scores in the placebo group. Treatment-emergent adverse events that occurred were: accidental injury, abnormal ECG, headache, hypertension, somnolence, vasodilatation and sinus bradycardia. However the incidence of these was not significantly different from that in the placebo group in any active-treatment group. There was no statistically significant overall difference among the treatment groups in the incidence of QT interval prolongation. MMSE scores, indicative of cognitive state, were not substantially changed from baseline in any treatment group, and no significant changes were seen in mean change scores among the four treatment groups. There was no report of follow-up of adverse events beyond the 24 hours of the study.

In summary, the Meehan et al. study showed that in comparison to placebo, IM olanzapine and lorazepam at the study dosages reduced DAA in hospital and nursing home patients within two hours of injection. The NNTs to achieve the defined clinical response in one patient was 4 (95% CI 3; 13) for the olanzapine 2.5 mg/day group, 3 (95% CI 2; 8) for the olanzapine 5.0 mg/day group and 3 (95% CI 2; 6) for the lorazepam 1.0 mg group. The changes were lessened after 24 hours. Interpretation of the results is affected by the study design and methodology. Within the 24 hours of the initial injection, there was no significant difference between the study arms regarding EPS, changes in cognitive state, QT interval prolongation or other adverse events.

3.2.2 Novel antipsychotic drugs for ongoing management of DAA

a) Olanzapine versus placebo

There were two RCTs comparing oral olanzapine with placebo.[24,30] Results from the trials could not be combined as the study populations differed (nursing home residents as opposed to outpatients) and scant information was available regarding the study by Satterlee et al.

The trial by Street et al.[30]

The RCT by Street et al. (n=206) compared the efficacy and safety of oral olanzapine at various fixed dosages (5 mg/day, 10 mg/day and 15 mg/day) with placebo, in 206 nursing home residents with DAA over a six-week period. Patients were assessed weekly.

Efficacy: The primary measure of efficacy was the mean change from baseline to end point in the sum of the NPI/NH item scores for the core symptoms (Core Total): Agitation/Aggression, Hallucinations and Delusions. The mean changes were –7.6 (95% CI –9.7; –5.5) in the olanzapine 5 mg/day group, –6.1 (95% CI –8.5; –3.7) in the olanzapine 10 mg/day group, –4.9 (95% CI –7.1; –2.7) in the olanzapine 15 mg/day group and –3.7 (95% CI –6.8; –0.6) in the placebo group. Analysis of variance of these scores showed the olanzapine 5 mg/day and 10 mg/day groups experienced significant improvement compared with the placebo group.

A clinical response, defined as ≥ 50% reduction from baseline in the NPI/NH Core Total, was seen in 36 out of 55 patients in the olanzapine 5 mg/day group (65.5%; Fisher's exact test; p=0.005 relative to placebo), 28 out of 49 patients in the olanzapine 10 mg/day group (57.1%; Fisher's exact test; p=0.04 relative to placebo), 22 out of 51 patients in the olanzapine 15 mg/day group (43.1%; Fisher's exact test; p=0.53 relative to placebo), and 16 out of 45 patients in the placebo group (35.6%). These data show the olanzapine 5 mg/day and 10 mg/day groups (but not the olanzapine 15 mg/day group) showed significantly higher responses relative to placebo.

Based on the above figures, the NNT for clinical response was 3 (95% CI 2; 10) for the olanzapine 5 mg/day group and 5 (95% CI 3; 69) for the olanzapine 10 mg/day group. The authors cited age-related pharmacokinetic changes and pharmacodynamic alterations, and the ongoing neuropathology of AD, as potentially contributing to the observed lack of significant efficacy in the olanzapine 15 mg/day group.

Harm/safety: Twenty-one patients withdrew from the trial due to adverse events: six in the olanzapine 5 mg/day group, four in the olanzapine 10 mg/day group, nine in the olanzapine 15 mg/day group and two in the placebo group.

It was reported that there was no statistically significant mean change in EPS, as measured by the SAS, BAS and AIMS, or in the categorical analysis of treatment-emergent adverse events. The incidence of spontaneously reported EPS was low among the olanzapine groups and no EPS event was statistically different from that seen in the placebo group. However, the scores for the scales, details of statistical analysis and incidences of EPS events were not reported.

Adverse events occurring due to treatment (incidence ≥ 10% or significantly greater than placebo) were: accidental injury, somnolence, pain, abnormal gait, anorexia, ecchymosis, fever, agitation, weight loss, increased cough, peripheral edema and nervousness. The incidence of

these events, except for somnolence and abnormal gait, was not significantly different from incidence in the placebo group. Weight gain for patients on olanzapine was also not significantly greater than that seen in the placebo group.

Four patients in the olanzapine groups withdrew from the study due to somnolence. The olanzapine groups had significantly higher rates of somnolence than the placebo group. The relative risks (RRs) of somnolence in the olanzapine groups, compared to the placebo group were: 3.8 (95% CI 1.2; 12.4) in the olanzapine 5 mg/day group, 4.1 (95% CI 1.2; 13.4) in the olanzapine 10 mg/day group and 5.6 (95% CI 1.8; 17.8) in the olanzapine 15 mg/day group. An analysis of covariance controlling for somnolence showed no significant effect of somnolence on the primary efficacy results, and the treatment effects remained statistically significant (i.e. the improvement in agitation was not due to somnolence).

The olanzapine 5 mg/day and 15 mg/day groups had significantly higher rates of abnormal gait than the placebo group. The RRs of abnormal gait in the olanzapine groups compared to the placebo group were: 9.2 (95% CI 1.2; 68.9) in the olanzapine 5 mg/day group and 8.0 (95% CI 1.1; 60.7) in the olanzapine 15 mg/day group. In the olanzapine 10 mg/day group, the RR was 6.6 (CI 95% 0.84; 61.5: not significant) compared to the risk in the placebo group.

The usefulness of the RRs that were estimated from the study data is tempered by wide confidence intervals, which are due to small sample sizes. (It should be noted that what had been presented as comparative risks in the paper reporting the trial were in fact odds ratios.)

The MMSE scores of patients in the olanzapine groups were not significantly different from baseline or from those in the placebo group. There were no clinically significant differences between placebo and olanzapine groups with respect to changes in vital signs, weight or ECG measures. There were no significant differences between placebo and olanzapine groups with respect to anticholinergic effects.

In summary, the Street et al. study showed that oral olanzapine at lower dosages (5 mg/day and 10 mg/day) reduced agitation in nursing home residents with dementia over a six-week period. The NNT for clinical response was 3 (95% CI 2; 10) for the olanzapine 5 mg/day group and 5 (95% CI 3; 69) for the olanzapine 10 mg/day group. No significant effect was demonstrated for olanzapine at 15 mg/day. There was no significant difference between olanzapine and placebo in EPS, changes in cognitive state, vital signs, weight, ECG measures or anticholinergic effects. Somnolence and abnormal gait were found to be significant adverse events in the olanzapine groups. However, the information on harm was derived from small sample sizes and detailed data for some non-significant events were not reported.

The trial by Satterlee et al.[24] (Abstract)
Information on the RCT conducted by Satterlee et al. (n=238) was derived from an abstract report part of a review article, and a portion of a monograph on olanzapine.[26,27] This was an early study conducted during the pre-registration development phase of olanzapine. The study assessed the safety and efficacy of oral olanzapine in 238 elderly outpatients with psychotic and behavioral manifestations associated with Alzheimer's dementia. The primary objective of the study was to establish the safety of olanzapine; efficacy was a secondary objective. The reason given for the order of objectives was that the study population was elderly and had multiple co-morbid conditions and medication usage.

The trial did not show any significant difference in efficacy (as measured on the BEHAVE-AD) between olanzapine (1 to 8 mg/day; mean modal maintenance dose 2.4 mg/day) and placebo. Lack of efficacy was a major reason for discontinuation; only about 52% of patients completed the study. With respect to harm/safety, there were no significant differences between olanzapine and placebo in adverse events reporting EPS (using the SAS, BAS and AIMS); ECG changes (including QT/QT_c interval times); vital signs; weight changes; nor laboratory changes across haematology, electrolyte, chemistry and prolactin measurements. Agitation was the predominant treatment-emergent adverse event in both olanzapine and placebo groups. Primary data were not available to assess these reported results.

b) Risperidone versus placebo
Two RCTs involving 969 patients (including 115 patients in a haloperidol treatment arm in one of the trials) in North America and Europe compared the effect of risperidone with placebo.[31,32] The RIS-US-63 trial by Katz et al. was conducted in nursing homes or chronic disease hospitals at sites around the US. The RIS-INT-24 trial by De Deyn et al. was an international trial involving institutionalized elderly patients in centres across seven European countries plus Canada. A third trial by Kirwan et al.,[25] involving 337 nursing home patients in Australia and New Zealand, was only reported as an abstract. The pharmaceutical company that supported the trial could not provide further details.

RIS-US-63[31]
Katz et al. studied 625 nursing home or chronic disease hospital patients, 55 years or older, for the effect of risperidone on agitation in dementia. Patients were given either oral risperidone (0.5, 1.0 or 2.0 mg/day) or placebo for 12 weeks.

Efficacy: The primary measure of efficacy in this study was the BEHAVE-AD total score. The mean changes in score from baseline to endpoint were –4.8 (95% CI –6.2; –3.4) in the risperidone 0.5 mg/day group, –6.5 (95% CI –7.9; –5.1) in the risperidone 1.0 mg/day group, –6.4 (95% CI –7.6; –5.2) in the risperidone 2.0 mg/day group and –4.2 (95% CI –5.4; –3.0) in the placebo group. Analysis of covariance showed only the risperidone 1.0 mg/day and 2.0 mg/day groups experienced significant improvement compared with the placebo group.

A clinical response, defined in *post hoc* analysis as a 50% or more reduction in BEHAVE-AD total scores, was reported in 45% of the risperidone 1.0 mg/day group (67 patients, p=0.02 relative to placebo), 50% of the 2.0 mg/day group (81 patients, p=0.002 relative to placebo) and 33% (53 patients) of the placebo group. The percentage in the risperidone 0.5 mg/day group was

not reported. Based on these figures, the NNT for clinical response was 8 (95% CI 4; 68) in the risperidone 1 mg/day group and 6 (95% CI 4; 16) in the risperidone 2 mg/day group.

Statistically significant improvements were noted in the CMAI and the CGI for the risperidone 1.0 mg/day and 2.0 mg/day groups compared with placebo, but not in the risperidone 0.5 mg/day group.

As there were dose-dependent increases in somnolence and EPS, the authors reanalysed outcomes in patients who did not experience these symptoms. Significantly greater improvements were still observed in patients in the risperidone 1.0 mg/day and 2.0 mg/day groups compared to placebo patients. Hence, it was concluded that the effects of risperidone on the target symptoms could not be attributed to indirect effects related to somnolence or EPS.

It was noted that the numbers of patients in each study arm that reached an endpoint did not tally with the number of patients initially assigned. This discrepancy was not explained: these patients may have withdrawn after randomisation and an endpoint evaluation may not have been performed.

Harm/safety: Ninety-six of 625 patients (15.4%) withdrew from the trial due to adverse events: 12 (8.1%) in the risperidone 0.5 mg/day group, 24 (16.2%) in the risperidone 1.0 mg/day group, 40 (24.2%) in the risperidone 2.0 mg/day group and 20 (12.3%) in the placebo group. The number of patients in the risperidone 0.5 mg/day, 1.0 mg/day, 2.0 mg/day and placebo groups, who developed any adverse event, were 125 (83.9%), 121 (81.8%), 146 (88.5%) and 138 (84.7%), respectively. The authors pointed out that the high proportion of patients experiencing any adverse event (including the placebo group patients) illustrated the difficulty in discerning true drug effects from intercurrent events. Ninety patients (21 placebo and 16, 24 and 29 risperidone 0.5 mg/day, 1.0 mg/day and 2.0 mg/day, respectively) experienced one or more serious adverse events: almost all were considered unrelated to medication, according to the investigators.

Thirty patients died during the trial or in the subsequent 30 days: (6, 13, 6 and 5 in the risperidone 0.5 mg/day, 1.0 mg/day, 2.0 mg/day and placebo groups respectively – not determined to be statistically significant). In all but three cases, the investigators judged the deaths were from intercurrent illnesses unrelated to the study medication. The serious associated adverse events in the three cases that were considered to be at least possibly drug-related were one patient each with: pneumonia (risperidone 0.5 mg/day group), dehydration and abnormal renal function (risperidone 1.0 mg/day group) and respiratory insufficiency and pulmonary embolism (risperidone 2.0 mg/day).

Extrapyramidal Symptom Rating Scale (ESRS) scores did not differ significantly between the risperidone 0.5 mg/day and 1.0 mg/day groups and the placebo group. Patients in the risperidone 2.0 mg/day group had significantly more EPS on this scale compared to the placebo group. One patient (who received placebo) developed tardive dyskinesia; none of the risperidone patients developed tardive dyskinesia.

Adverse events reported by at least 10% of patients in any treatment group were: injury, somnolence, falls, extrapyramidal disorder, urinary tract infection, peripheral edema, purpura, fever, pain, coughing, agitation, rhinitis and upper respiratory tract infection. There were dose-related increases in somnolence, EPS and peripheral edema (all occurrences of peripheral edema were mild).

It was reported that there were no consistent, clinically significant changes in laboratory measures or vital signs. ECG values were similar across treatment groups. The mean changes in MMSE from baseline to endpoint were not significantly different across all the treatment groups.

In summary, the RIS-US-63 trial showed that oral risperidone at dosages of 1.0 mg/day and 2.0 mg/day reduced psychotic and behavioral symptoms in institutionalized elderly patients with dementia over a 12-week period. The NNT for clinical response was 8 (95% CI 4; 68) in the risperidone 1 mg/day group and 6 (95% CI 4; 16) in the risperidone 2 mg/day group. No statistically significant effect was observed for risperidone at 0.5 mg/day. Several patients experienced one or more serious adverse events, but the investigators considered most of them to be unrelated to medication. Of 30 deaths that occurred, three had serious associated adverse events that could possibly be drug-related. Patients on risperidone 2.0 mg/day had significantly more EPS compared to the placebo group. There were dose-related increases in occurrences of somnolence, EPS and mild peripheral edema. There was no significant difference between risperidone and placebo in changes in cognitive state, laboratory measures, vital signs or ECG measures.

RIS-INT-24[32]

De Deyn et al. studied 344 institutionalized patients, 55 years or older, comparing flexible dose risperidone (mean dose at endpoint = 1.1 mg/day; only 4 out of 115 patients received a dose ≥ 2 mg/day at endpoint) and haloperidol (mean dose at endpoint = 1.2 mg/day) with placebo for DAA over 12 weeks. The portions of the study relating to the haloperidol treatment arm will be covered in the section on studies comparing risperidone with haloperidol.

Efficacy: Clinical improvement, the primary outcome of the study, was defined a priori as the percentage of patients with a 30% or greater improvement (from baseline to endpoint) on the BEHAVE-AD total score. The percentage of patients showing clinical improvement at endpoint in the risperidone, haloperidol and placebo groups were 54% (62 of 115 patients), 63% (72 or 73 of 115 patients) and 47% (54 of 114 patients), respectively. These changes from baseline were analysed using analysis of covariance models with factors for treatment, country, the treatment/country interaction and baseline scores as covariates. The analysis showed that there was no statistically significant difference between the risperidone and placebo group outcomes ($p = 0.25$, risperidone relative to placebo).

Risperidone fared better against placebo in the secondary outcomes for the study. The risperidone group showed a significant improvement over placebo at endpoint in the BEHAVE-AD aggression cluster and the CMAI aggressive scores (total, physical and verbal cluster) ($p<0.05$) in all cases, risperidone relative to placebo. There was also global improvement (CGI severity rating) in the risperidone group versus placebo at endpoint ($p < 0.05$, Cochran-Mantel-Haenszel test).

The authors felt that the prior definition of the primary endpoint as percentages of patients with 30% or greater reduction in BEHAVE-AD total scores was a limitation in the design of the study. This contrasts with the study by Katz et al., in which a post hoc criterion of 50% or greater reduction in BEHAVE-AD total scores was selected to determine categorical responses.

Harm/safety: One hundred and twenty-one of 344 patients (35%) withdrew from the study after randomization (47 on risperidone, 34 on haloperidol and 40 on placebo). Sixty-one patients (50.4% of all withdrawals) withdrew due to adverse events, while 53 patients (43.8%) withdrew due to lack of efficacy: the authors reported that there were no significant between-group differences.

The severity of EPS at endpoint was not significantly different in the risperidone and placebo groups [least square mean shifts from baseline in the ESRS total scores of –0.3 and –1.4 respectively (increased score indicates more severe symptoms)]. The incidence of EPS-like adverse events was not significantly different in patients receiving risperidone (15%) or placebo (11%).

Adverse events were reported in 88 (76.5%) patients in the risperidone group and 83 (72.8%) patients in the placebo group. Adverse events occurring in 10% or more of patients in any one group were fall, injury, agitation, somnolence and bruises caused by injuries or falls. Only somnolence occurred in more patients receiving active treatment than in placebo patients (risperidone 14 [12.2%]; placebo 5 [4.4%]). There were no significant between-group differences in the occurrence of serious or severe adverse events.

The authors reported that endpoint MMSE scores showed no cognitive deterioration with risperidone. The least square mean changes were also not significantly different between the risperidone (-0.5) and placebo (0.5) groups ($p < 0.05$). There was no difference between all the treatments on FAST ratings, indicating no negative effects on daily functioning.

The authors reported no consistent changes or clinically relevant abnormalities in vital signs (blood pressure and heart rate), laboratory safety parameters, body weight or ECGs. Actual data were not reported.

In summary, the RIS-INT-24 trial did not demonstrate a significant difference between risperidone (mean dose 1.1 mg/day) and placebo in managing behavioral symptoms in patients with dementia over 12 weeks, using a pre-defined clinical endpoint of 30% or greater improvement on the BEHAVE-AD total score. Significant improvements were seen in the risperidone group compared with the placebo group in the secondary outcomes of BEHAVE-AD aggression cluster scores, CMAI aggressive scores and CGI. There was no significant difference between risperidone and placebo in terms of MMSE, FAST, EPS, vital signs, laboratory safety parameters or ECG changes. Of reported adverse events, only somnolence occurred in more patients on risperidone than placebo group patients. Detailed harm/safety information was not reported.

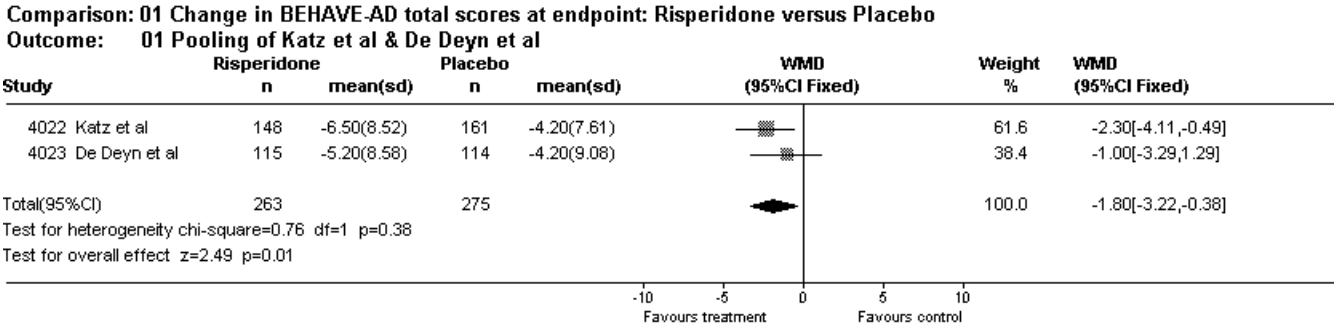
The trial by Kirwan et al.[25] (Abstract)
Kirwan et al. randomized 337 nursing home patients with dementia (AD, vascular dementia or both) to either flexible dose oral risperidone (0.5 to 2.0 mg/day; mean dose 0.95 mg/day) or placebo for 12 weeks. They reported a significant difference between groups for the change from baseline to endpoint in the CMAI aggression score [risperidone –7.8 (95% CI –5.84; –9.76); placebo –2.8 (95% CI –0.92; –4.68)]. They also reported a statistically significant difference in the CGI change from baseline to endpoint, but no figures were stated.

Sixty-seven percent of the placebo patients and 73% of the risperidone patients completed the trial. Principal reasons for withdrawal were adverse events (placebo 8.2%, risperidone 13.2%) and insufficient response (placebo 19.4%, risperidone 13.2%). At least one adverse event was reported in 92% of the placebo group and 94% of the risperidone group. Somnolence and urinary tract infection were more common in the risperidone group, whereas agitation was more common in the placebo group.

3.2.3 Meta-analysis of RIS-US-63 study and RIS-INT-24 study for BEHAVE-AD score as outcome

The BEHAVE-AD total score was part of the primary measure of efficacy in both RIS-US-63 and RIS-INT-24. Data provided in both papers were sufficient to allow the pooling of the baseline to endpoint changes in BEHAVE-AD total scores for risperidone and placebo groups. The weighted mean difference (WMD) between the changes in BEHAVE-AD total score for the risperidone and placebo groups was –1.80 (95% CI –3.22; –0.38). (Figure 4) The chi-square test for heterogeneity showed the studies were not statistically heterogeneous (p = 0.38), but only two studies were pooled.

Figure 4: Meta-analysis of RCTs comparing risperidone and placebo



The clinical response outcome was not pooled as the definitions used by the two trials differed significantly: RIS-INT-24 defined clinical improvement as an improvement of 30% or greater on the BEHAVE-AD total score, whereas RIS-US-63 used a threshold of 50% or greater improvement, which was defined *post hoc*. Other secondary outcomes were not pooled, as insufficient data were available (e.g. means are reported, but not standard errors or standard deviations).

c) Risperidone versus haloperidol

There were two RCTs comparing risperidone against haloperidol, a conventional antipsychotic, for DAA.[32,33] The RIS-INT-24 study by De Deyn et al. (described above) primarily compared efficacy of risperidone with placebo and only compared the tolerability of risperidone with haloperidol as a secondary objective. The study by Chan et al. was conducted in both hospitalized patients and outpatients in Hong Kong to assess the efficacy of risperidone in a Chinese population. The differences in study conditions and populations did not allow pooling and the studies are reported separately.

The trial by Chan et al.[33]

The trial by Chan et al. assessed the efficacy and safety of risperidone (mean daily dose at week 12 = 0.85 ± 0.50 mg) compared with haloperidol (mean daily dose at week 12 = 0.90 ± 0.45 mg) in flexible doses, for the treatment of behavioral and psychological symptoms of dementia, over a 12-week period. The study was carried out with 58 patients aged 55 years or older. Patients were started on 0.5 mg of either drug and this was increased as needed by 0.5 mg, no faster than every other day. The target dose for the study was 1 mg/day, but the dose could be raised to 2 mg/day for poorly controlled symptoms. Aside from baseline assessments, psychometric and side effect evaluations were done at weeks 4, 8 and 12. Additional CMAI ratings were performed at weeks 2, 6 and 10. Standard 12-lead ECGs were obtained at the end of the study.

Efficacy: There was no statistically significant difference in CMAI total scores and BEHAVE-AD sub-scale scores between the risperidone and haloperidol patient groups, as tested by repeated measures analysis of variance (ANOVA): $p>0.05$ for CMAI total score and BEHAVE-AD sub-scale scores for psychosis, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances and anxieties and phobias.

It was recognized by the authors that the small sample size was a limitation of the study which precluded analysis of the individual sub-items of BEHAVE-AD and CMAI. Another limitation was the heterogeneous nature of the study population (hospitalized patients and outpatients).

Harm/safety: The authors reported that there was no significant increase in the SAS, BAS or AIMS for the risperidone group at the end of the study. There was a significant increase in the SAS in the haloperidol group ($p < 0.001$); the authors did not mention whether there were any changes in the BAS or AIMS for the haloperidol group. Although a graph showing the changes in SAS was provided, no data were given for any of the scores. Reproduction of the statistical analysis or any further analysis were therefore not possible.

Mean changes from baseline in MMSE scores for both groups were not statistically significant (–0.15 for the haloperidol group, $p=0.84$; –0.42 for the risperidone group, $p=0.70$). The authors reported there was no significant change in vital signs including postural hypotension.

With regard to adverse events, in the haloperidol group two patients complained of constipation, and another three had drug-related somnolence. In the risperidone group, one patient complained of nausea and another suffered from acute retention of urine, which was later found to be unrelated to the study medication.

Three patients withdrew from the study. A patient in the haloperidol group withdrew due to somnolence associated with treatment. In the risperidone group, one patient stopped owing to a lack of efficacy, while another patient suffered a fracture of neck of femur, which was attributed as likely due to environmental factors. The authors claim that, since only three of 58 patients (5.2%) had withdrawn from the trial, per treatment analysis was an acceptable alternative to intent-to-treat analysis for this trial.

In summary, the Chan et al. trial showed no statistically significant difference in efficacy between risperidone and haloperidol at the study dosages. However, at the end of the trial, patients on haloperidol had a significant increase in EPS as measured on the SAS; patients on risperidone showed no significant increase in EPS as measured on the SAS, BAS or AIMS. Adverse events reported included constipation and somnolence in the haloperidol group, and nausea in the risperidone group. This study was limited by the small sample size and heterogeneous study population.

RIS-INT-24[32]

The study by De Deyn et al. has been described in the section on studies comparing risperidone with placebo. This 12-week RCT included a haloperidol treatment arm. A secondary objective of the trial was to compare the tolerability (particularly EPS) and general safety of risperidone with that of haloperidol. There were 115 patients each in the haloperidol group (mean dose 1.2 mg/day) and risperidone (mean dose 1.1 mg/day) group.

The percentages of patients with clinical improvement (at least 30% reduction from baseline to endpoint in BEHAVE-AD total score) were 54%, 63% and 47% in the risperidone, haloperidol and placebo groups respectively. Whether the risperidone results were significant relative to haloperidol was not reported. *Post hoc* analysis found significant improvements in the risperidone group relative to the haloperidol group on the BEHAVE-AD aggressiveness score and the CMAI total and verbal aggressive scores at week 12.

There was no cognitive deterioration measured for patients in the risperidone group compared with those in the placebo group. However, least square mean changes in MMSE compared between the haloperidol and placebo groups (placebo 0.5, haloperidol –2.1; $p < 0.05$) suggested cognitive deterioration with haloperidol.

The incidence of EPS-like adverse events was significantly higher ($p=0.023$) in the haloperidol group (22%) than the risperidone group (15%). More severe EPS were also seen in the haloperidol group compared to the risperidone group (least square mean shifts from baseline in the ESRS total scores were +1.6 and –0.3 respectively; $p < 0.05$).

4 DISCUSSION

The literature search for this systematic review found seven RCTs that met the criteria for inclusion. Of these, only two studies were considered to be of high quality. Although there are eight novel antipsychotics produced, only RCTs involving olanzapine and risperidone were identified. No RCTs involving the other novel antipsychotics, amisulpride, clozapine, quetiapine, sertindole, ziprasidone or zotepine, were identified.

In 1998, Serdolect® (sertindole) was withdrawn from all countries by its manufacturer, Lundbeck Ltd., subsequent to suspension of marketing permission by the Dutch authorities.[34] The concerns were reports of cardiac arrhythmias and sudden cardiac deaths associated with the use of the drug. The Bulgarian Drug Agency in the Ministry of Health had also withdrawn sertindole because of serious adverse reactions worldwide.[35] Aside from olanzapine, risperidone and quetiapine, it would appear that the manufacturers of the other novel antipsychotics are not actively pursuing their use for DAA.

Olanzapine: Our assessment identified evidence examining the use of olanzapine for both the rapid management and ongoing management of agitation in nursing home residents. With respect to rapid management, IM olanzapine (2.5 mg and 5.0 mg doses) was effective in reducing agitation (defined as a 40% improvement in PANSS-EC score) within two hours of the injection. There was no significant difference between olanzapine and placebo in the incidence of adverse events within 24 hours of injection. The NNTs for IM olanzapine 2.5 mg and 5.0 mg were 4 (95% CI 3; 13) and 3 (95% CI 2; 6), respectively. This compares with the NNT of 3 for IM lorazepam 1.0 mg. If efficacy and safety of a new therapy is equivalent to that of existing therapies, cost could become a significant factor in choice of therapy.

Regarding the ongoing management of DAA, there was evidence from one six-week RCT that oral olanzapine at 5 mg/day and 10 mg/day reduced agitation in nursing home recipients with dementia. The NNTs for oral olanzapine 5 mg/day and 10 mg/day were 3 and 5, respectively. Efficacy was not demonstrated for olanzapine at 15 mg/day. Somnolence and abnormal gait were significant adverse events from olanzapine use. Another early RCT did not demonstrate efficacy: however, the trial's primary objective was to establish the safety of olanzapine and there was no significant difference between olanzapine and placebo in terms of adverse events.

Risperidone: There were two moderate to high quality RCTs involving risperidone. The RIS-US-63 study showed that oral risperidone (1 mg/day and 2 mg/day) produced a clinical response (defined *post hoc* as a 50% or greater reduction in BEHAVE-AD total scores) in institutionalized elderly patients with dementia over 12 weeks. The NNTs for oral risperidone 1 mg/day and 2 mg/day were 8 and 6, respectively. Efficacy was not demonstrated for risperidone 0.5 mg/day. In contrast, the RIS-INT-24 study showed no significant difference between risperidone (1.1 mg/day) and placebo, using an *a priori* definition of clinical response as 30% or greater reduction in the BEHAVE-AD total scores. However, significant improvements were shown in secondary parameters like BEHAVE-AD aggression cluster, the CMAI aggressive score and the CGI.

Pooling of the two studies was possible and it was found that the WMD for the change from baseline to endpoint of the BEHAVE-AD total score for risperidone compared to placebo was –1.80 (95% CI –3.22; –0.38).

With respect to harm, three of 30 deaths during the RIS-US-63 study were considered to be at least possibly drug-related. Patients on risperidone 2 mg/day had significantly more EPS compared to patients in the placebo group. Dose-related increases in occurrences of somnolence, extrapyramidal symptoms and mild peripheral edema were seen. Somnolence was a significant side effect in risperidone compared to placebo in the RIS-INT-24 study.

In the RCTs comparing risperidone and haloperidol, there was no significant difference in efficacy between the two drugs; however, patients on haloperidol had more frequent and severe EPS. In the RIS-INT-24 study, there was a suggestion of cognitive deterioration with haloperidol, which was not seen with risperidone.

Note: On 11 October 2002, while the draft of this systematic review was in external review, Janssen-Ortho Inc. issued an advisory with important drug safety information.[36] The advisory warned that Risperdal® (risperidone) in patients with dementia might be associated with an increased incidence of reports of cerebrovascular adverse events (CVAEs) such as stroke and transient ischaemic attacks, including fatalities. Physicians were advised to reassess the risks and benefits of using Risperdal in elderly patients with dementia, taking into account risk predictors for stroke in the individual patient. They were also advised to counsel their patients and the patients' caregivers to immediately report signs and symptoms of potential CVAEs.

The advisory published background information on clinical trial data from RCTs comparing Risperdal with placebo. Two of these trials, AUS-5 and BEL-14, were hitherto unknown to us and Janssen-Ortho Inc. declined to provide further details.

The incidence of reported CVAEs as reported in the advisory is reproduced in the following table:

Table 5: Incidence of reported CVAEs in four placebo-controlled, dementia trials in elderly patients taking Risperdal, within the approved dosage range, for 4 to 12 weeks

Study No.	Risperdal	Placebo
	Patients with CVAEs	**Patients with CVAEs**
AUS-5	9% (15/167)	2% (3/170)
INT-24	8% (9/115)	2% (2/114)
USA-63	1% (5/462)	1% (2/163)
BEL-14	0% (0/20)	0% (0/19)
Total	4% (29/764)	2% (7/466)

Source: Janssen-Ortho Inc. healthcare advisory for risperdal and cerebrovascular adverse events[36]

Four patients died in the Risperdal group versus one patient in the placebo group. Review of the global post-marketing database for the elderly dementia population, representing over 2.4 million patient years, identified 37 cases of CVAEs. Of these 37 cases, 16 were fatal. The advisory pointed out that as only a small proportion of suspected adverse events are usually reported, caution should be exercised in estimating the incidence of adverse events.

Limitations: The lack of a standard method of assessing the degree of severity of behavioral and psychological symptoms in dementia adds complexity to interpretation of studies of drugs for these symptoms. This is compounded by the absence of a common definition of what would constitute an acceptable clinical response in judging the efficacy of a drug. In this review, we have seen that two studies applied different thresholds for clinical response on the same assessment scale (30% or better improvement on the BEHAVE-AD total score versus 50% or better improvement). Similarly, in the assessment of EPS, at least three different rating scales (SAS, BAS and AIMS) are commonly used. This limits the ability to synthesize the information from the various trials.

By our standards, pooling was only possible in one instance owing to the non-comparability of study data. We found one other meta-analysis of RCTs on the use of novel antipsychotics in DAA.[37] Davidson et al. chose to pool results from De Deyn et al., Katz et al. and Street et al., although one of the trials examined a drug that differed from the drugs studied in other two. De Deyn and Katz published a *post hoc* analysis of their combined trials in which they used primary data and recategorised the patient groups.[38] Their analysis of the integrated patient data did not include an assessment in terms of clinical response.

No study included in our review lasted longer than 12 weeks. Long-term safety beyond six weeks for olanzapine and 12 weeks for risperidone has not been examined in any RCT. The existing trials may not have been sufficiently powered to detect adverse events which are rare.

There were high placebo response rates in the trials, which varied from 33 to 47%. This is common in psychiatric drug trials. Four of the seven studies included in this review mentioned they allowed concomitant use of lorazepam; this could have contributed to the high response rate seen in placebo groups.

Ongoing research: In March 2001, subject recruitment began on a large multi-centre trial in the US to examine the effectiveness of novel antipsychotics in patients with psychosis associated with AD.[39] The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Alzheimer Disease Trial will involve 450 patients with psychosis in AD at 36 sites across much of the US.

The trial is a double-blind RCT comparing risperidone, olanzapine, quetiapine, citalopram (a selective serotonin reuptake inhibitor) and placebo in patients with AD, with delusions, hallucinations, or agitation severe enough to warrant the use of antipsychotic medications. The trial will focus on effectiveness and broader outcome measures, rather than efficacy alone. It will also examine cost-effectiveness, be as inclusive as possible and provide data on the optimum choices of antipsychotics in different subgroups, appropriate dosage ranges and any unique safety issues within each group.

The primary specific aims of the trial are:

1. to compare the acute efficacy and effectiveness of risperidone, olanzapine, and quetiapine as well as treatment algorithms over the course of 36 weeks in treating psychosis and severe agitation in outpatients with AD; and
2. to assess the relative effectiveness of the antipsychotics and citalopram in the maintenance of clinical improvement up to 36 weeks.

The strengths of this trial are its large sample size, long period of study and focus on effectiveness in practice, and its intention to conduct an economic evaluation of the results of the trial. It is to go on for five years; results will be important for future assessments of the role of novel antipsychotics in patients with AD.

5 CONCLUSIONS

Novel antipsychotics were developed to overcome the significant side effects seen with conventional antipsychotics drugs, yet to be equal or superior in efficacy. This review focuses on use of novel antipsychotics in a specific patient group – those with agitation associated with dementia. In total, eight drugs in this class have been developed. Only seven relevant trials were located; these only examined two of the eight antipsychotics, olanzapine and risperidone. For the clinical indication of interest, no trials were found that compared different novel antipsychotics to each other. Olanzapine has been studied for use in both rapid (within two hours) and longer term (6 week) management of DAA whereas risperidone trials examined only longer term (12 week) treatment.

With respect to olanzapine, one trial found its efficacy for the rapid treatment of DAA to be comparable to that achieved with lorazepam and better than placebo for institutionalized elderly patients; adverse events at 24 hours did not differ for the three groups of patients. For longer term DAA management (six to eight weeks), two RCTs, using different scales to assess outcomes, reported opposite effects on agitation outcomes. Olanzapine increase somnolence and abnormal gait.

For risperidone as compared with placebo, one RCT examining management over 12 weeks showed a positive effect on the behaviour of institutionalized elderly patients, measured using a behavioural rating scale. A second trial only showed improvements on secondary scale measures. Risperidone showed a dose-related increase in somnolence, EPS and mild peripheral edema. When compared with haloperidol in two 12-week trials, the efficacy of risperidone with respect to behavioural scores was not significantly different. However, haloperidol increased the incidence of EPS.

Limited harm/safety data exist for the use of these drugs for patients with DAA: 6-week data for olanzapine (N=444 total) and12-week data for risperidone (N=1364 total). These drugs are expensive relative to older alternatives therefore cost may be a significant factor. Cost-effectiveness analyses may clarify relative costs and benefits.

A 36-week RCT in the US (n=450) comparing risperidone, olanzapine, quetiapine, citalopram (a selective serotonin reuptake inhibitor) and placebo is underway; it should provide comparative evidence when completed in 2006.

NOTE

After our report was completed, a 12-week RCT comparing risperidone (n=167) and placebo (n=170) for the treatment of aggression, agitation and psychosis in elderly nursing home patients was published (Brodaty et al., 2003).[40] Patients were 55 years or older and were diagnosed as having dementia (MMSE scale scores `23). The mean and modal doses of risperidone used in the trial were 0.95 mg (SE=0.03) and 0.99 mg (SE=0.05), respectively.

Risperidone-treated patients showed improvement (decrease) over placebo-treated patients through measurement of CMAI total aggression subscale scores [-4.4 (95%CI -6.75; -2.07)], CMAI total non-aggression subscale scores [-4.5 (95%CI -7.39; -1.70)] and total BEHAVE-AD scale scores [-4.5 (95%CI -6.45; -2.46)]. Serious adverse events (defined as life-threatening, requiring hospitalization or resulting in significant disability or incapacity) were experienced by 15 patients (8.8%) in the placebo group and 28 patients (16.8%) in the risperidone group. Four patients (2.4%) in placebo group and six (3.6%) in the risperidone group died during the course of the trial. Somnolence occurred in 61 (36.5%) of the patients in the risperidone group and 43 (25.3%) of the patients in the placebo group. Thirty-nine patients in the risperidone group (23.4%) and 27 patients (15.9%) in the placebo group had one or more EPS-like adverse events.

In summary, in this trial, treatment of patients with dementia using risperidone resulted in improvement in aggression, agitation and psychosis as measured by various scales. However, the incidence of adverse events was higher in the risperidone group as well. Although our analysis was not regenerated to include these new data, the results of this trial would not change the conclusions of our report.

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Appendix 1: Databases Searched and Search Strategies

?	Truncation symbol, one character only
*	Truncation symbol, any number of characters
n	Near/next (i.e., terms are near/next to one another, any order)
" "	Phrase
l	Link (i.e., to subheading)
ti	Title
ab	Abstract
au	Author
de	Descriptor
dt	Publication type
tn	Trade name
mn	Manufacturer name
nd	Device name
md	Device manufacturer
rn	Registry number (i.e., CAS)
tw	Text word

DATABASES	LIMITS	KEYWORDS/DESCRIPTORS
DIALOG®		Clinical Search (RCTs):
AgeLine BIOSIS Previews® EMBASE® MEDLINE® PASCAL PsycINFO® ToxFile	Human *(BIOSIS, EMBASE, MEDLINE only)* 1985-	AgeLine: dementia/de OR delirium/de BIOSIS: alzheimer disease/de OR alzheimer's dementia/de OR alzheimer's disease/de OR dementia/de OR creutzfeld-jakob disease/de OR lewy body disease/de OR pick's disease/de OR huntington disease/de OR huntington's disease/de OR delirium/de EMBASE: creutzfeldt jakob disease/de OR senile dementia!/de OR alzheimer disease/de OR diffuse lewy body disease/de OR frontotemporal dementia/de OR huntington chorea/de OR mental deterioration/de OR multiinfarct dementia/de OR pick presenile dementia/de OR presenile dementia/de OR cognitive defect/de OR wernicke korsakoff syndrome/de OR korsakoff psychosis/de OR binswanger encephalopathy/de OR progressive supranuclear palsy/de OR organic brain syndrome/de MEDLINE/ToxFile: alzheimer disease!/de OR creutzfeldt-jakob syndrome/de OR dementia, vascular!/de OR kluver-bucy syndrome/de OR lewy body disease/de OR pick disease of the brain/de OR huntington disease/de OR delirium/de OR wernicke encephalopathy/de OR korsakoff syndrome/de PsycINFO: dementia!/de OR delirium/de OR huntingtons disease/de OR wernickes syndrome/de OR korsakoffs psychosis/de OR alzheimers disease/de OR progressive supranuclear palsy/de

		All databases: dement*/ti,ab OR alzheimer* OR creutzfeld(1n) jakob OR CJD/ti,ab OR JCD/ti,ab OR "kluver bucy" OR "lewy (body OR bodies)" OR deliri*/ti,ab OR "pick* disease*" OR "lobar hyperact*" OR "brain hyperact*" OR huntington* OR binswanger* OR wernicke* OR korsakoff* OR (cognit* OR memor* OR mental*)(3n)(declin* OR impair* OR losing OR loss OR losses OR deteriorat*)/ti,ab OR chronic(3n) cerebrovascular/ti,ab OR "organic brain (disease* OR syndrome*)" OR "supra nuclear pals*" OR "normal pressure hydrocephalus" OR shunt*/ti,ab OR "benign senescent forgetfulness" OR cerebr*(3n)deterior*/ti,ab OR cerebr*(3n)insufficien*/ti,ab OR confusion/ti,ab OR confused/ti,ab *AND* AgeLine: agitation/de OR aggression/de OR delusions/de OR hallucinations/de BIOSIS: agitation/de OR aggression/de OR aggressiveness/de OR aggressive behavior/de OR delusions/de OR hallucinations/de EMBASE: agitation/de OR aggression!/de OR delusion/de OR hallucination/de MEDLINE/ToxFile: psychomotor agitation!/de OR aggression!/de OR delusions/de OR hallucinations/de PsycINFO: agitation/de OR aggression/de OR aggressive behavior/de OR delusions/de OR hallucinations/de All databases: agitat*/ti,ab OR (increased OR elevated OR excessive)(5n)"motor activit*"/ti,ab OR psychomotor(1n)(excitement* OR hyperact* OR restless*)/ti,ab OR "inner tension"/ti,ab OR "inwardly tense"/ti,ab OR aggression*/ti,ab OR aggressive*/ti,ab OR delusion/ti,ab OR hallucinat*/ti,ab *AND* BIOSIS: clozapine/de OR risperidone/de OR olanzapine/de OR quetiapine/de OR ziprasidone/de OR amisulpride/de OR sertindole/de RN=106266-06-2 OR RN= 5786-21-0 OR RN=132539-06-1 OR RN=111974-69-7 OR RN=146939-27-7 OR RN=71675-85-9 OR RN=106516-24-9 EMBASE: clozapine/de OR risperidone/de OR olanzapine/de OR quetiapine/de OR ziprasidone/de OR amisulpride/de OR aripiprazole/de OR iloperidone/de OR sertindole/de RN=106266-06-2 OR RN= 5786-21-0 OR RN=132539-06-1 OR RN=111974-69-7 OR RN=146939-27-7 OR RN=71675-85-9 OR

		RN=106516-24-9 MEDLINE/ToxFile: clozapine/de OR risperidone/de PsycINFO: clozapine/de OR risperidone/de All databases: clozapine OR risperidone OR olanzapine OR quetiapine OR ziprasidone OR amisulpride OR aripiprazole OR iloperidone OR zotepine OR sertindole OR seroquel OR clozaril OR leponex OR risperdal OR belivon OR rispolin OR zyprexa OR deniban OR solian OR sulamid OR geodon OR abilitat OR zomaril OR zoleptil OR serdolect OR "atypical antipsycho*" OR "new generation antipsycho*" OR "second generation antipsycho*" OR "novel antipsycho*" OR "unconventional antipsycho*" OR "atypical neuroleptic*" ***AND*** AgeLine: controlled clinical trials/de OR randomized controlled trials/de OR meta analysis/de OR dt=meta analysis BIOSIS: multicenter study/de OR randomized controlled trial/de OR randomized clinical trial/de OR randomized trial/de OR evidence-based medicine/de OR meta-analysis/de EMBASE: major clinical study/de OR multicenter study/de OR controlled study!/de OR randomized controlled trial/de OR drug comparison!/de OR evidence based medicine!/de MEDLINE/ToxFile: controlled clinical trials!/de OR epidemiologic research design!/de OR dt=meta-analysis OR dt=multicenter study OR dt=randomized controlled trial OR dt=controlled clinical trial PsycINFO: meta analysis/de All databases: random* OR "single (blind* OR dumm* OR mask*)" OR "double (blind* OR dumm* OR mask*)" OR "triple (blind* OR dumm* OR mask*)" OR "treble (blind* OR dumm* OR mask*)" OR placebo* OR "meta analy*" OR metaanaly* OR "quantitative* (review* OR overview?*" OR "systematic* (review* OR overview*)" OR "methodologic* (review* OR overview*)" OR "control* (study OR studies OR trial*)" OR RCT? OR "comparative (study OR studies)" OR (drug OR drugs)(3n)comparison*/ti,ab *Performed 17 May 2002* *131 unique hits* *AgeLine - 0 records*

		BIOSIS – 2 records *EMBASE: 83 records* *MEDLINE – 35 records* *Pascal – 6 records* *PsycINFO – 5 records* *ToxFile – 0 records*
DIALOG® AgeLine BIOSIS Previews® EMBASE® MEDLINE® PASCAL PsycINFO® ToxFile	Human *(BIOSIS, EMBASE, MEDLINE only)* 1985-2002	Clinical Search (soft study design): *Same descriptors and keywords as per DIALOG RCT search, excluding RCT filter and adding:* AgeLine: longitudinal study/de BIOSIS: case control study/de OR case control studies/de OR retrospective study/de OR cohort study/de OR longitudinal study/de OR prospective study/de EMBASE: clinical study!/de MEDLINE/ToxFile: epidemiologic studies!/de PsycINFO: retrospective studies/de OR prospective studies/de OR longitudinal studies/de OR followup studies/de All databases: "case control (study OR studies OR trial*)" OR "retrospective (study OR studies OR trial*)" OR "cohort (study OR studies OR trial*)" OR "longitudinal (study OR studies OR trial*)" OR "prospective (study OR studies OR trial*)" OR "observational (study OR studies OR trial*)" OR "follow-up (study OR studies OR trial*)" OR "follow up (study OR studies OR trial*)" OR "followup (study OR studies OR trial*)" OR "open label (study OR studies OR trial*)" OR "open-label (study OR studies OR trial*)" *Performed 17 May 2002* *131 unique hits (excludes overlap with RCT results)* *AgeLine - 0 records* *BIOSIS – 0 records* *EMBASE: 114 records* *MEDLINE – 13 records* *Pascal – 3 records* *PsycINFO – 1 records* *ToxFile – 0 records*

The Cochrane Collaboration & Update Software Ltd. The Cochrane Library, 2002, Issue 1		alzheimer disease!/de OR creutzfeldt-jakob syndrome/de OR dementia, vascular!/de OR huntington disease/de OR delirium/de OR wernicke encephalopathy/de OR dement* OR alzheimer* OR (creutzfeld AND jakob) OR CJD OR JCD OR "kluver bucy" OR "lewy bod*" OR deliri* OR "pick* disease*" OR "lobar hyperact*" OR "brain hyperact*" OR huntington* OR binswanger* OR wernicke* OR korsakoff* OR ((cognit* OR memor* OR mental*) AND (declin* OR impair* OR losing OR loss OR losses OR deteriorat*)) OR (chronic AND cerebrovascular) OR "organic brain (disease* OR syndrome*)" OR (cerebr* AND (deterior* OR insufficien*)) OR confusion OR confused *AND* psychomotor agitation!/de OR agitat* OR (psychomotor AND (excitement OR hyperactive? OR restlessness*)) OR ((increased OR elevated OR excessive) AND ("motor activity")) *AND* clozapine/de OR risperidone/de OR clozapine OR risperidone OR olanzapine OR quetiapine OR ziprasidone OR amisulpride OR aripiprazole OR iloperidone OR zotepine OR sertindole OR "atypical antipsycho*" OR "new generation antipsycho*" OR "second generation antipsycho*" OR "novel antipsycho*" OR "atypical neuroleptic*" OR seroquel or clozaril OR leponex OR risperidal OR belivon OR rispolin OR zyprexa OR deniban OR solian OR sulamid OR geodon OR abilitat OR zomaril OR zoleptil *The Cochrane Database of Systematic Reviews = 25 complete reviews, 3 protocols; Database of Reviews of Effectiveness = 2 references; The Cochrane Controlled Trials Register = 19 references; 1 abstract by INAHTA and other healthcare agencies*
Websites of HTA and related agencies; clinical trial registries; other databases		NZHTA; NICE; ECRI; National Research Register; University of York NHS Centre for Reviews and Dissemination – CRD databases; LILACS, etc.

Appendix 2: Scales used to Measure Clinical Outcomes in Patients with DAA

Scales for agitation/behavioural and psychological symptoms of dementia

Agitation-Calmness Evaluation Scale (ACES): The ACES is a Lilly Research Laboratories scale, internally developed, to assess agitation, ranging from 1=marked agitation to 9=unarousable.[29]

Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD): The BEHAVE-AD is a relatively simple scale consisting of two sections: symptomatology and global rating. The symptomatology section evaluates 25 symptoms in seven categories: delusions, hallucinations, aggressiveness, activity disturbances, diurnal rhythm disturbances, affective disturbances and anxiety. Caregivers rate each of the items on a 4-point scale with reference to the patient's behaviour over the preceding two weeks (0=not present; 1=present; 2=present, generally with an emotional component; 3=present, generally with an emotional and physical component). The maximum possible score for symptomatology is 75. The other section is a global assessment of the severity of BPSD by the caregiver, on the following scale: 0=not at all troubling to the caregiver or dangerous to the patient; 1=mildly troubling to the caregiver or dangerous to the patient; 2=moderately troubling to the caregiver or dangerous to the patient; 3=severely troubling or intolerable to the caregiver or dangerous to the patient.[41]

Cohen-Mansfield Agitation Inventory (CMAI): The CMAI is a rating scale that has been used for the evaluation of treatments for BPSD. It is a 7-point rating scale that assesses the frequency with which patients manifest up to 29 agitated behaviours (e.g. cursing or verbal aggression, kicking, screaming, general restlessness). Each item is scored with reference to the preceding two weeks using the following ratings: 1=never, 2=less than once a week; 3=one to two times per week; 4=several times per weeks; 5=once or twice per day; 6=several times per day; 7=several times per hour. The maximum possible score is 203.[41]

Neuropsychiatric Inventory/Nursing Home version (NPI/NH): The NPI was created to assess a wide range of neuropsychiatric disturbances and distinguish between different types of dementia. The reliability and validity of the NPI/NH have been established using nursing home patients. The NPI/NH consists of 10 behavioural and two neurovegetative items. The score of each item (if present) represents the product of symptom frequency (1=occasionally to 4=very frequently) and severity (1=mild to 3=severe). For each item, an Occupational Disruptiveness score is obtained and encompasses the work, effort, time or distress a particular behaviour causes the caregiver (0=no disruption to 5=very severe or extreme).[30,42]

Positive and Negative Syndrome Scale (PANSS): The PANSS is designed to measure the severity of psychopathology in adult patients with schizophrenia, schizoaffective disorder and other psychotic disorders. It emphasizes positive and negative symptom dimensions. This scale includes three scales and 30 items: seven items make up the Positive scale (examples are delusions, conceptual disorganization and hallucinatory behavior), seven items make up the Negative scale (examples are blunted affect, emotional withdrawal, poor rapport and passive/apathetic social withdrawal) and 16 items make up the general psychopathology scale

(examples are somatic concerns, anxiety, guilt feeling, mannerisms and posturing, motor retardation, uncooperativeness, disorientation, poor impulse control and preoccupation). The PANSS excited component (PANSS-EC) subscale consists of five items of the PANSS: poor impulse control, tension, hostility, uncooperativeness and excitement.[29,43]

PANSS-derived Brief Psychiatric Rating Scale (BPRS): The BPRS was originally developed to evaluate treatment effects in psychopharmacology research in young or middle-aged adults. The BPRS contains 16 items (the number may vary in some versions) chosen on the basis of their usefulness in measuring response to therapy in patients with psychiatric disorders, mainly schizophrenia (e.g. anxiety, hostility, uncooperativeness). Each item is rated on a seven-point scale of severity ranging from 0=not present to 6=extremely severe.[29,42]

Scales for EPS or movement disorders

Abnormal Involuntary Movement Scale (AIMS): The AIMS was designed to record the occurrence of dyskinesias in patients on neuroleptic medication. It is a 12-item scale assessing orofacial movements, extremity and truncal dyskinesias, global severity, incapacitation due to the movements and the distress associated with them.[43]

Barnes Akathisia Rating Scale (BAS): This is a 4-item scale to measure drug-induced akathisia. Three items (objective akathisia, subjective awareness of restlessness and subjective distress related to restlessness) are rated on a 4-point scale (0-3). The fourth item, the global clinical assessment of akathisia, uses a 5-point scale (0-4).[43]

Extrapyramidal Symptom Rating Scale (ESRS): The ESRS was originally developed for a study of tardive dyskinesia in schizophrenic outpatients on long-term neuroleptic treatment. It consists of a questionnaire of parkinsonian symptoms (9 items), a physician's examination of parkinsonism and dyskinetic movements (8 items), and a clinical global impression of tardive dyskinesia.[44]

Simpson-Angus Extrapyramidal Rating Scale or Rating Scale for Extrapyramidal Side Effects (SAS): This scale is used to assess parkinsonian and related extrapyramidal side effects. It has ten items including gait, arm dropping, shoulder shaking, elbow rigidity, wrist rigidity, akathisia, head dropping, glabella tap, tremor and salivation. Each item is rated on a 5-point scale, with 0=the absence of the condition or normal and 4=the most extreme form of the condition.[43]

Other scales

Clinical Global Impressions (CGI) Scale: The CGI scale is a standardized assessment tool to estimate rate and severity of illness, change over time and efficacy of medication. It is widely used in psychopharmacology trials as an outcome. The CGI scale consists of three global subscales: (i) severity of illness subscale ranges from 1=not ill at all to 7=among the most extremely ill, (ii) global improvement subscale goes from 1=very much improved to 7=very much worse and (iii) efficacy index in which the score ranges from 0=marked improvement and no side effects to 4=unchanged or worse and side effects outweigh therapeutic effects.[43]

Functional Assessment Staging (FAST): The FAST is a 16-item scale derived from the functioning and self-care axis of the Brief Cognitive Rating Scale. It was developed to stage dementia of the Alzheimer's type but may be applied for functional staging of adults with cognitive disturbances of varying aetiology.[45,46]

Mini-Mental State Examination (MMSE): The MMSE is an assessment of cognitive mental status that is fast and relatively easy to administer. It consists of 11 tasks or questions that are asked of the patient, which test the patient's orientation, registration, attention and calculation, recall, and language. A Cantonese version was used in the study by Chan et al. In the context of the studies examined in the review, the MMSE was not used as a marker of primary outcome; rather, it was a measure of whether the therapy adversely affected cognition.[33,47]

Appendix 3: Quality Assessment Form

Study Quality

RM # _____ Reviewer _____

Randomization: Total Points: ☐ 0 ☐ 1 ☐ 2

A trial reporting that it is "randomized" is to *receive one point.* Trials describing an appropriate method of randomization (table of random numbers, computer generated) *receive an additional point.* However, if the report describes the trial as randomized and uses an inappropriate method of randomization (date of birth, hospital numbers) *a point is deducted.*

Double-blinding: Total Points: ☐ 0 ☐ 1 ☐ 2

A trial reporting that it is "double blind", is to *receive one point.* Trials that describe an appropriate method of double blinding (identical placebo, active placebo) are to *receive an additional point.* However, if the report describes the trial as double blind and uses an inapropriate method (e.g. comparison of tablets versus injection with no double dummy), *a point is deducted.*

Withdrawals and dropouts: Total Points: ☐ 0 ☐ 1

A trial reporting the number and reason for withdrawals is to *receive one point.* If there is no statement, *no point* is given.

TOTAL Score ☐ Low (0-2 points) ☐ Moderate (3-4 points) ☐ High (5 points)

Allocation concealment: ☐ Adequate ☐ Inadequate ☐ Unclear

Adequate: Central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy, serially numbered, opaque, sealed envelopes, etc.

Inadequate: Alternation; reference to case record # or date of birth, etc.

Unclear: Allocation concealment approach is not reported or fits neither of the above categories.

Appendix 4: Data Extraction Form

Efficacy Study Results: Acute/Maintenance **Reviewer Inititals** _____

Study No:
REFERENCE:

Industry sponsorship: Yes / No / No info

Are the patients randomly assigned to the treatment conditions: Yes / No
Is the study double blinded: Yes / No Parallel / Crossover
Type of patients: Inpatient / Outpatient

Criterion for diagnosis of agitation:

Exclusion criteria:

Study arms				
Dose & frequency				
Duration of treatment				
Pretreatment washout period				
Other drugs allowed during the trial				
Number of patients	Screened			
	Eligible			
	Randomized			
	Evaluable			
	Drop-outs due to adverse events			
	Total drop-outs			
Sex	M/F			
Age (years)				
Dementia status as measured by MMSE or any other scale				

Symptom resolution

Study arm			
Improvement in Cohen-Mansfield Inventory (CMAI)			
Improvement in Neuropsychiatry Inventory-Nursing home version (NPI/NH)			
Improvement in Behavioral pathology in Alzheimer's Disease Rating scale (BEHAVE-AD) score			
Improvement in Clinical Global Impression scale (CGI)			
Improvement in MMSE			
Responders			
Rate of hospitalisation / re-hospitalisation			

Adverse effects

Incidence of tardive dyskinesia			
Barnes Akathisia Scale scores			
Incidence of tardive dyskinesia and EPS			
Simpson-Angus Scale scores (EPS)			
Incidence of all injury (including falls)			
Incidence of falls			
Incidence of injury other than falls			
Somnolence			
Abnormal gait			
Extrapyramidal Symptoms Rating Scale (ESRS)			

Appendix 5: List of Excluded References

1. References excluded after examining the full articles

a) *Post hoc* or subgroup analysis of one of the included studies

Clark WS, Street JS, Feldman PD, Breier A. The effects of olanzapine in reducing the emergence of psychosis among nursing home patients with Alzheimer 's disease. **J Clin Psychiatry** 2001;62(1):34-40.

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Mintzer J, Faison W, Street JS, Sutton VK, Breier A. Olanzapine in the treatment of anxiety symptoms due to Alzheimer 's disease: a post hoc analysis. **Int J Geriatr Psychiatry** 2001;16 Suppl 1:S71-7.

Street JS, Clark WS, Kadam DL, Mitan SJ, Juliar BE, Feldman PD, et al. Long-term efficacy of olanzapine in the control of psychotic and behavioral symptoms in nursing home patients with Alzheimer 's dementia. **Int J Geriatr Psychiatry** 2001;16 Suppl 1:S62-70.

b) Review articles

Daniel DG. Antipsychotic treatment of psychosis and agitation in the elderly. **J Clin Psychiatry** 2000;61 Suppl 14:49-52.

De Deyn PP. Risperidone in the treatment of behavioral and psychological symptoms of dementia. **Int Psychogeriatr** 2000;12 Suppl 1:263-9.

De Deyn PP, Katz IR. Control of aggression and agitation in patients with dementia: efficacy and safety of risperidone. **Int J Geriatr Psychiatry** 2000;15 Suppl 1:S14-22.

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Laks J, Engelhardt E, Marinho V, Rozenthal M, De Castro e Souza, Bacaltchuk J, et al. Efficacy and safety of risperidone oral solution in agitation associated with dementia in the elderly. **Arq Neuropsiquiatr** 2001;59(4):859-64.

Rainer MK, Masching AJ, Ertl MG, Kraxberger E, Haushofer M. Effect of risperidone on behavioral and psychological symptoms and cognitive function in dementia. **J Clin Psychiatry** 2001;62(11):894-900.

Workman RH, Orengo CA, Bakey AA, Molinari VA, Kunik ME. The use of risperidone for psychosis and agitation in demented patients with Parkinson's disease. **J Neuropsychiatry Clin Neurosci** 1997;9(4):594-7.

d) Retrospective case series, case reports or case-control studies

Belzie LR. Risperidone for AIDS-associated dementia: a case series. **Aids Patient Care STDS** 1996;10(4):246-9.

Duffy JD, Kant R. Clinical utility of clozapine in 16 patients with neurological disease. **J Neuropsychiatry Clin Neurosci** 1996;8(1):92-6.

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Gutzmann H. Erfahrungen mit Risperidon in der Behandlung nichtkognitiver Störungen bei Demenz. **Nervenheilkunde** 2000;19(2):102-3.

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