ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Atypical antipsychotics for the behavioural and psychological symptoms of dementia in the elderly

Systematic Review and Network Meta-Analysis

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INTRODUCTION

Background

Dementia is a syndrome characterized by a decline in cognitive capacities that results in impairment in function, but not in alertness or attention. Common types of dementia are Alzheimer's Disease (AD), Lewy body dementia (DLB) and vascular or frontotemporal dementia (1). It is largely seen in individuals later in life, and more specifically in populations aged 65 years or older where prevalence is estimated to be 9 to 13% (2). A recent cohort study of Ontario, Canada home care clients revealed that as many as 22% had a diagnosis of dementia (3). Behavioural and psychological symptoms of dementia (BPSD) may include depression/dysphoria, anxiety, irritability/lability, agitation/aggression, apathy, aberrant motor behavior, sleep disturbance and appetite/eating disturbance, delusions and hallucinations, and disinhibition and elation/euphoria (4).

Significant financial, physical or emotional burden may accompany the care of people with dementia, and most forms have no known cure (5). Drug and non-drug treatment of dementia focuses on maintenance of function and the well-being of patients and their caregivers (6). A variety of drugs are used on and off-label for individuals with behavioural and psychological symptoms of dementia, yet clinicians continue to struggle to find the 'right' pharmacologic treatment. Atypical antipsychotics (AAP) are increasingly being used to control symptoms of dementia in both community and long-term care settings, however, the use of these medications is controversial given that benefit has not been definitely established and any perceived efficacy may need to be counterbalanced by a potential increase in adverse events. In addition, as many as eight of the nine AAPs licensed for use in Canada may be prescribed off-label to combat symptoms of dementia, and there is concern about the appropriate use of this class of drugs in this vulnerable population.

Objectives

The objective of this review is to summarize comparative data on the efficacy, effectiveness, and safety of atypical antipsychotics in both community and long-term care settings. The review is intended for a broad audience and aims to inform provincial funding agencies, clinicians, patients and their care providers so that they make informed choices about the use of AAPs in older adults with BPSD.

Research Questions

1. What is the efficacy and safety of AAPs for the treatment of the behavioural and psychological symptoms of dementia in older adults?

2. Does the efficacy or safety of atypical antipsychotics differ in those who live in community settings when compared to those in long-term care?

Inclusion Criteria

Studies were eligible for inclusion in the systematic review if they satisfied specific **P**opulation, **I**ntervention, and **C**omparators of interest (the **PIC** portion of the **PICO** Statement) described in

Exhibit 1; including the study design of interest. Studies were not excluded based on outcomes reported; however, data were only extracted for those studies reporting outcomes of interest (Exhibit 2). No language restrictions were set.

Exhibit 1: Eligibility Criteria for Study Inclusion

Study Population	Older adults (≥ 65 years of age) with BPSD; all forms of diagnosed dementia were included including Alzheimer's Disease, Vascular, Lewy Body and Mixed Dementia.
Index Node	Placebo
Comparisons	**AAPs:** aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone. • AAPs vs. placebo • Head to head comparisons of the AAPs • Active-controlled trials comparing AAPs to any other medication • Fixed and flexible doses as well as all routes of administration
Study Design	Randomized controlled trials (RCTs). No limits were placed on study duration or patient follow-up.
Exclusions	• RCTs with < 10 participants • Studies not conducted in humans • Herbal comparators • Discontinuation studies

Only data from the first period of crossover designs were included and, similar to the parallel studies, analysis of results from the first period of the crossover studies was conducted where data were available.

Exhibit 2: Efficacy and Safety Outcomes of Interest

Outcomes of Interest	**EFFICACY:** Scales addressing the following five (5) categories were considered:	**SAFETY:** The following four (4) safety and adverse event outcomes were considered:

	• BPSD*
	  • Psychosis, agitation, and aggression subscales
	• Caregiver burden
	• Global measures/Impressions
	• Cognition
	• Activities of Daily Living
		• All-cause mortality**
		  • Individual treatments and pooled analyses
		• Falls
		• Extrapyramidal Symptoms (EPS)
		• Weight change

* NMAs of BPSD subscales were part of sensitivity analyses

** A pooled all-cause mortality NMA was completed as part of a sensitivity analysis

METHODS

Literature Search Strategy

The strategy used to build the evidence base for the efficacy and safety of AAPs in older adults with BPSD consisted of three fundamental steps:

1) We searched for a comprehensive, well-conducted and recently published (within 5 years) evidence synthesis that met the PICO requirements laid out in our inclusion criteria;

2) The search strategies of eligible evidence syntheses were made available to an experienced medical information specialist (IS) who appraised each for appropriateness of literature sources, breadth, potential bias, and barriers that could limit the ability for updating the search. In parallel, two clinical reviewers assessed the quality of eligible evidence syntheses using the "Assessment of Methodological Quality of Systematic Reviews" (AMSTAR) instrument and critically appraised the methodology of particular components of the review in further detail to ensure completeness of included studies. Reviews that both the IS and the clinical review team deemed to be comprehensive in both search and review methodology were used to form the existing evidence base for the systematic review. Included studies from selected evidence syntheses were identified and imported in full-text format into an online systematic review software tool, DistillerSR (7). Use of the online tool by the review team maximizes efficiency in the review process and facilitates consistency across reviewers for literature screening, selection and data extraction. Individual studies were independently screened using the project eligibility criteria prior to inclusion in this review.

3) A medical IS experienced in evidence syntheses, and specifically with network meta-analyses, designed an search strategy to augment the available randomized evidence extracted from the evidence syntheses. Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Embase Classic+Embase and PsycINFO on October 10, 2014. CENTRAL in the Cochrane Library on Wiley on the same date was also searched. Strategies utilized included a combination of controlled vocabulary (e.g., Dementia, Clozapine, and Risperidone) and keywords (*e.g.*, Alzheimer, atypical antipsychotics, Clozaril). Vocabulary and syntax were adjusted across the databases. A validated filter to identify randomized controlled trials was also employed during the search. Additional references were sought through hand-searching of appendices and reference lists. A grey literature search of relevant databases and web sites was also performed using resources listed in CADTH's Grey Matters Light (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters/grey-matters-light). All citations were imported into electronic reference management software (EndNote X7) (8). The complete search strategy is reported in Appendix A.

Eligibility and Study Selection

Selection eligibility criteria were applied to each title and abstract by two independent review authors in

a standardized method using electronic tools customized to the project in DistillerSR. Any uncertainties were resolved by discussion and, if required, consensus was reached with a third review author (SK or GAW). Attempts were made to obtain all studies that meet the selection criteria in full-text format. The eligibility criteria (Exhibit 3) were then applied, and a final decision was made for inclusion. The reviewers were not blinded as to the study authors or centre of publication prior to study selection because this can complicate the review process and only weak evidence suggests that this would improve the results.

Exhibit 3: Eligibility Criteria for Full-Text Article Screening

CATEGORY	INCLUSION	EXCLUSION
Databases	OVID Medline, Ovid MEDLINE® In-Process and other non-indexed citations, Embase Classic, Embase, and PsychINFO	Other databases not recommended by IS
Grey Literature	Clinicaltrials.com, Health Canada and US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products, CADTH Grey Matters Light.	Other grey literature sources
Languages	English	None
Populations	Humans only Adults ≥ 65 years of age years with BPSD It is possible that RCTs will include a broader age group of dementia patients. In this case, RCTs will meet the population inclusion criteria if the mean age of participants is ≥ 65.	Animal Studies Psychosis or symptoms unrelated to BPSD Other psychiatric conditions. Population included in study arms with a mean age under 65.
Study Design	Original data RCTs, Health Canada, US Food and Drug Administration reports, labels and warnings Crossover RCTs must report first period treatment results for efficacy. If not, they will be formally included but no study data will be analyzed.	Letters, editorials, or any other publications that have no original data. Publication of original study data in abstract form only

Interventions	As specified in the PICO statement	All interventions or comparators not explicitly identified in the PICO. Behavioural or non-drug interventions Complex interventions where interventions and comparators are only one component of many.
Duration	All	No exclusions on study duration.
Outcomes	Any – Inclusion decisions for primary studies will not be made based on the outcomes reported. Studies reporting the safety and efficacy outcomes identified in the study protocol will be analyzed.	No exclusions based on outcome reporting

Data Management and Extraction

All information was extracted using standardized data extraction forms developed specifically for the review in consultation with clinical experts. All forms were piloted in a calibration exercise prior to data extraction using a random sample of five articles. Data was extracted by a single review author and checked for accuracy by a second independent review author. Specifically, the following data were extracted from included RCTs:

1. Study characteristics (Design, setting, funding);
2. Population Characteristics (Age, sex, ethnicity, diagnosis);
3. Eligibility and exclusion criteria
4. Study medications:
    a. Interventions (dose, durations, route of administration)
    b. Comparators(dose, durations)
    c. Concomitant medications allowed
5. Numbers screened, eligible, enrolled, lost-to-follow-up;
6. Methods of outcome ascertainment; and,
7. Results for each outcome of interest at end of study.

The primary publication for each unique RCT was used as the principle source for data extraction. Where companion publications were located for a unique RCT, the most recently adjudicated data for each outcome specified *a priori* was extracted.

Studies included from existing evidence syntheses went through de novo data extraction process following identical methods and procedures as articles identified in the updated literature search. Data from all studies, regardless of source, were abstracted into a single dataset

Extraction of Efficacy and Safety Outcomes

Data were extracted for seven continuous outcomes of interest (BPSD overall and three subscales Caregiver Burden, Global Measures/Impressions, Cognition, Activities of Daily Living, EPS, Weight Change) and two dichotomous outcomes (all-cause mortality, falls).

Continuous data was extracted in the form of change scores (from baseline to endpoint for each trial arm) along with the associated measure of variation (standard deviation or error). Dichotomous data were extracted by the frequency of events for all-cause mortality and the number of patients who experienced at least one event for falls.

For safety outcomes (EPS, weight change, all-cause mortality, falls), we extracted the safety population (number of patients who took at least one dose of medication). If a sample size for a change score or safety population was not provided, the number randomized was extracted.

If studies reported a change from baseline score using more than one scale within a single outcome category, we preferentially extracted scales reporting changes in 'total' scores from baseline to endpoint over any sub-scale value.

Data Synthesis

The data were first summarized descriptively. In preparation for statistical analysis, we imputed missing values using methods described in the Cochrane Handbook for Systematic Reviews of Interventions (6). Specifically, when included studies did not provide a change score standard deviation, it was imputed using a correlation coefficient of ρ=0.8.

Clinical experts were consulted to determine a strategy for combining data reported by different measurement scales across single outcome categories. Experts advised on the appropriateness of merging data from various outcome measurement scales and recommended a methodology based on the outcome most representative of older adults with BPSD given the data reported by the included studies. In order to limit the level of clinical diversity, trials that were very short (*e.g.* 24 hours) and very long (*e.g.* 6 months) were eliminated from all primary analyses (81% of trials were between five and twelve weeks long, inclusive).

Study arms comparing various fixed doses of the same drug were pooled together to form a single composite 'flexible-dose' arm for analysis. For example, a four-arm trial comparing placebo to three fixed doses of risperidone (0.5, 1.0 and 2.0 mg/d) was collapsed into two arms for analysis: *placebo (Arm 1)* and *risperidone, oral tablet, 0.5 -2mg/d (Arm 2)*. Routes of administration were not analysed separately.

Statistical Analysis

When data were available, sufficiently similar, and of sufficient quality, Bayesian network meta-analyses (NMAs) were conducted using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) (9, 10) for

each efficacy and safety outcome, specified *a priori*.

Both fixed- and random-effects NMAs were conducted. Model fit for Bayesian analyses was based on the Deviance Information Criterion (DIC) and comparison of residual deviance to number of unconstrained data points (11-14). Selection of the model/measure depended on the outcome of interest and the availability of data. Heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols was carefully assessed. We also considered sensitivity analyses including removal of studies from the network of therapies that were not scored as being of high quality. We formally (14) and informally assessed consistency between direct and indirect evidence by comparing direct estimates obtained from pair-wise meta-analysis with estimates from the Bayesian network meta-analysis (12, 13). Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic were also assessed to ensure model convergence. At least two chains will be fit in WinBUGS for each analysis, each employing at least 40,000 iterations, with a burn-in of at least 20,000 iterations (10, 12).

For continuous outcomes, the effect size was expressed in terms of the mean difference (MD) when change scores from the same scale were analyzed together (*e.g.,* cognition) and standardized mean difference (SMD) when change scores from a variety of scales were pooled together for analyses. Effect estimates for dichotomous outcomes (all-cause mortality, falls) are reported using odds ratios with 95% credible intervals.

The methods and procedures followed were those developed by the Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (ccNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research. A protocol was developed using guidance from the PRISMA Statement and following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions. It was peer-reviewed by clinical experts and those with expertise in pharmacology, statistics, and systematic review methodology**.** The protocol was posted publicly to solicit stakeholder feedback.

Assessment of Heterogeneity

We assessed data for both clinical and methodological diversity. Clinical diversity was assessed by checking that the participants, interventions, and comparators were not too different from each other such that combining them was not appropriate. Methodological diversity was assessed by checking that the studies were similar in terms of study design.

Staircase Diagrams

Staircase diagrams have been assembled to present results for mean differences (continuous outcomes) and odds ratios (dichotomous outcomes) generated by the network meta-analyses (random-effects model) of the various treatment strategies.

Exhibit 4 provides a guide to the interpretation of the results in each staircase diagram presented in the

results section.

Exhibit 4: Interpretation of Results Presented in a Staircase Diagram of Mean Differences and Odds Ratios

Treatment 1			
Mean difference or odds ratio of treatment 2 compared to treatment 1	**Treatment 2**		
Mean difference or odds ratio of treatment 3 compared to treatment 1	Mean difference or odds ratio of treatment 3 compared to treatment 2	**Treatment 3**	
Mean difference or odds ratio of treatment 4 compared to treatment 1	Mean difference or odds ratio of treatment 4 compared to treatment 2	Mean difference or odds ratio of treatment 4 compared to treatment 3	**Treatment 4**

Mean difference= MD (standard deviation), Odds ratio= OR (95% Credible Interval)
Note: **Bolded** numbers in the table indicate statistical significance

RESULTS

Selection of Previously Published Evidence Syntheses

We identified two comprehensive, well-conducted and recently published (2010 and 2011) syntheses of available randomized evidence on the efficacy and safety of AAPs in older adults with BPSD (15, 16):

1. **Drug Class Review: Atypical Antipsychotic Drugs: Final Update 3**. Produced by the Oregon Health & Science University (A review completed for the Drug effectiveness review Program (DERP) available at: http://www-ncbi-nlm-nih gov.proxy.bib.uottawa.ca/books/NBK50583/pdf/TOC.pdf.

2. **Off-Label Use of Atypical Antipsychotics: An Update**. Comparative Effectiveness Review Number 43. Prepared by the Southern California Evidence-based Practice Centre for the Agency for Healthcare Research and Quality (AHRQ). Available at: http://effectivehealthcare.ahrq.gov/ehc/products/150/778/CER43_Off-LabelAntipsychotics_20110928.pdf

Both evidence syntheses reported on efficacy and safety of atypical antipsychotics across a wide range of indications (e.g., schizophrenia, dementia, eating disorders), however, only studies meeting our eligibility criteria were included in this review (*i.e.*, those reporting on populations of patients with BPSD).

Based on the results of the appraisal by the IS and the clinical review team, the AHRQ report was chosen as the primary evidence synthesis to form the basis for the existing RCTs. A total of 42 unique RCTs and seven companion articles were imported directly into DistillerSR for screening of full text.

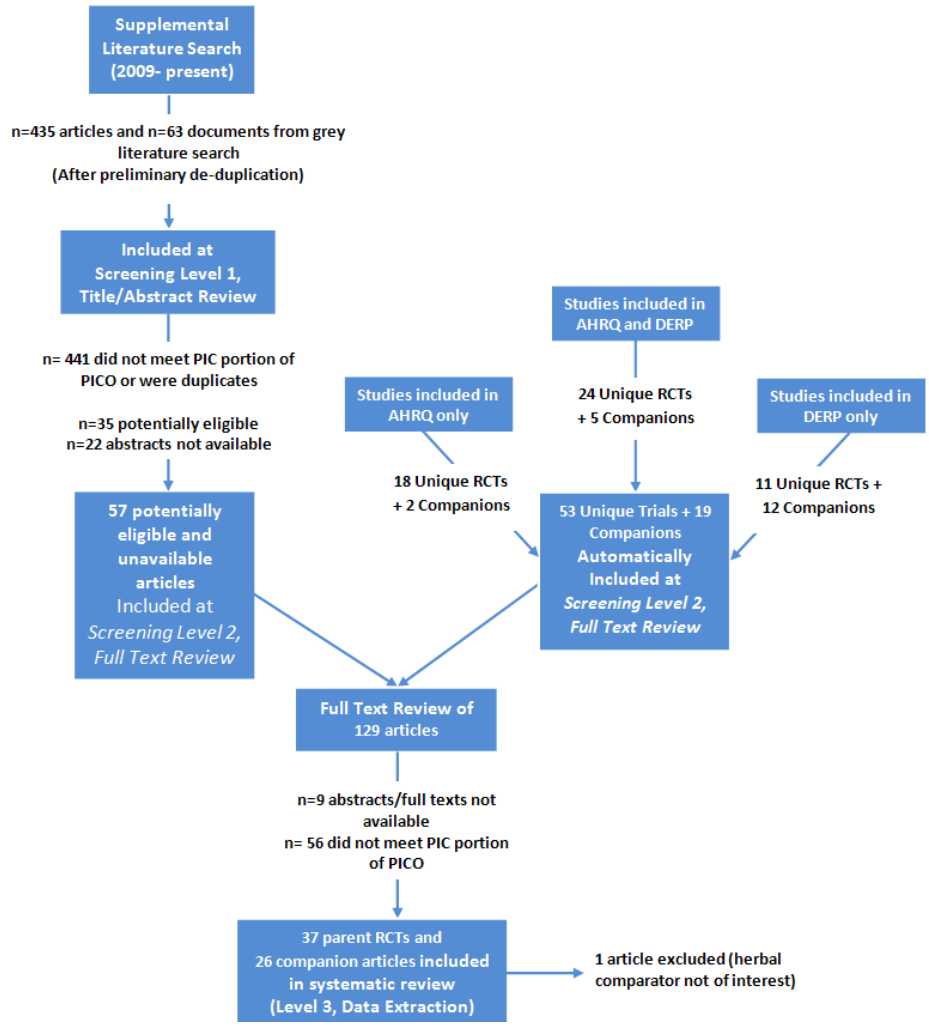
To ensure robustness of the evidence base, we additionally incorporated 11 unique and 12 companion articles from the DERP review (16).

Search Results

The literature search update (2009 to present) returned a total of 435 unique database abstracts and 68 grey literature documents (Exhibit 4). Following a review of the titles and abstracts 378 were excluded as they did not meet our eligibility criteria or were duplicates. A total of 129 articles were assessed using the full-text publication: Thirty-five articles from the database search, 72 articles identified from the AHRQ and DERP reviews and 22 abstracts that could not be located that were moved to the full-text screening level to ensure comprehensiveness. Thirteen articles became available during various stages of the literature selection process, and were reviewed as they were obtained. Nine articles remained unavailable for assessment. No grey literature documents were included.

Following a detailed assessment of the full text publications, a total of 37 unique RCTs were included along with 26 companion publications.

Exhibit 5: Literature Search and Study Selection Process



Characteristics of Included Studies

All studies were published between 1995 and 2014. Study and patient characteristics for 32 studies that reported at least one outcome of interest are reported below. A summary of study characteristics is located in Appendix B.

Five (17-21) of the 37 included studies either failed to report an efficacy or safety outcome of interest, or failed to report data from the first phase of a cross-over study. No data were extracted for these studies (Appendix C).

Duration of Treatment

The most common study duration (baseline to last day of double-blind treatment) was six weeks (9/32 or 28%) (22-30). Five studies each lasted eight (31-35), ten (36-40) or twelve (41-45) weeks (16%). Two studies (46, 47) were five weeks long. Three studies had a duration that lasted more than one month:

one lasted six months (48), another lasted six and a half months (49), and the longest RCT included for review lasted 9 months (50). Three other studies had a duration of two weeks or less: two studies lasted 24 hours (51, 52), and one study lasted two weeks (53).

Interventions and Comparators of Interest

Of the nine AAPs of interest, only four were identified in the 32 included studies reporting outcomes of interest (aripiprazole, olanzapine, quetiapine, and Risperidone). Risperidone, quetiapine, and olanzapine intervention arms were distributed equally across the included studies and aripiprazole was least frequently used as an intervention.

AAPs were compared to placebo in 19 RCTs (23, 26, 27, 29, 30, 35-41, 43, 44, 48-52), to another AAP in 14 RCTs (23, 25, 27, 30, 31, 34, 36, 37, 39, 43, 50-53), and to an active comparator in 13 RCTs (24, 28, 33, 34, 38, 41, 42, 45-47, 49, 51, 54). Seven studies compared the efficacy and safety of different fixed doses of the same type of AAP. Four compared risperidone to olanzapine (23, 34, 36, 53), and one study each compared risperidone to quetiapine (31) and risperidone to olanzapine and quetiapine (25). A single study compared the efficacy and safety of different formulations of the same drug (25).

When an AAP was compared to an active comparator, eight unique drugs were identified across the 32 included studies reporting outcome data. Five compared an AAP to haloperidol (38, 41, 42, 46, 47), three compared an AAP to one of three selective serotonin reuptake inhibitors (SSRIs) (citalopram (45), escitalopram (24), and fluvoxamine (33)). Other active comparators included rivastigmine (n=2) (28, 49), the anticonvulsant topiramate (n=3) (54), benzodiazepine (lorazepam, n=1) (51), or a typical/first generation antipsychotic (promazine, n=1) (34).

Doses and Routes of Administration

AAPs were administered in a number of different doses that fell within the categorization of (titration up to) 'fixed' dose, or 'flexible' dose ranges. Evidence was available for the following methods of administration: oral tablet, capsule, solution, and intramuscular injection (IM). The route of administration was not specified in six of the included RCTs (23, 29, 30, 36, 40, 49). Exhibit 6 summarizes the clinical doses and routes employed in the AAP intervention arms of the 32 studies that reported efficacy and safety outcomes of interest.

Exhibit 6: Dose Categorization for AAPs in the Treatment of BPSD in the Elderly

	FIXED DOSES REPORTED (Routes of administration)	FLEXIBLE DOSES REPORTED (Routes of administration)
Risperidone	• **0.5 mg/d** (oral tablet) • **1 mg/d** (oral tablet, *k=2*; oral capsule) • **2.0 mg/d** (oral tablet)	• **0-2.5 mg/d** (oral capsule) • **0.5-1.5 mg/d** (oral tablet) • **0.5–2 mg/d** (oral tablet, *k=2*; oral capsule, *k=2;* oral, *k=2*; oral solution; route unspecified) • **0.5-4 mg/d** (oral, oral solution, and route unspecified) • **1-2 mg/d** (oral)

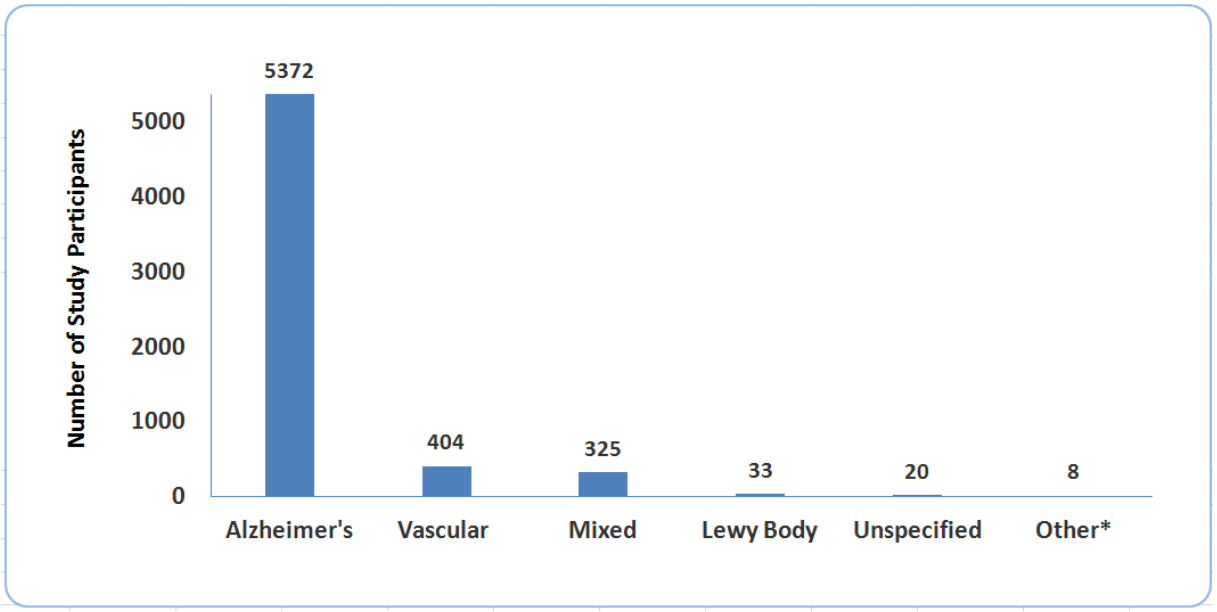
	FIXED DOSES REPORTED (Routes of administration)	FLEXIBLE DOSES REPORTED (Routes of administration)
Quetiapine	• **100 mg/d** (oral tablet) • **200 mg/d** (oral tablet)	• **0-200 mg/d** (oral capsule) • **25-225 mg/d** (oral) • **25-400 mg/d** (oral) • **25- 600 mg/d** (oral capsule) • **50-100 mg/d** (route unspecified) • **50-300 mg/d** (oral tablet, *k=4;* two of which were either extended release (XR) and immediate release (IR) oral tablets) • **50-400 mg/d** (oral)
Olanzapine	• **1 mg/d** (oral capsule) • **2.5 mg/d** (oral capsule; IM after 2 hours) • **4.71 mg** (average oral capsule dose at start of study period II) • **5 mg/d** (oral capsule; tablet; IM after 2 hours) • **7.5 mg/d** (oral capsule) • **10 mg/d** (oral tablet) • **15 mg/d** (oral tablet)	• **0-17.5 mg/d** (oral capsule) • **2.5-10 mg/d** (oral; route unspecified, *k=2*) • **5-10 mg/d** (oral)
Aripiprazole	• **2 mg/d** (route unspecified) • **5 mg/d** (IM; route unspecified) • **10 mg/d** (IM; route unspecified) • **15 mg/d** (IM)	• **2-15 mg/d** (route unspecified)
Active Comparator: Haloperidol	• **1.75 mg** (average oral capsule dose at start of study period II)	• **0.5-2 mg/d** (oral tablet) • **0.5-4 mg/d** (oral; oral solution) • **0.5- 12 mg/d** (oral capsule) • **1-6 mg/d** (oral capsule; oral tablet)
All Other Active Comparators	• **Rivastigmine, 6 mg/d** (oral capsule) • **Escitalopram**, **10 mg/d** (oral tablet) • **Lorazepam**, **1.0 mg** (after 2 hrs IM)	• **Rivastigmine, 6 - ≥ 9 mg/d** (route unspecified) • **Citalopram**, **10-40 mg/d** (oral capsule) • **Topiramate**, **25-50 mg/d** (oral tablet) • **Fluvoxamine**, **25-200 mg/d** (oral) • **Promazine**, **50-100 mg/d** (oral)

Study Participants and Setting

Analysis of the patient characteristics from the 32 included studies reporting outcome data of interest revealed an elderly, mostly female, patient population. Overall, 68% of participants were female and the mean age of all study participants was 80 ± 8.5 (SD) years.

As illustrated in **Error! Reference source not found.**, the three most common types of dementia diagnosed in study participants were Alzheimer's Disease (AD), vascular and mixed dementia (a combination of AD and VD). Most of the participants had AD (87.2% of participants).

Exhibit 7: Breakdown of Dementia Diagnosis across included studies



* Includes a diagnosis of viral encephalitis, subdural hematoma, multi-infarct dementia, fronto-temporal lobe dementia, dementia syndrome, or Lewy Body disease (number of patients in each group could not be determined)

One study (23) reported that all 29 participants had been diagnosed with AD, however, the criteria used to form that diagnosis was not reported. Of the remaining 31 studies that did report this information, five different types of criteria were used. These included: 1) the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) and its 'text revision' form (DSM-IV-TR), the 2) National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), 3) the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), as well as the 4) National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences. Finally, one study (35) confirmed a diagnosis of AD in its study participants using criteria as defined by Jest and Finke (2000) (55).

Just under half of included studies (49%) used the DSM-IV exclusively to make a dementia diagnosis, while six (19%) studied used criteria set out by both the DSM-IV and the NINCDS-ADRDA to assess this type of baseline diagnosis in participants. In two studies (22, 46) the ICD-10 criteria were used exclusively to form a dementia diagnosis in participants.

Across all studies, participants were based in three types of care settings: *Long term care* (nursing homes, assisted living facilities, and long term care facilities), *hospital* (inpatients), and the *community* (outpatients, participants living with a caregiver, or those living in their own homes). The most common RCT setting was long term care (34%). Three studies each reported that participants resided only in hospitals (24, 33, 46), or the community (31, 32, 48). Four studies did not define the care setting (22, 23, 26, 34).

Results Overview: Efficacy and Safety Outcomes

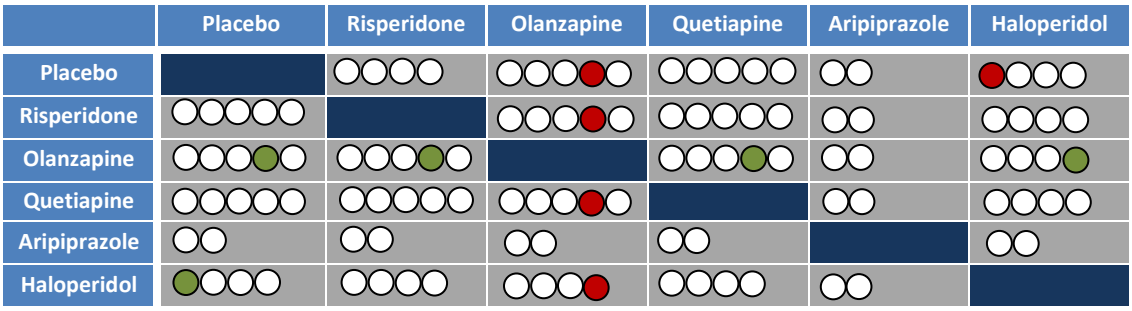
A set of network meta-analyses were conducted for five efficacy outcomes (including three subscale BPSD outcomes), and four safety outcomes.

Efficacy

Network meta-analyses were conducted for BPSD, three BPSD subscale measures (psychosis, aggression, and agitation), Global Measures/Impressions, Cognition, Activities of Daily Living, and Caregiver Burden. The choice of these outcomes for NMA was based on their importance and the sufficiency of the data available to derive robust network models.

Exhibit 8 provides an overall summary of the NMA results for both head-to-head and placebo comparisons across the AAPs and haloperidol for the five efficacy outcomes at end of study.

Exhibit 8: Comparisons Across AAPs, Placebo, and Haloperidol for the Efficacy Outcomes: BPSD, Global Measures/Impressions, Cognition, Activities of Daily living, and Caregiver Burden at End of Study



The five contiguous circles correspond, from **LEFT** to **RIGHT** (respectively) to five efficacy outcomes: **BPSD (overall), Global Measures/ Impressions, Cognition, Activities of Daily Living,** and **Caregiver Burden**

- A **green circle** indicates that the "row" AAP is **significantly (statistically) better** compared with the "column" AAP
- A **red circle** indicates that the "row" AAP is **significantly (statistically) worse** compared with the "column" AAP
- An **open circle** indicates that there is **no statistically significant difference** between the "row" and "column" AAP
- A **missing circle** indicates that the **outcome was not available** for analysis

Results for each of the five outcomes reported in Exhibit 8 are discussed separately below.

Behavioural and Psychological Symptoms of Dementia (BPSD): Overall and Sub-scale Analyses

Two NMAs were completed for BPSD: 1) efficacy of individual AAPs as measured by total BPSD score on the outcome scale, and 2) efficacy of individual AAPs using three BPSD subscales: psychosis, agitation, and aggression.

The results for each are presented below.

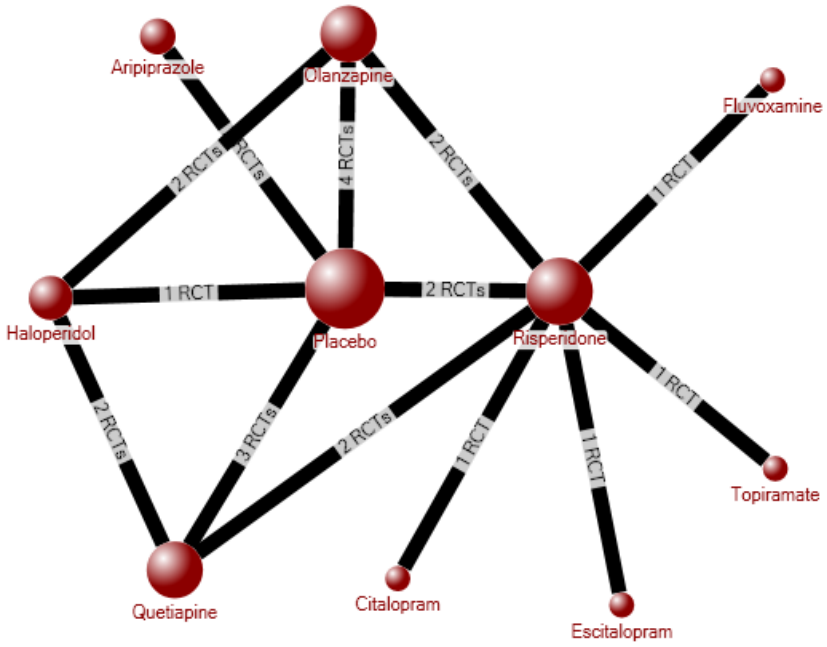
Behavioural and Psychological Symptoms of Dementia (BPSD): Overall Analyses

Nearly all studies (30/32 or 94%) that reported an outcome of interest also reported at least one outcome scale measuring change in BPSD. A variety of scales were reported; however, to preserve

clinical homogeneity, only BPSD outcomes reported using th Neuropsychiatric Inventory (NPI), Neuropsychiatric Inventory- Nursing Home version (NPI-NH), and NPI-NH version 2 were considered for the NMA. Of the eighteen studies reporting these scales, only data from fifteen studies were analyzed. One study was excluded because of study duration (14 days) (53), and another due to insufficient data (22). Data from a five week trial were also excluded because of the intervention (immediate *vs*. extended release quetiapine (25)).

Following the NMA for BPSD, the standardized mean difference scores generated were converted back to the NPI-NH scale for reference. Exhibit 9 shows the most frequent comparator was placebo and the most frequent AAP was risperidone.

Exhibit 9: Geometry of the Evidence Network for BPSD (Total)



NMA results for BPSD (

Exhibit 10) show that haloperidol was the only treatment to significantly decrease NPI-NH scores when compared to placebo (random-effects model) (-5.46 (SD 2.37)). Lower scores indicate total improvement in BPSD. None of the other treatments, when compared against each other, showed significant improvement in behavioural symptoms.

Exhibit 10: BPSD- Mean Differences (SD) in NPI-NH Scores for All Treatment Comparisons (Random-Effects Model)

Placebo								
-1.46 (1.82)	Risperidone							
-1.82 (1.46)	-0.36 (1.82)	Olanzapine						
-2.18 (1.82)	-0.91 (2.18)	-0.36 (2.00)	Quetiapine					
-4.00 (2.37)	-2.73 (3.09)	-2.18 (2.73)	-1.82 (2.91)	Aripiprazole				
-5.46 (2.37)	-4.19 (2.91)	-3.64 (2.55)	-3.28 (2.55)	-1.46 (3.28)	Haloperidol			
-5.10 (6.01)	-3.64 (5.82)	-3.28 (6.01)	-2.73 (6.19)	-0.91 (6.55)	0.36 (6.55)	Fluvoxamine		
6.19 (6.73)	7.46 (6.37)	8.01 (6.73)	8.37 (6.73)	10.19 (7.10)	11.6 (7.10)	11.28 (8.55)	Escitalopram	
7.28 (6.92)	8.74 (6.55)	9.10 (6.92)	9.65 (6.92)	11.47 (7.28)	12.74 (7.10)	12.38 (8.74)	1.09 (8.92)	Topiramate
-8.37 (7.83)	-7.10 (7.46)	-6.55 (7.64)	-6.19 (7.83)	-4.37 (8.19)	-2.91 (8.01)	-3.46 (9.65)	-14.56 (9.65)	-15.65 (9.46)

Behavioural and Psychological Symptoms of Dementia (BPSD): Sub-scale Analyses

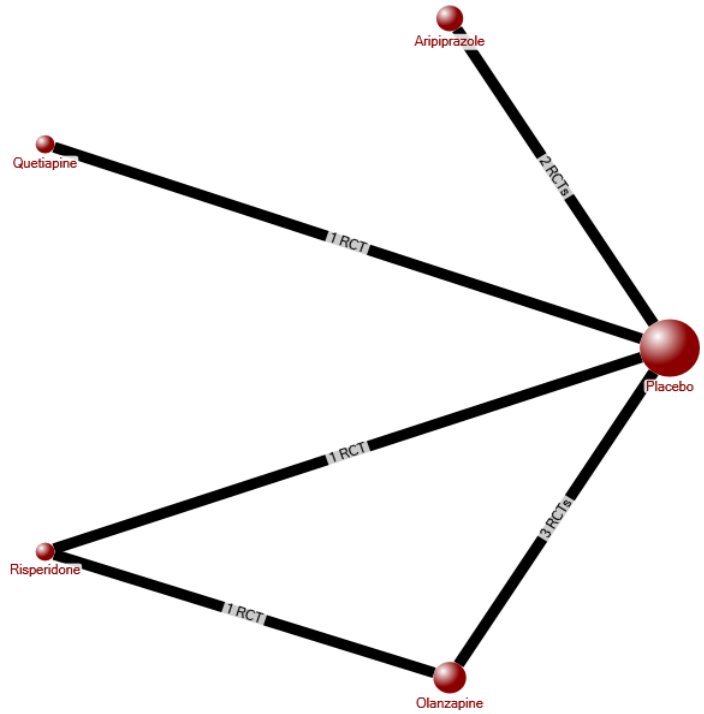
Three separate NMAs were conducted for psychosis, agitation, and aggression subscales. Results are presented below for each.

Behavioural and Psychological Symptoms of Dementia (BPSD): Psychosis

Fourteen studies (44%) reported patients' change from baseline on at least one psychosis subscale. As the most common subscales reporting psychosis outcomes were the NPI and NPI-NH, our NMA was limited to studies reporting psychosis using these subscales (k=6). Importantly, while one additional study (47) reported psychosis outcomes using the NPI-psychosis subscale, the questions that formed the basis of their measurement differed slightly from the other six. Accordingly, in an effort to preserve clinical homogeneity, data from this study was excluded from the analysis.

The geometry of the evidence network for psychosis is shown in Exhibit 11.

Exhibit 11: Geometry of the Evidence Network for BPSD- Psychosis



The NMA for psychosis showed no significant mean differences in any treatment compared to placebo, or when AAPs were individually compared head-to-head (random effects model) (Exhibit 12 **).**

Exhibit 12: BPSD- Psychosis- Mean Differences (SD) in NPI/NPI-NH Scores for All Treatment Comparisons (Random-Effects Model)

Placebo				
-0.10 (1.59)	**Risperidone**			
-0.38 (1.04)	-0.28 (1.57)	**Olanzapine**		
0.35 (1.93)	0.45 (2.49)	0.73 (2.19)	**Quetiapine**	
-0.48 (1.20)	-0.38 (1.98)	-0.10 (1.59)	-0.83 (2.27)	**Aripiprazole**

Behavioural and Psychological Symptoms of Dementia (BPSD): Aggression

A total of six studies (19%) reported a change in participants' level of aggression from baseline to end of study using at least one type of aggression subscale. Only data from studies using the BEHAVE-AD-

aggression subscale, when sufficient for analysis, were analyzed within our NMA for this outcome (k=4).

The most frequent comparator was placebo and the most frequent AAP was risperidone (Exhibit 13).

Exhibit 13: Geometry of the Evidence Network for BPSD- Aggression

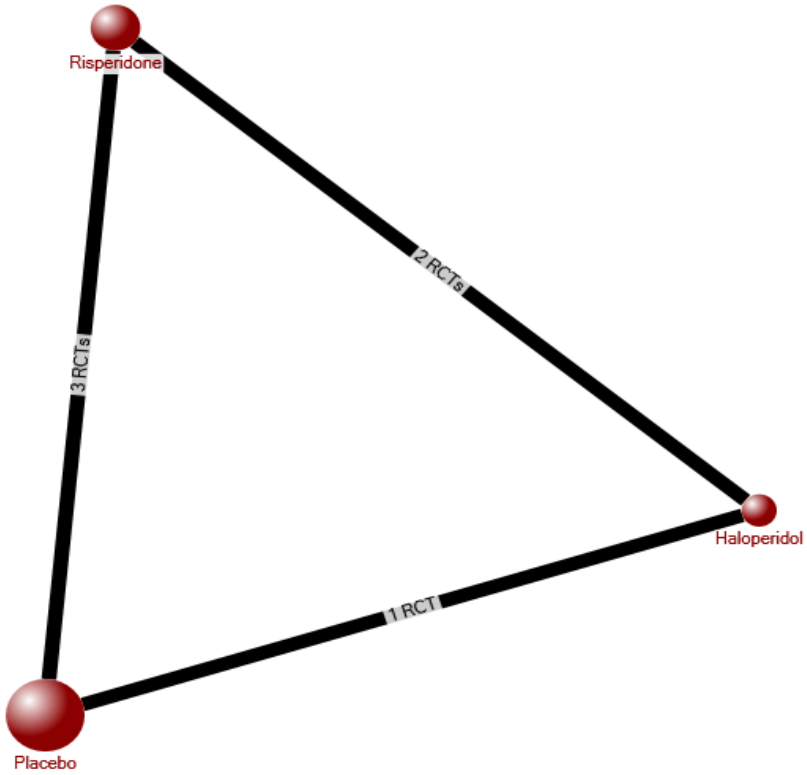


Exhibit 14 provides a summary of the NMA results for aggression. None of treatments, when compared against each other, showed significant improvement in aggression symptoms.

Exhibit 14: BPSD-Aggression- Mean Differences (SD) in the BEHAVE-AD Aggressiveness Subscale for All Treatment Comparisons (Random-Effects Model)

Placebo		
-0.75 (0.79)	**Risperidone**	
-0.32 (1.09)	0.44 (0.96)	**Haloperidol**

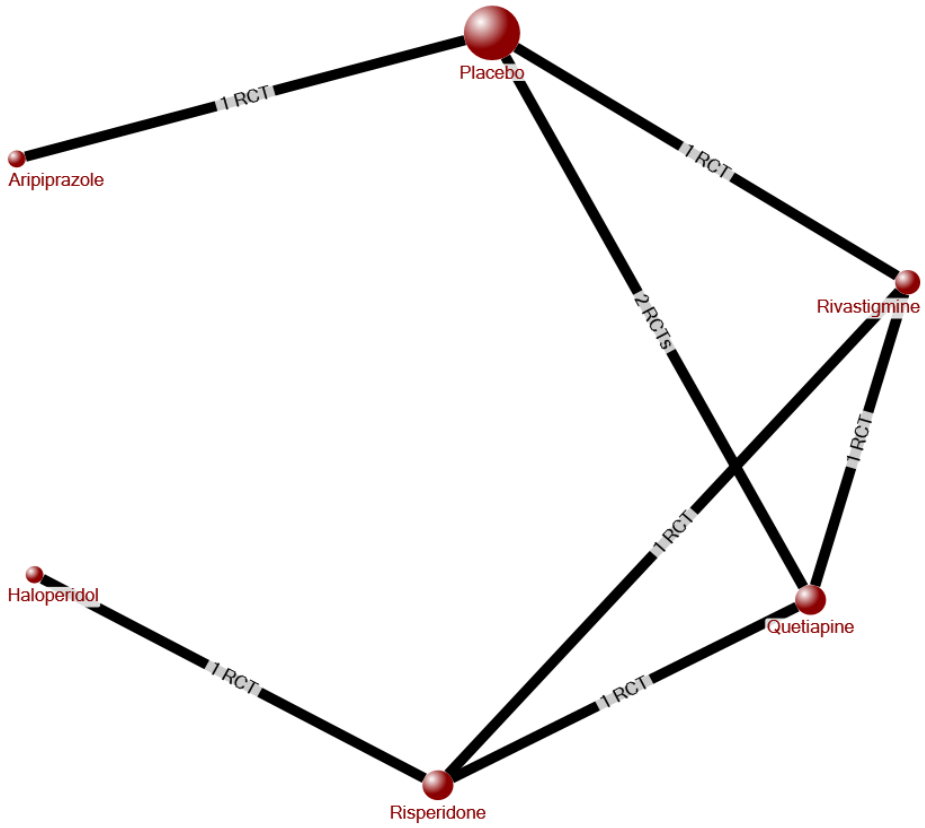
Behavioural and Psychological Symptoms of Dementia (BPSD): Agitation

Fifty-three percent of studies (k=17) reported a change in participants' level of agitation from baseline to end of study, as measured by at least one overall scale or subscale. Of the scales reported, the CMAI was the most common. As such, only data from those studies using the CMAI that was 'complete' (incorporable within the NMA), were analyzed in the baseline analysis (k=6).

The geometry of the evidence network for agitation is shown in

Exhibit 15.

Exhibit 15: Geometry of the Evidence Network for BPSD- Agitation



NMA results for agitation (

Exhibit 16) show that rivastigmine was the only treatment to significantly increase CMAI scores (equivalent to an increase in agitation) when compared to risperidone [(random effects model, MD 10.13 (SD 5.09)]. Caution is advised when interpreting these results, as data for rivastigmine was available from only one study (49) and effect variations may exist that are difficult to account for.

None of the other treatments, when compared against each other, showed significant improvement in, or worsening of, agitation symptoms.

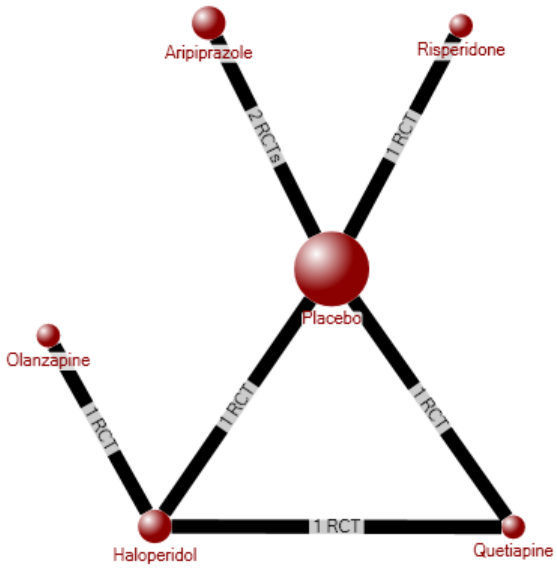
Exhibit 16: BPSD- Agitation- Mean Differences (SD) in the CMAI Scale for All Treatment Comparisons (Random-Effects Model)

Placebo					
-6.03 (4.85)	Risperidone				
-1.05 (3.27)	4.99 (3.77)	Quetiapine			
-3.30 (3.47)	2.73 (5.96)	-2.25 (4.75)	Aripiprazole		
-8.02 (6.23)	-1.98 (3.92)	-6.97 (5.43)	-4.72 (7.12)	Haloperidol	
4.10 (4.71)	**10.13* (5.09)**	5.15 (4.39)	7.40 (5.85)	12.11 (6.42)	Rivastigmine

Global Measures/Impressions

Fourteen studies (44%) reported at least one global impression outcome measure. To preserve clinical homogeneity, only change scores reported using the Clinical Global Impression - Severity (CGI-S) subscale were considered (7 RCTs). Two studies were excluded from analysis. One study (53) was excluded due to short trial duration (14 days) and another due to the interventions used (immediate *vs.* extended release quetiapine (25)). As shown in Exhibit 17, the most frequent comparator was placebo.

Exhibit 17: Geometry of the Evidence Network for Global Measures/Impressions



The NMA results for Global Measures/Impressions (Exhibit 18) showed no significant mean differences in any treatment compared to placebo or any other active comparators in the random-effects model.

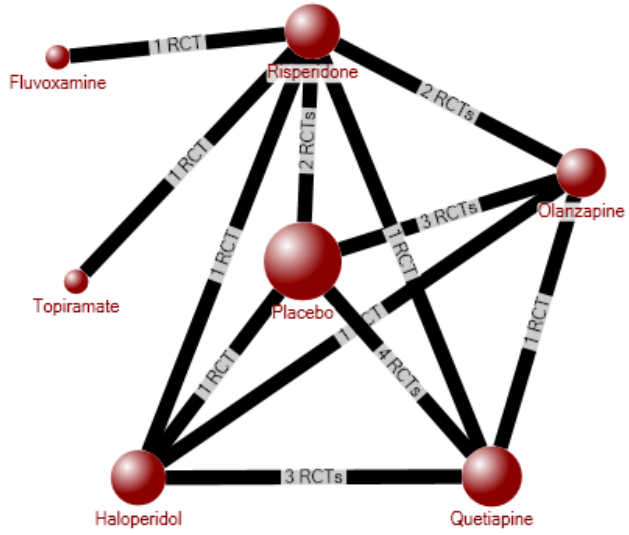
Exhibit 18: Global Measures/Impressions: Mean Differences (SD) in CGI-S Scores for All Treatment Comparisons (Random Effects Model)

Placebo					
-0.31 (1.77)	Risperidone				
0.22 (2.52)	0.52 (3.09)	Olanzapine			
-0.13 (1.79)	0.17 (2.54)	-0.35 (2.55)	Quetiapine		
-0.12 (1.27)	0.19 (2.18)	-0.33 (2.84)	0.02 (2.21)	Aripiprazole	
-0.06 (1.78)	0.24 (2.51)	-0.28 (1.79)	0.07 (1.79)	0.05 (2.18)	Haloperidol

Cognition

Twenty studies reported at least one cognition outcome of interest. The Mini Mental State Examination (MMSE) was the most commonly reported scale for this outcome (n=17 RCTs) and the analysis was limited to studies reporting this scale (Exhibit 19). Data from thirteen studies were included for analysis. One study was excluded because of short duration (24 hours) (52) and two others were excluded due to insufficient data (31, 43). A third study (25) was excluded due to the interventions used (immediate *vs.* extended release quetiapine).

Exhibit 19: Geometry of the Evidence Network for Cognition



The NMA results for the Cognition outcome (

Exhibit 20) showed no significant mean differences in any treatment compared to placebo or any other active comparators in the random-effects model.

Exhibit 20: Cognition: Mean Differences (SD) in MMSE Scores for All Treatment Comparisons (Random- Effects Model)

Placebo						
-0.06 (0.54)	Risperidone					
0.01 (0.44)	0.08 (0.54)	Olanzapine				
-0.29 (0.44)	-0.23 (0.60)	-0.31 (0.56)	Quetiapine			
-0.07 (0.61)	0.00 (0.69)	-0.08 (0.67)	0.23 (0.57)	Haloperidol		
0.43 (1.29)	0.49 (1.18)	0.41 (1.28)	0.72 (1.31)	0.49 (1.36)	Fluvoxamine	
-0.20 (0.97)	-0.13 (0.83)	-0.21 (0.98)	0.10 (1.02)	-0.13 (1.08)	-0.62 (1.45)	Topiramate

Activities of Daily Living

Four studies (33, 38, 46, 50) reported baseline to end of study differences in Activities of Daily Living. Data were reported using four different scales: the *Physical Self Maintenance Scale* (PSMS), the *Alzheimer's Disease Cooperative Study- Activities of Daily Living Inventory* (ADCS-ADL), the *Instrumental Activities of Daily Living Dimension of the Nurses' Observation Scale for Geriatric Patients* (NOSGER-IADL), as well as the *Functional Independence Measure* (FIM). Given that these scales are unique, we highlight the ADL items they are each said to measure:

- The **FIM** assesses thirteen items related to basic activities of daily living (*e.g.:* eating, grooming, and bathing, as well as toileting and stair climbing), but also includes an assessment of five items related to socio-cognition (comprehension, expression, social interaction, problem solving, and memory).

- The **PSMS** measures physical functioning across six different basic ADL items: toileting, feeding, dressing, grooming, physical ambulation, and bathing

- The **ADCS-ADL** is a twenty-three item scale that covers patients' abilities to perform basic (*e.g.:* eating, bathing, and toileting) to more complex (*e.g.* shopping and using the telephone) ADL activities.

- The **NOSGER-IADL** is a five-item subscale of the NOSGER, which measures patients' ability to perform what can be described as 'instrumental ADL outcomes'. These include: following favorite radio or television programs, attempting to keep his/her room tidy, shopping for small items (*e.g.* groceries), enjoyment of certain events (*e.g.* visits or parties), and whether or not the patient is orientated when in unusual surroundings.

The evidence network diagram for this outcome is shown in Exhibit 21.

Exhibit 21: Geometry of the Evidence Network for Activities of Daily Living

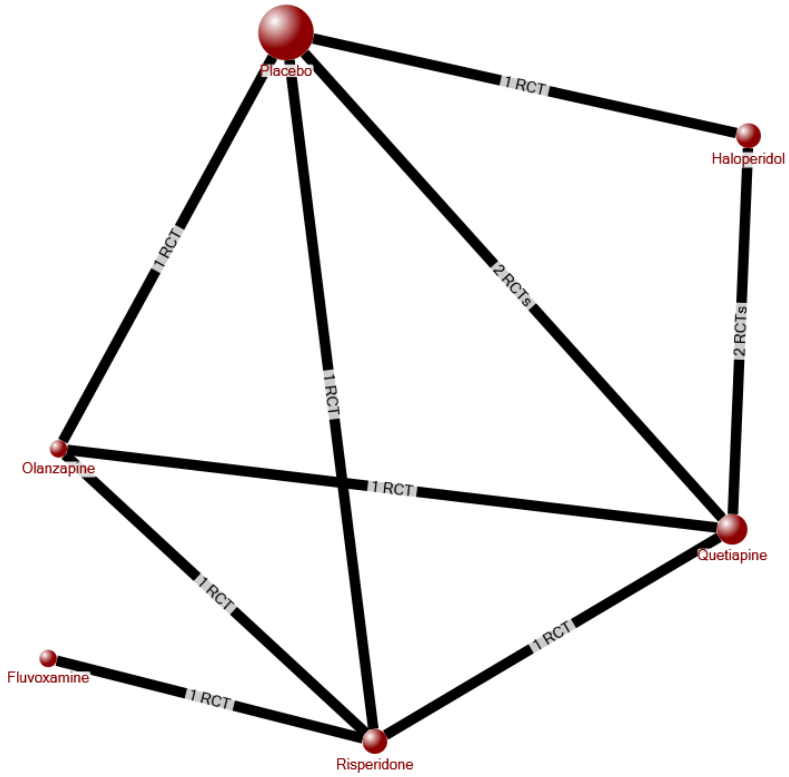


Exhibit 22 provides a summary of study level data for the four studies reporting ADL outcomes. Generally, patients treated with AAPs risperidone and olanzapine and active comparators haloperidol and fluvoxamine experienced worsening functional outcomes over the course of study treatment. In one study (38), quetiapine significantly improved ADL outcomes (PSMS scale). In another study (50), patients treated with placebo showed significant improvement in functional symptoms when compared to olanzapine.

Exhibit 22: Study Level Data: Activities of Daily Living

Study	Scale Used to Measure ADL*	Change from Baseline (SD) by Treatment	Study Significance
Teranishi *et. al.* (2013) (33)	FIM	**Risperidone, oral, 0.5-2.0 mg/d:** -1.4 (19.1) **Fluvoxamine oral, 25- 200 mg/d:** -4.48 (20.1)	No significant within-group changes from baseline were found.
Tariot *et. al.* (2006) (38)	PSMS	**Placebo, oral capsule:** -0.47 (2.24) **Quetiapine, oral capsule, 25mg/day - 600mg/day:** 0.01 (3.38) **Haloperidol, oral capsule, 0.5mgday - 12mg/day:** -1.59 (3.06)	Those treated with haloperidol had significantly worse functional outcomes compared to quetiapine ($p<0.05$)
Schneider *et. al.* (2006) (50)	ADCS-ADL	**Placebo, oral capsule:** 0.5 (8.4) **Risperidone (Risperdal), oral capsule, 0 -2.5mg/day:** -1.1 (8.8) **Quetiapine (Seroquel), oral capsule, 0 - 200mg/day:** -1.0 (7.7) **Olanzapine (Zyprexa), oral capsule, 0 - 17.5mg/day:** -6.1 (8.2)	Olanzapine was significantly worse than placebo at improving ADL ($p< 0.001$)
Savaskan *et. al.* (2006) (46)	NOSGER-IADL	**Quetiapine, oral, 25 - 225mg/day:** 2.0 (3.97) **Haloperidol, oral, 0.5 - 4mg/day:** -2.0 (4.0)	Significance not discussed. Those treated with quetiapine showed functional improvement.

* Higher scores in PSMS and NOSGER-IADL indicate worsening of functional ability, whereas higher scores in ADCS-ADL and FIM indicate improvement. For the sake of comparison, all change scores shown in this table have been adjusted such that higher (more positive) scores indicate improvement in functional ability.

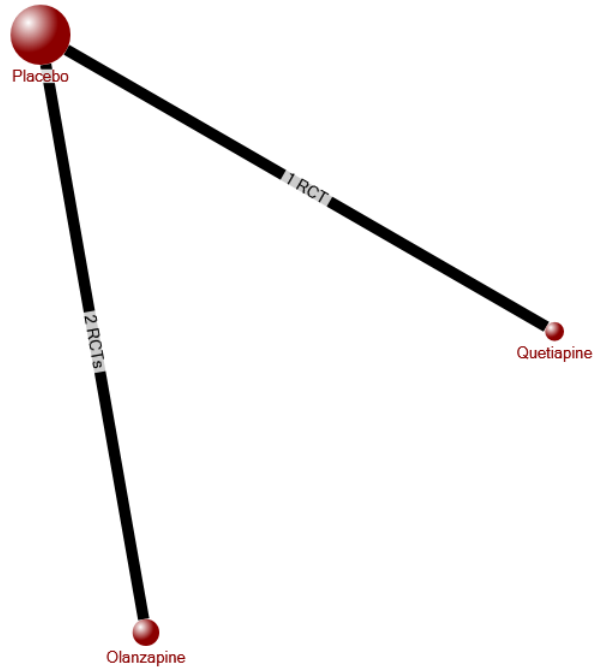
Data from each of these four scales (PSMS, FIM, and ADCS-ADL), and one subscale (NOSGER-IADL) were combined together within the NMA performed for this outcome. Preliminary NMA results from this analysis generated standardized mean difference scores from an NMA that were converted back to the PSMS scale for reference. Briefly, the random-effects model NMA for Activities for Daily Living showed that olanzapine significantly decreased PSMS scores (indicating improvement) compared with placebo, risperidone, and quetiapine. PSMS scores increased significantly (indicating a worsening of symptoms) with haloperidol when compared to patients taking olanzapine (mean difference: 5.23, SD 1.85).

Given the content diversity present across these four scales, as well as the small number of studies that reported data for this outcome, the results of this NMA should be interpreted with caution. The mechanism of action leading to these differences is unclear, and this may be a statistical anomaly and we continue to investigate.

Caregiver Burden

Six studies (27, 37, 39, 44, 50, 54) reported baseline to end of study differences in Caregiver Burden. Four studies (27, 37, 39, 54) reported this outcome using the *NPI Part 2 'Occupational Disruptiveness of Caregivers' subscale*, one study used the *Caregiver Activity Survey* (50)**,** another study (44) administered the *Modified Nursing Care Assessment Scale (Total Strain Domain).* Only data from the four studies reporting a caregiver burden outcome using the Occupational Disruptiveness subscale of the NPI were eligible for the NMA. During the data preparation process, the results from one study (54) were found to be disconnected from the network, and thus, were excluded from analysis.
The evidence network diagram for this outcome is shown in Exhibit 23.

Exhibit 23: Geometry of the Evidence Network for Caregiver Burden



The NMA results for the Caregiver Burden (

Exhibit 24) show no significant mean differences in any of the comparisons under the random-effects model.

Exhibit 24: Caregiver Burden: Mean Differences (SD) in the NPI-NH Occupational Disruptiveness Scale for All Treatment Comparisons (Random-Effects Model)

Placebo		
-1.20 (1.63)	**Olanzapine**	
-0.21 (2.40)	0.99 (2.89)	**Quetiapine**

Safety

A set of network meta-analyses were conducted for two continuous (Extrapyramidal Symptoms, or EPS, and Weight Change) and two dichotomous (falls and all-cause mortality) safety outcomes. Measures of treatment effect were reported using mean differences and their corresponding standard deviations for the continuous outcomes scales. The relative effect estimates for the dichotomous outcomes are presented as odds ratios and 95% credible intervals.

Exhibit 25 provides an overall summary of the NMA results for both head-to-head and placebo comparisons across the AAPs and haloperidol for the four safety outcomes at end of study. Previous reviews have found an association between AAPs and mortality; however the data from those reports were not readily available and could not be integrated into the NMA until verified. Results here should be interpreted with caution until these data are verified and appropriately incorporated into the network.

Exhibit 25: Comparisons Across AAPs, Placebo, and Haloperidol for the Safety Outcomes: Mortality, Falls, EPS, and Weight Change

	Placebo	Risperidone	Olanzapine	Quetiapine	Aripiprazole	Haloperidol
Placebo		○○○○	○○○○	○○○○	○○○○	○○●○
Risperidone	○○○○		○○○○	○○○○	○○○○	○○●○
Olanzapine	○○○○	○○○○		○○○○	○○○○	○○●○
Quetiapine	○○○○	○○○○	○○○○		○○○○	○○●○
Aripiprazole	○○○○	○○○○	○○○○	○○○○		○○○○
Haloperidol	○○●○	○○●○	○○●○	○○●○	○○○○	

The five contiguous circles correspond, from **LEFT** to **RIGHT** (respectively) to five efficacy outcomes: **Mortality (individual treatments), Falls, EPS** and **Weight Change** outcomes.

- A **green circle** indicates that the "row" AAP is **significantly (statistically) better** compared with the "column" AAP
- A **red circle** indicates that the "row" AAP is **significantly (statistically) worse** compared with the "column" AAP
- An **open circle** indicates that there is **no statistically significant difference** between the "row" and "column" AAP

Results for each of the four safety outcomes reported in Exhibit 25 are discussed separately below.

All-Cause Mortality: Individual Treatment Effects and Pooled Analysis

Two NMAs were conducted to evaluate the safety of AAPs for mortality. The first addressed individual treatment effects by comparing individual treatments to each other. For the second NMA, a pooled analysis was completed. Specifically, all AAPs, active comparators, and placebos were grouped together to form three broad comparator groups.

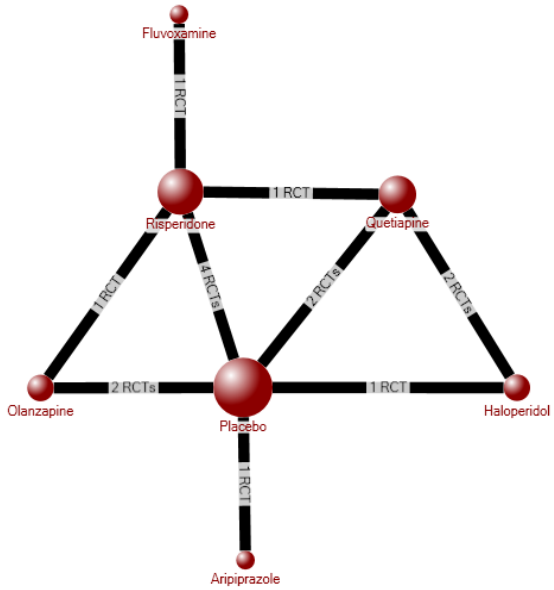
The results of each of these two NMAs are discussed separately in the following two sub-sections that follow directly.

All-Cause Mortality: Individual Treatments

Seventeen studies (53%) reported all-cause mortality; however, six studies (25, 29, 49-52) were excluded from analysis. Four studies were excluded due to short or long duration of treatment. Two additional studies were excluded from analysis due to the interventions used (immediate *vs.* extended release quetiapine (25), and because of a study design change (29).

Six of the eleven studies included in the treatment effects NMA reported all deaths occurring within the trial period (22, 31, 33, 36, 38, 44). Five trials (35, 37, 39, 40, 43) reported all deaths occurring during treatment period or within 30 days after trial completion. The geometry of the evidence network for this outcome is shown in Exhibit 26.

Exhibit 26: Geometry of the Evidence Network for All-cause Mortality (Individual Treatments)



Results for the all-cause mortality analysis by all treatments (

Exhibit 27) showed no significant increase in mortality in patients treated with placebo, any AAP, or

other active comparator.

Exhibit 27: All-cause Mortality (Individual Treatments): Odds Ratios (95% Credible Intervals) for All Treatment Comparisons (Random-Effects Model)

Placebo						
1.59 (0.88,2.98)	**Risperidone**					
2.00 (0.73,5.74)	1.26 (0.44,3.84)	**Olanzapine**				
1.39 (0.58,3.89)	0.88 (0.31,2.69)	0.70 (0.18,2.63)	**Quetiapine**			
7.01 (0.82,145.10)	4.50 (0.46,95.09)	3.56 (0.33,86.25)	4.92 (0.50,118.30)	**Aripiprazole**		
1.78 (0.53,7.42)	1.09 (0.31,4.95)	0.89 (0.18,4.30)	1.27 (0.41,3.94)	0.25 (0.01, 3.13)	**Haloperidol**	
0.39 (0.01,8.62)	0.24 (0.01,4.90)	0.20 (0.00,4.44)	0.26 (0.01,7.49)	0.05 (0.00,2.78)	0.21 (0.00,5.93)	**Fluvoxamine**

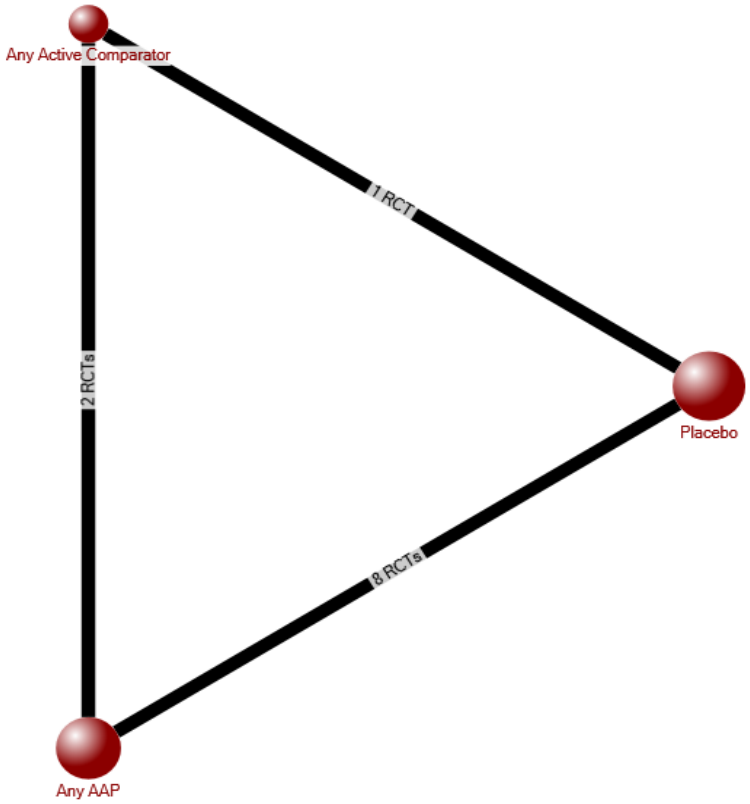
All-Cause Mortality: Pooled Analysis

In the pooled analysis for all-cause mortality, risperidone, olanzapine, quetiapine, and aripiprazole were grouped together as a single AAP treatment group. Likewise, haloperidol and fluvoxamine were combined to form a single active comparator group.

Rainer *et al.* (2007) (31) was excluded from this analysis as it completed a head-to-head randomized controlled trial comparing the efficacy and safety of risperidone to quetiapine. The combination of these two arms (as individual AAPs) left no comparator group, and thus, data that was unincorporable within the pooled mortality NMA.

The most frequent AAP comparator was placebo (Exhibit 28)

Exhibit 28: Geometry of the Evidence Network for All-cause Mortality (Pooled Analysis)



Results of the pooled analysis for all-cause mortality (Exhibit 29) show a significant increase in the odds of mortality in patients treated with any AAP when compared to placebo. None of the other treatments, when compared against each other, showed a significant increase in the odds of mortality.

Exhibit 29: All-Cause Mortality (Pooled Analysis): Odds Ratios (95% Credible Intervals) for All Treatment Comparisons (Random-Effects Model)

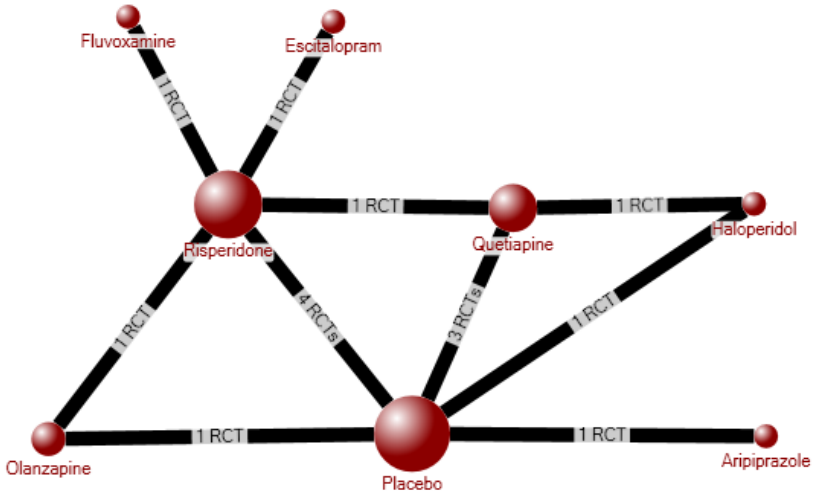
Placebo		
1.90* **(1.19, 3.16)**	**Any AAP**	
2.01 (0.69, 5.82)	1.05 (0.38, 2.77)	**Any Active Comparator**

Falls

Nineteen studies reported data on falls and eleven were included in the NMA. Three of the eight studies excluded from the analysis (25, 41, 42) reported falls as an outcome without presenting data that could be used in the analysis (*e.g. "Adverse events occurring in ≥ 10% of patients in any one group were*

falls…") (41). Three studies (22, 27, 50) reported falls as part of a composite outcome (e.g. all 'accidental injuries' reported, which included falls or fractures) and the exact number of falls occurring in each study arm could not be elucidated. Two studies (52, 53) were excluded due to a short study duration (24 hours (52) and 14 days (53)**.** The geometry of the evidence network for this outcome is shown in Exhibit 30.

Exhibit 30: Geometry of the Evidence Network for Falls



NMA results for falls (Exhibit 31) showed no significant differences in falls in patients treated with placebo, AAP, or any other active comparators under the random-effects model.

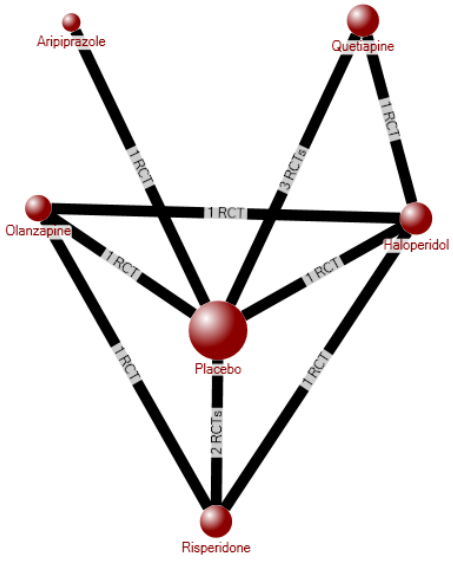
Exhibit 31: Falls: Odds Ratios (95% Credible Intervals) for All Treatment Comparisons (Random-Effects Model)

Placebo							
0.92 (0.67,1.29)	Risperidone						
1.31 (0.65,2.75)	1.42 (0.71,2.87)	Olanzapine					
0.96 (0.61,1.54)	1.04 (0.59,1.79)	0.73 (0.30, 1.69)	Quetiapine				
1.53 (0.47,5.33)	1.66 (0.47,5.93)	1.16 (0.29,4.97)	1.59 (0.44,5.98)	Aripiprazole			
0.98 (0.51,1.86)	1.07 (0.50,2.17)	0.76 (0.28,1.95)	1.02 (0.52,2.03)	0.65 (0.16,2.52)	Haloperidol		
0.79 (0.05,9.10)	0.86 (0.05,9.64)	0.60 (0.03,8.18)	0.82 (0.04,9.91)	0.52 (0.02,8.05)	0.81 (0.04,10.38)	Fluvoxamine	
0.15 (0.01,1.82)	0.16 (0.01,1.97)	0.11 (0.00,1.63)	0.15 (0.01,2.02)	0.10 (0.00,1.53)	0.15 (0.01,2.06)	0.17 (0.00,7.69)	Escitalopram

Extrapyramidal Symptoms (EPS)

Twenty-two studies reported at least one outcomes scale measuring EPS. A total of six different scales measuring baseline to endpoint change scores in EPS were reported. Of these, the *Simpson-Angus Scale* (SAS) was the most frequently reported (11 RCTs) and studies reporting the SAS were included in the NMA for this outcome. Data from eight studies were included (Exhibit 32). Data from two studies (53, 56) were excluded due to duration of study (24 hours and 2 weeks) and one study (31) was excluded due to insufficient data. The geometry of the evidence network for this outcome is shown in Exhibit 32.

Exhibit 32: Geometry of the Evidence Network for EPS



Compared to placebo, SAS scores increased significantly in patients treated with haloperidol (MD 3.57 (SD 0.78) (Exhibit 33). Positive scores indicate worsening EPS while negative scores indicate improvement. SAS scores also increased significantly in the haloperidol group when compared to risperidone and quetiapine. Olanzapine showed significant improvement in EPS when compared to haloperidol (MD-2.86 (SD 0.98)).

Exhibit 33: EPS: Mean Differences (SD) in the SAS scale for All Treatment Comparisons (Random-Effects Model)

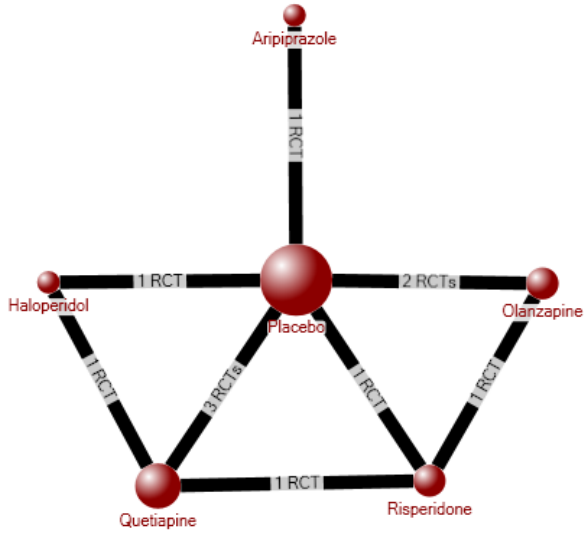
Placebo			
1.12 (0.65)	Risperidone		
0.71 (0.89)	-0.40 (0.87)	Olanzapine	
-0.10 (0.63)	-1.22 (0.87)	-0.81 (1.05)	Quetiapine

0.69 (1.16)	-0.42 (1.33)	-0.02 (1.46)	0.79 (1.32)	**Aripiprazole**	
3.57 **(0.78)**	**2.46** **(0.76)**	**2.86** **(0.98)**	**3.67** **(0.91)**	2.88 (1.39)	**Haloperidol**

Weight Change

Nine studies (Exhibit 34) reported a change in participants' mean weight (in kilograms (kg)) from baseline to end of study and seven studies were included in the NMA. Two studies were excluded from the analysis, one due to differences in the interventions studied (immediate *vs*. extended release quetiapine) (25) and the other (50) due to insufficient data.

Exhibit 34: Geometry of the Evidence Network for Weight Change



The NMA results for weight change (

Exhibit 35) showed no significant differences in any AAP when compared to placebo or any other active comparators under the random-effects model.

Exhibit 35: Weight Change (Kg): Mean Differences (SD) for All Treatment Comparisons (Random-Effects Model)

Placebo

0.28 (0.79)	**Risperidone**				
0.99 (0.65)	0.71 (0.83)	**Olanzapine**			
0.72 (0.62)	0.43 (0.91)	-0.28 (0.87)	**Quetiapine**		
0.50 (0.90)	0.21 (1.20)	-0.50 (1.11)	-0.22 (1.11)	**Aripiprazole**	
0.01 (0.89)	-0.27 (1.15)	-0.98 (1.09)	-0.71 (0.90)	-0.49 (1.27)	**Haloperidol**

DISCUSSION

Bayesian NMA allows for inferences into the comparative effectiveness of interventions that have been directly and indirectly evaluated against each other. A meta-analysis, by contrast, allows only for inferences to be made about the comparative effectiveness of interventions that have been directly evaluated against each other. Previous reviews have employed meta-analyses (15, 82-84) in examination of research questions similar to those investigated here. To our knowledge, this is the first NMA providing a comprehensive evaluation of currently available evidence on the efficacy and safety of AAPs in elderly men and women with dementia and BPSD.

We conducted a series of NMAs to compare AAPs for their efficacy and safety across nine different outcomes (five efficacy and four safety). Our analyses included data from placebo controlled, head-to-head, and active-controlled trials. While other reviews of multiple AAPs (15, 82-84) have limited their analyses to placebo-controlled trial data, head-to-head trials, or trials with haloperidol as an active control, we included all available active comparators in our analyses, including combination treatments.

Efficacy

Behavioural and Psychological Symptoms of Dementia: Overall Analysis

Our results showed that haloperidol significantly reduced behavioural symptoms when measured by overall NPI scores and compared to placebo. None of the other treatments evaluated, when compared against each other, showed significant improvement in overall behavioural and psychological symptoms as assessed using NPI scores.

Evidence relating to the efficacy of AAPs on BPSD differs across existing reviews. At least one drug class review (15) found that risperidone had a significant effect on reducing BPSD in elderly populations with dementia. This review also concluded that aripiprazole was no more effective in reducing BPSD than placebo, whereas Ma *et al.* (82) found a significant difference in the efficacy of aripiprazole for BSPD versus placebo. We found no significant difference in the efficacy of aripiprazole compared to placebo for BPSD. Further, our analysis revealed no significant difference with regard to the efficacy of quetiapine when compared to placebo in reducing BPSD - supporting conclusions reached by AHRQ. The study by Ma *et al.* (82), by contrast, concluded that quetiapine was more efficacious in reducing behavioural symptoms in elderly patients with BPSD when compared to placebo.

It is worth noting that our analysis approach for BPSD (overall) differed from those of previous reviews. Our analysis of BPSD symptoms was based entirely on overall (or total) NPI scores - the most widely used neuropsychiatric scale measuring behaviour in AD (85). Others (AHRQ included), combined more than one overall BPSD scale in their analyses (*e.g.* BEHAVE-AD total scores were used in combination with NPI total scores).

Behavioural and Psychological Symptoms of Dementia: Subscale Analyses

Although BPSD subscales may not be psychometrically-tested, there is a suggestion through related recommendations from Canadian clinical practice guidelines and expert opinion (86) that these subscales are likely more sensitive to differences in the individual agents (as opposed to the overall score).

In general, we found no significant mean differences in any AAP treatment compared to placebo, or when AAPs were themselves compared head-to-head across psychosis, aggression, or agitation outcomes. The only significant finding was with respect to agitation, where rivastigmine was found to significantly increase CMAI scores (indicating a worsening of agitation symptoms) when compared to risperidone (random effects model, MD 10.13 (SD 5.09). As this finding is based on data from a single study, it may not be generalizable to the wider study population.

Ma *et. al.* (2014) (82) meta-analyzed CMAI change scores from placebo controlled AAP trials and found that CMAI scores for patients taking risperidone significantly improved compared to those who took placebo. It is worth noting that our analysis approach for this outcome differed from Ma *et al.* (2014) in that their analysis incorporated CMAI- aggression subscale change scores within their analysis when overall scores were not provided by the primary article. By contrast, we restricted our NMA to overall CMAI scores, which could account for the differences in conclusions reached.

AHRQ (15) completed meta-analyses of placebo controlled AAP trials measuring mean change (from baseline to study endpoint) in participants' agitation and psychosis symptoms. Again, whereas AHRQ incorporated a variety of scales and subscales within each of their analyses, we limited our analyses to a single, representative, scale for each outcome. The AHRQ report found that patients who received risperidone showed significantly improved agitation and psychosis symptoms compared to those who took placebo. Our analysis, in contrast, showed no such differences. Indeed, the contrasting approaches taken to perform the analyses could account for the differences in findings across these subscale outcomes.

Global Measures/Impression

Our NMA results for global measures/impression showed no significant mean differences in any agent compared to placebo or any other active comparator. There are two distinct categories of global impression measurements: severity and degree of change, as judged by clinician interview. In an effort to preserve clinical homogeneity, we limited our base-case NMA for this outcome to data reported using the CGI-S (severity scale). This decision resulted in a small number of studies (n=5) being included in our analysis.

Our results for this outcome may be attributable to differences in included studies when compared to previous reports of this outcome; however, we believe that the small number of studies best reflects the evidence base for CGI-S. Ma *et al.* (82) analyzed both change and severity scales of the CGI for this outcome compared to placebo and found significant improvement in patients assigned to aripiprazole

and risperidone in five included studies. AHRQ (15) did not report this outcome. We included only 3 of the 5 studies included in the Ma *et al.* analysis, in addition to 2 other studies not included in Ma *et al*. One study (30) was excluded from analysis due to study design (switch to open label) and another (43) due to missing end-of-study data for the CGI-S outcome.

Cognition

The results of our NMA showed no significant mean differences in any treatment compared to placebo or any other active comparators in the random-effects model of 12 included studies. Cognition was not studied in many previous reviews (15, 82-83); however, Schneider (2006) (84) meta-analyzed MMSE scores in seven placebo controlled RCTs of four AAPs. They concluded that aripiprazole, olanzapine, and risperidone significantly worsened cognition as measured by MMSE, although findings for aripiprazole were based on a single RCT and two studies of risperidone.

Activities of Daily Living and Caregiver Burden

The NMA for Activities for Daily Living is based on a composite pooling of outcomes across four unique ADL scales. Results showed that olanzapine significantly decreased PSMS scores (indicating improvement) compared with placebo, risperidone, and quetiapine. PSMS scores increased significantly (indicating a worsening of symptoms) with haloperidol when compared to patients taking olanzapine (mean difference: 5.23, SD 1.85).

Results for both ADL and caregiver burden should be interpreted with caution. The outcome scales are diverse and have differing psychometric properties (ADL). Further, a small number of studies were available for analyses (ADL and caregiver burden). The mechanism of action leading to differences in ADL for olanzapine is unclear and we are unsure if these results may be a statistical anomaly.

Safety

All-cause Mortality: Individual Effects and Pooled Analysis

The increased risk of mortality associated with AAPs in this population is well documented in the literature, and noted in the individual product monographs. Further, Health Canada has also issued warnings for these treatments (89). Our pooled analysis of all-cause mortality in patients who took any AAP compared to those who took placebo or any active comparator showed a similar trend. Specifically, we found that participants who took any AAP had 1.9 times the odds of death from any cause (95% Crl 1.19, 3.16) compared to those who took placebo.

Previously completed pooled analyses of mortality in patients who took any AAP compared to those who took placebo showed a similar risk increase: OR 1.54, 95% CI 1.06 to 2.23 (83) and OR 1.52, 95% CI 1.06, 2.18 (82). A meta-analysis of RCTs by the US Food and Drug Administration (using data not in the public domain) also suggested a significant increase in mortality (OR 1.7) (88).

With respect to individual treatment effects, our NMA showed no significant increase in mortality across patients treated with placebo, any individual AAPs, or active comparator. Ma (82) and Schneider (83)

also examined all-cause mortality with respect to individual treatment comparisons and found no significant increase in the odds of mortality across any comparison of aripiprazole, olanzapine, quetiapine or risperidone to placebo.

Differences were noted, however, in event data reported in studies analyzed in both Ma (2014) (82) and Schneider (2005) (83) that we continue to explore. Specifically, Ma *et al*. (82) included a study by De Deyn (1999) (41) reporting one death in the risperidone group, and five deaths in the placebo group. Three independent clinical reviewers examined the publication and found no deaths were directly reported in the primary publication. Following a thorough reference check, we located a related pooled analysis (87) reporting mortality data in the De Deyn *et al.* (41) study; however, we could not confirm results based on the data supplied in the pooled analysis.

Both Ma and Schneider *et al*. (82-83) recorded six deaths in the olanzapine group and no deaths in the placebo group of an RCT by Street (2000) (27). This study was not included in our analysis as mortality data was not explicitly reported in the primary publication or any of its companion articles. References for the mortality data pointed to conference proceedings no longer in print (2004). We continue to endeavor to clarify these results by following up with industry and study authors before we consider including them in our analysis.

Falls

We found no significant differences in the number of falls in elderly patients with BPSD and dementia who were treated with placebo, AAP, or any other active compactor under the random-effects model. Similar reviews (82) for this outcome also found no important differences in risk of falls in elderly adults taking olanzapine, quetiapine, or risperidone when compared to placebo. Their pooled analysis of all AAPs compared to placebo also revealed no significant increase in falls. Similarly, our NMA revealed no significant differences across all drug comparisons.

It may be worth noting that although our findings agree with regard to significance, we noted that falls data used in Ma *et al.* (82) were similar to ours with the exception of one study, Deberdt (2005) (36). Specifically, zero falls were recorded in the risperidone group, four in the olanzapine group and two in the placebo group. These numbers do not match with the data extracted from the same study based on percentages provided in the primary publication.

Although an increase in falls has been documented in large, observational cohorts of dementia patients, we were unable to confirm these findings with evidence from RCTs. Although RCTs protect well against sources of bias that can be found in their non-randomized counterparts, reporting of adverse events is uneven, and limited by the duration and focus of the studies (90). Additionally, although we identified 19 studies that reported falls, data from only 11 of those studies could be included in the NMA. For example, some studies (25, 41, 42) reported falls as an outcome without presenting data that could be incorporated within our analysis (*e.g. "Adverse events occurring in ≥ 10% of patients in any one group were falls…")* (41). Three additional studies (22, 27, 50) reported falls as part of a composite outcome

(*e.g.* all 'accidental injuries' reported, which included falls or fractures) thus, the exact number of falls occurring in each study arm could not be elucidated.

Extrapyramidal Symptoms

We examined the safety of AAPs with regard to their role in the development of EPS by analyzing changes from baseline to end of study on the Simpson Angus Scale (SAS). This ten-item instrument assesses a variety of symptoms, such as: gait, head dropping, salivation, and tremor. We identified three previously published systematic reviews that also analyzed the relationship between AAPs and EPS (15, 82, 84)), however, these studies used binary or adverse 'event' data to complete each of their meta-analyses for this outcome.

Our NMA results for EPS showed no significant differences in any AAP when compared to placebo under the random-effects model. When compared to placebo, however, SAS scores increased significantly in patients treated with haloperidol (MD 3.57 (SD 0.78)). SAS scores also increased significantly in the haloperidol group when compared to risperidone and quetiapine, and olanzapine showed significant improvement in EPS when compared to haloperidol (MD-2.86 (SD 0.98)). These results are not unexpected given that the incidence of EPS symptoms resulting in use first generation antipsychotics is well-documented (91).

Due to differences in the type of data considered and analysis approach, it is difficult to directly compare our results with those in previous reviews.

Weight Change

Our NMA results for weight change showed no significant differences in any AAP when compared to placebo or any other active comparators under the random-effects model. Our approach using continuous outcome data (mean increase or decrease in weight over the trial period) differed from the AHRQ drug class review (15), which addressed weight using binary event data (number of patients whose weight increased or decreased). As a result, we can only compare our results at a very high level.

AHRQ noted that olanzapine significantly increased appetite or weight in patients who took olanzapine compared to those who took placebo. The authors also found a similar significant trend when comparing risperidone to placebo, while we did not reach the same conclusion.

We present results for weight change as a safety outcome; however, it is difficult to discuss weight without specifically addressing subgroups of elderly patients who may find either benefit or harm with a change in weight. In the frail elderly, even a small weight loss can be dangerous to their health and validates a safety concern. Conversely, weight gain may be beneficial in this same population. Further weight gain may be a safety issue in obese individuals or those with other medical complications. Additional investigation into subgroups may be warranted for future reviews to clarify the impact of weight change on elderly patients with dementia.

Community Setting Subgroup Analysis

We continue to explore opportunities for meaningful subgroup analyses with respect to community setting (long term care and community). The findings from such analyses will be described in our full technical report.

Conclusions

Efficacy evidence from this review suggests that there is limited benefit from the use of AAPs in elderly patients with BPSD, although further investigation is warranted to explore differences in the individual symptom scales, notably for BPSD. Given the concern over increased risk of death noted in the product monographs and in warnings from Health Canada and the US FDA, clinical judgment is required when applying these research findings to every day practice.

KEY MESSAGES

Efficacy

Behavioural and Psychological Symptoms of Dementia:

- In general, there were no significant differences in the improvement of BPSD with the AAPs (risperidone, quetiapine, olanzapine, aripiprazole) when compared to placebo.
- Haloperidol was the only agent significantly better than placebo in improving BPSD (MD: -5.46, SD 2.37) on the Neuropsychiatric Inventory-Nursing Home edition Scale.
- In elderly patients with dementia and BPSD, none of the AAPs compared showed significant overall symptom improvements when compared to each other or haloperidol.
- Rivastigmine is significantly worse than risperidone in reducing agitation (MD: 10.13, SD 5.09). As data for rivastigmine was available from only one study, caution is advised when interpreting these results.
- Generally, there were no significant differences in the improvement of agitation or psychosis with the AAPs (risperidone, quetiapine, olanzapine, aripiprazole) when compared to placebo, each other, or with any other active comparator.

Global Impressions/Impressions, Cognition, and Caregiver Burden:

- There were no significant differences amongst the AAPs in the improvement of Global Measures/Impressions, Cognition, or Caregiver Burden outcomes when compared to placebo or any other active comparator.

Activities of Daily Living:

- Olanzapine is significantly better than placebo, risperidone, quetiapine and haloperidol for improving Activities of Daily Living outcomes in elderly patients with dementia. The mechanism of action leading to these differences is unclear, and may be a statistical anomaly. We continue to investigate this result.

Safety

All-cause Mortality, Falls, and Weight Change:

- In general, there are no significant differences in all-cause mortality, falls or weight change when comparing AAPs to placebo or any other active comparator.
- There is an increased risk of all-cause mortality in the elderly with dementia and BPSD who take any AAP compared to those who take placebo (OR: 1.9, CI 1.19, 3.16).

Extrapyramidal Symptoms:

- Haloperidol was the only agent to significantly increase EPS symptoms in elderly patients with dementia experiencing BPSD compared to placebo, risperidone, quetiapine, or olanzapine.

Appendix A: Literature Search Strategy

AAP – Dementia – Elderly
2014 Oct 10 – Final Strategy

Database: Embase Classic+Embase <1947 to 2014 October 09>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, PsycINFO <1806 to October Week 2 2014> Search Strategy:
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1 exp Dementia/ (420833)
2 (dement* or amentia$1 or pseudodement*).tw. (225806)
3 alzheimer*.tw. (261150)
4 (progressive adj2 aphasi*).tw. (3381)
5 PPA syndrome*.tw. (45)
6 (senile or senility).tw. (43078)
7 (Mesulam* adj1 syndrome*).tw. (7)
8 binswanger*.tw. (1723)
9 (spongiform encephalopath$3 adj1 (subacute or sub-acute)).tw. (392)
10 "Kosaka-Shibayama".tw. (6)
11 ("diffuse neurofibrillary" adj tangle$1 adj5 calcif*).tw. (76)
12 ((frontotemporal or fronto-temporal) adj lobar degeneration).tw. (4967)
13 FTLD.tw. (3945)
14 DDPAC.tw. (12)
15 (Pick$2 adj1 disease*).tw. (6302)
16 (FLDEM or FTD-GRN or FTD-PGRN or FTDP-17 or FTLD-17 GRN or FTLD-TDP or HDDD1 or HDDD2).tw. (1622)
17 "Wilhelmsen-Lynch".tw. (2)
18 ((brain or lobar) adj2 atroph*).tw. (11166)
19 Huntington*.tw. (32829)
20 ("Kluver-Bucy" or "Kleuver-Bucy").tw. (604)
21 (temporal lobectomy behavio?r adj2 syndrome*).tw. (0)
22 (Lewy bod$3 adj2 disease*).tw. (3728)
23 CADASIL.tw. (2253)
24 ((mental* or cognit*) adj2 (declin* or degenerat* or deteriorat* or loss* or losing or lost)).tw. (51865)
25 or/1-24 (585723)
26 (atypical antipsychotic* or atypical anti-psychotic*).tw. (25430)
27 (new generation antipsychotic* or new generation anti-psychotic*).tw. (311)
28 (second generation antipsychotic* or second generation anti-psychotic*).tw. (6293)
29 (2nd generation antipsychotic* or 2nd generation anti-psychotic*).tw. (75)
30 (novel antipsychotic* or novel anti-psychotic*).tw. (2121)
31 (atypical neuroleptic* or new generation neuroleptic* or second generation neuroleptic* or 2nd generation neuroleptic* or novel neuroleptic*).tw. (3997)
32 (aripiprazole or Abilify or Abilitat or Discmelt or HSDB 7320 or Opc 14597 or OPC 31 or OPC-14597 or UNII-82VFR53I78).tw. (8553)
33 aripiprazole.rn. (9825)

34 (Asenapine or Org 5222 or EINECS 265-829-4 or UNII-JKZ19V908O or Saphris or Sycrest).tw. (879)
35 Asenapine.rn. (707)
36 Clozapine/ (37170)
37 (Clozapine or "BRN 0764984" or CCRIS 9171 or Alemoxan or Azaleptin or Clopine or Clopsine or Clorazil or Clozapin or Clozapina or Clozapinum or Clozaril or Denzapine or Dorval or Dozapine or EINECS 227-313-7 or Elcrit or Fazaclo or HF 1854 or HF1854 or HSDB 6478 or Iprox or Lapenax or Leponex or Lozapin or Lozapine or LX 100-129 or Sizopin or UNII-J60AR2IKIC or Versacloz or W-801 or Zapen or Zaponex).tw. (28879)
38 Clozapine.rn. (31923)
39 (Lurasidone or Latuda or MK 3756 or MK3756 or SM-13496 or SM13496 or SMP-13496 or SMP13496 or UNII-22IC88528T).tw. (590)
40 Lurasidone.rn. (426)
41 (Olanzapine or Anzatric or Lanopin or Lanzac or LY 170053 or LY170053 or Meltolan or Midax or Olace or Oladay or Olan or Olandus or Olanex or Olansek or Olapin or Olazax or Oleanz or Olexar or Oltal or Olzap or Onza or Ozapin or Psychozap or Relprevv or UNII-N7U69T4SZR or Zalasta or Zelta or Zypadhera or Zydis or Zyprexa*).tw. (22648)
42 Olanzapine.rn. (27851)
43 (Paliperidone or Invega or 9-hydroxyrisperidone or 9-hydroxy-risperidone or 9-OH-risperidone or R 76477 or RO76477 or UNII-838F01T721 or xeplion).tw. (2572)
44 Paliperidone.rn. (1763)
45 (quetiapine or Seroquel or "ICI 204,636" or ICI 204636 or Co-Quetiapine or HSDB 7557 or Socalm or Tienapine or UNII-BGL0JSY5SI).tw. (12555)
46 Quetiapine.rn. (17048)
47 Risperidone/ (35954)
48 (Risperidone or Risperdal or Risperidal or Riperidon or "R-64,766" or R-64766 or Belivon or Consta or Neripros or Noprenia or Pexidone or RN 4891881 or HSDB 7580 or Psychodal or R 64 766 or "R 64,766" or R 64766 or Risolept or Rispen or Risperidona or Risperidonum or Risperin or Rispid or Rispolept or Rispolet or Rispolin or Rizodal or Sequinan or Spiron or UNII-L6UH7ZF8HC or Zargus or Zofredal).tw. (24245)
49 Risperidone.rn. (30703)
50 (Ziprasidone or CP 88059 or CP 88059-01 or "CP-88,059" or "CP-88,059-01" or "CP-88,059-1" or Geodon or HSDB 7745 or UNII-6UKA5VEJ6X or Zeldox or Zeldrox or Ziprazidone or Zipsydon).tw. (5381)
51 Ziprasidone.rn. (7551)
52 or/26-51 (111217)
53 25 and 52 (7414)
54 (controlled clinical trial or randomized controlled trial).pt. (482489)
55 clinical trials as topic.sh. (175785)
56 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1609346)
57 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (327622)
58 trial.ti. (328390)
59 or/54-58 (2038136)
60 53 and 59 (1165)
61 exp Animals/ not (exp Animals/ and Humans/) (9168750)
62 60 not 61 (1157)
63 (comment or editorial or interview or letter or news).pt. (2894548)
64 62 not 63 (1137)

65 64 use prmz (349)
66 exp dementia/ (420833)
67 (dement* or amentia$1 or psuedodement*).tw. (225478)
68 alzheimer*.tw. (261150)
69 (progressive adj2 aphasi*).tw. (3381)
70 PPA syndrome*.tw. (45)
71 (senile or senility).tw. (43078)
72 (Mesulam* adj1 syndrome*).tw. (7)
73 binswanger*.tw. (1723)
74 (spongiform encephalopath$3 adj1 (subacute or sub-acute)).tw. (392)
75 "Kosaka-Shibayama".tw. (6)
76 ("diffuse neurofibrillary" adj tangle$1 adj5 calcif*).tw. (76)
77 ((frontotemporal or fronto-temporal) adj lobar degeneration).tw. (4967)
78 FTLD.tw. (3945)
79 DDPAC.tw. (12)
80 (Pick$2 adj1 disease*).tw. (6302)
81 (FLDEM or FTD-GRN or FTD-PGRN or FTDP-17 or FTLD-17 GRN or FTLD-TDP or HDDD1 or HDDD2).tw. (1622)
82 "Wilhelmsen-Lynch".tw. (2)
83 ((brain or lobar) adj2 atroph*).tw. (11166)
84 Huntington*.tw. (32829)
85 ("Kluver-Bucy" or "Kleuver-Bucy").tw. (604)
86 (temporal lobectomy behavio?r adj2 syndrome*).tw. (0)
87 (Lewy bod$3 adj2 disease*).tw. (3728)
88 CADASIL.tw. (2253)
89 ((mental* or cognit*) adj2 (declin* or degenerat* or deteriorat* or loss* or losing or lost)).tw. (51865)
90 or/66-89 (585536)
91 exp atypical antipsychotic agent/ (75226)
92 (atypical antipsychotic* or atypical anti-psychotic*).tw. (25430)
93 (new generation antipsychotic* or new generation anti-psychotic*).tw. (311)
94 (second generation antipsychotic* or second generation anti-psychotic*).tw. (6293)
95 (2nd generation antipsychotic* or 2nd generation anti-psychotic*).tw. (75)
96 (novel antipsychotic* or novel anti-psychotic*).tw. (2121)
97 (atypical neuroleptic* or new generation neuroleptic* or second generation neuroleptic* or 2nd generation neuroleptic* or novel neuroleptic*).tw. (3997)
98 aripiprazole/ (10335)
99 (aripiprazole or Abilify or Abilitat or Discmelt or HSDB 7320 or Opc 14597 or OPC 31 or OPC-14597 or UNII-82VFR53I78).tw. (8553)
100 aripiprazole.rn. (9825)
101 asenapine/ (750)
102 (Asenapine or Org 5222 or EINECS 265-829-4 or UNII-JKZ19V908O or Saphris or Sycrest).tw. (879)
103 Asenapine.rn. (707)
104 clozapine/ (37170)
105 (Clozapine or "BRN 0764984" or CCRIS 9171 or Alemoxan or Azaleptin or Clopine or Clopsine or Clorazil or Clozapin or Clozapina or Clozapinum or Clozaril or Denzapine or Dorval or Dozapine or EINECS 227-313-7 or Elcrit

or Fazaclo or HF 1854 or HF1854 or HSDB 6478 or Iprox or Lapenax or Leponex or Lozapin or Lozapine or LX 100-129 or Sizopin or UNII-J60AR2IKIC or Versacloz or W-801 or Zapen or Zaponex).tw. (28879)
106 Clozapine.rn. (31923)
107 lurasidone/ (512)
108 (Lurasidone or Latuda or MK 3756 or MK3756 or SM-13496 or SM13496 or SMP-13496 or SMP13496 or UNII-22IC88528T).tw. (590)
109 Lurasidone.rn. (426)
110 olanzapine/ (28320)
111 (Olanzapine or Anzatric or Lanopin or Lanzac or LY 170053 or LY170053 or Meltolan or Midax or Olace or Oladay or Olan or Olandus or Olanex or Olansek or Olapin or Olazax or Oleanz or Olexar or Oltal or Olzap or Onza or Ozapin or Psychozap or Relprevv or UNII-N7U69T4SZR or Zalasta or Zelta or Zypadhera or Zydis or Zyprexa*).tw. (22648)
112 Olanzapine.rn. (27851)
113 paliperidone/ (2117)
114 (Paliperidone or Invega or 9-hydroxyrisperidone or 9-hydroxy-risperidone or 9-OH-risperidone or R 76477 or RO76477 or UNII-838F01T721 or xeplion).tw. (2572)
115 paliperidone.rn. (1763)
116 quetiapine/ (17897)
117 (quetiapine or Seroquel or "ICI 204,636" or ICI 204636 or Co-Quetiapine or HSDB 7557 or Socalm or Tienapine or UNII-BGL0JSY5SI).tw. (12555)
118 quetiapine.rn. (17048)
119 risperidone/ (35954)
120 (Risperidone or Risperdal or Risperidal or Riperidon or "R-64,766" or R-64766 or Belivon or Consta or Neripros or Noprenia or Pexidone or RN 4891881 or HSDB 7580 or Psychodal or R 64 766 or "R 64,766" or R 64766 or Risolept or Rispen or Risperidona or Risperidonum or Risperin or Rispid or Rispolept or Rispolet or Rispolin or Rizodal or Sequinan or Spiron or UNII-L6UH7ZF8HC or Zargus or Zofredal).tw. (24245)
121 Risperidone.rn. (30703)
122 ziprasidone/ (7131)
123 (Ziprasidone or CP 88059 or CP 88059-01 or "CP-88,059" or "CP-88,059-01" or "CP-88,059-1" or Geodon or HSDB 7745 or UNII-6UKA5VEJ6X or Zeldox or Zeldrox or Ziprazidone or Zipsydon).tw. (5381)
124 Ziprasidone.rn. (7551)
125 or/91-124 (125637)
126 90 and 125 (8100)
127 randomized controlled trial/ or controlled clinical trial/ (971067)
128 exp "clinical trial (topic)"/ (118674)
129 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1609346)
130 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (327622)
131 trial.ti. (328390)
132 or/127-131 (2177494)
133 126 and 132 (1447)
134 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38770859)
135 exp humans/ or exp human experimentation/ or exp human experiment/ (29332576)
136 134 not 135 (9439953)

137 133 not 136 (1438)
138 (editorial or letter).pt. (2564173)
139 137 not 138 (1410)
140 139 use emczd (885)
141 exp dementia/ (420833)
142 (dement* or amentia$1 or pseudodement*).tw. (225806)
143 alzheimer*.tw. (261150)
144 (progressive adj2 aphasi*).tw. (3381)
145 PPA syndrome*.tw. (45)
146 (senile or senility).tw. (43078)
147 (Mesulam* adj1 syndrome*).tw. (7)
148 binswanger*.tw. (1723)
149 (spongiform encephalopath$3 adj1 (subacute or sub-acute)).tw. (392)
150 "Kosaka-Shibayama".tw. (6)
151 ("diffuse neurofibrillary" adj tangle$1 adj5 calcif*).tw. (76)
152 ((frontotemporal or fronto-temporal) adj lobar degeneration).tw. (4967)
153 FTLD.tw. (3945)
154 DDPAC.tw. (12)
155 (Pick$2 adj1 disease*).tw. (6302)
156 (FLDEM or FTD-GRN or FTD-PGRN or FTDP-17 or FTLD-17 GRN or FTLD-TDP or HDDD1 or HDDD2).tw. (1622)
157 "Wilhelmsen-Lynch".tw. (2)
158 ((brain or lobar) adj2 atroph*).tw. (11166)
159 Huntington*.tw. (32829)
160 ("Kluver-Bucy" or "Kleuver-Bucy").tw. (604)
161 (temporal lobectomy behavio?r adj2 syndrome*).tw. (0)
162 (Lewy bod$3 adj2 disease*).tw. (3728)
163 CADASIL.tw. (2253)
164 ((mental* or cognit*) adj2 (declin* or degenerat* or deteriorat* or loss* or losing or lost)).tw. (51865)
165 or/141-164 (585723)
166 (atypical antipsychotic* or atypical anti-psychotic*).tw. (25430)
167 (new generation antipsychotic* or new generation anti-psychotic*).tw. (311)
168 (second generation antipsychotic* or second generation anti-psychotic*).tw. (6293)
169 (2nd generation antipsychotic* or 2nd generation anti-psychotic*).tw. (75)
170 (novel antipsychotic* or novel anti-psychotic*).tw. (2121)
171 (atypical neuroleptic* or new generation neuroleptic* or second generation neuroleptic* or 2nd generation neuroleptic* or novel neuroleptic*).tw. (3997)
172 aripiprazole/ (10335)
173 (aripiprazole or Abilify or Abilitat or Discmelt or HSDB 7320 or Opc 14597 or OPC 31 or OPC-14597 or UNII-82VFR53I78).tw. (8553)
174 (Asenapine or Org 5222 or EINECS 265-829-4 or UNII-JKZ19V908O or Saphris or Sycrest).tw. (879)
175 clozapine/ (37170)
176 (Clozapine or "BRN 0764984" or CCRIS 9171 or Alemoxan or Azaleptin or Clopine or Clopsine or Clorazil or Clozapin or Clozapina or Clozapinum or Clozaril or Denzapine or Dorval or Dozapine or EINECS 227-313-7 or Elcrit or Fazaclo or HF 1854 or HF1854 or HSDB 6478 or Iprox or Lapenax or Leponex or Lozapin or Lozapine or LX 100-

129 or Sizopin or UNII-J60AR2IKIC or Versacloz or W-801 or Zapen or Zaponex).tw. (28879)
177 (Lurasidone or Latuda or MK 3756 or MK3756 or SM-13496 or SM13496 or SMP-13496 or SMP13496 or UNII-22IC88528T).tw. (590)
178 olanzapine/ (28320)
179 (Olanzapine or Anzatric or Lanopin or Lanzac or LY 170053 or LY170053 or Meltolan or Midax or Olace or Oladay or Olan or Olandus or Olanex or Olansek or Olapin or Olazax or Oleanz or Olexar or Oltal or Olzap or Onza or Ozapin or Psychozap or Relprevv or UNII-N7U69T4SZR or Zalasta or Zelta or Zypadhera or Zydis or Zyprexa*).tw. (22648)
180 (Paliperidone or Invega or 9-hydroxyrisperidone or 9-hydroxy-risperidone or 9-OH-risperidone or R 76477 or RO76477 or UNII-838F01T721 or xeplion).tw. (2572)
181 quetiapine/ (17897)
182 (quetiapine or Seroquel or "ICI 204,636" or ICI 204636 or Co-Quetiapine or HSDB 7557 or Socalm or Tienapine or UNII-BGL0JSY5SI).tw. (12555)
183 risperidone/ (35954)
184 (Risperidone or Risperdal or Risperidal or Riperidon or "R-64,766" or R-64766 or Belivon or Consta or Neripros or Noprenia or Pexidone or RN 4891881 or HSDB 7580 or Psychodal or R 64 766 or "R 64,766" or R 64766 or Risolept or Rispen or Risperidona or Risperidonum or Risperin or Rispid or Rispolept or Rispolet or Rispolin or Rizodal or Sequinan or Spiron or UNII-L6UH7ZF8HC or Zargus or Zofredal).tw. (24245)
185 (Ziprasidone or CP 88059 or CP 88059-01 or "CP-88,059" or "CP-88,059-01" or "CP-88,059-1" or Geodon or HSDB 7745 or UNII-6UKA5VEJ6X or Zeldox or Zeldrox or Ziprazidone or Zipsydon).tw. (5381)
186 or/166-185 (110389)
187 165 and 186 (7366)
188 clinical trials/ (54654)
189 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1609346)
190 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (327622)
191 trial.ti. (328390)
192 or/188-191 (1809091)
193 187 and 192 (1137)
194 exp Animals/ not (exp Animals/ and Humans/) (9168750)
195 193 not 194 (1128)
196 195 use prmz (297)
197 195 use emczd (608)
198 195 not (196 or 197) (223)
199 65 or 140 or 198 (1457)
200 limit 199 to yr="2009-current" (554)
201 remove duplicates from 200 (431) [TOTAL UNIQUE HITS]
202 201 use prmz (89) [MEDLINE UNIQUE HITS]
203 201 use emczd (323) [EMBASE UNIQUE HITS]
204 201 not (202 or 203) (19) [PSYCINFO UNIQUE HITS]

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Search Name: AAPs Elderly - Dementia
Date Run: 10/10/14 17:20:55.349

Description: Ottawa Heart Institute - 2014 Oct 10

ID	Search	Hits
#1	[mh Dementia]	3831
#2	(dement* or amentia* or pseudodement*):ti,ab,kw	5174
#3	alzheimer*:ti,ab,kw	4979
#4	(progressive near/2 aphasi*):ti,ab,kw	8
#5	(PPA next syndrome*):ti,ab,kw	0
#6	(senile or senility):ti,ab,kw	897
#7	(Mesulam* near/1 syndrome*):ti,ab,kw	0
#8	binswanger*:ti,ab,kw	6
#9	(spongiform next encephalopath*) near/1 (subacute or sub-acute):ti,ab,kw	0
#10	"Kosaka-Shibayama":ti,ab,kw	0
#11	("diffuse neurofibrillary" next tangle*) near/5 calcif*:ti,ab,kw	0
#12	((frontotemporal or fronto-temporal) next lobar degeneration):ti,ab,kw	14
#13	FTLD:ti,ab,kw	8
#14	DDPAC:ti,ab,kw	0
#15	(Pick* near/1 disease*):ti,ab,kw	11
#16	(FLDEM or FTD-GRN or FTD-PGRN or FTDP-17 or FTLD-17 GRN or FTLD-TDP or HDDD1 or HDDD2):ti,ab,kw	3
#17	"Wilhelmsen-Lynch":ti,ab,kw	0
#18	(brain or lobar) near/2 atroph*:ti,ab,kw	171
#19	Huntington*:ti,ab,kw	265
#20	"Kluver-Bucy" or "Kleuver-Bucy":ti,ab,kw	34
#21	("temporal lobectomy" next behavio*r) near/2 syndrome*:ti,ab,kw	0
#22	(Lewy next bod*) near/2 disease*:ti,ab,kw	74
#23	CADASIL:ti,ab,kw	14
#24	(mental* or cognit*) near/2 (declin* or degenerat* or deteriorat* or loss* or losing or lost):ti,ab,kw	987
#25	{or #1-#24}	10001
#26	atypical next (antipsychotic* or anti-psychotic*):ti,ab,kw	1105
#27	"new generation" next (antipsychotic* or anti-psychotic*):ti,ab,kw	23
#28	"second generation" next (antipsychotic* or anti-psychotic*):ti,ab,kw	303
#29	"2nd generation" next (antipsychotic* or anti-psychotic*):ti,ab,kw	4
#30	novel next (antipsychotic* or anti-psychotic*):ti,ab,kw	152
#31	(atypical or "new generation" or "second generation" or "2nd generation" or novel) next neuroleptic*:ti,ab,kw	119
#32	(aripiprazole or Abilify or Abilitat or Discmelt or HSDB 7320 or OPC 14597 or OPC 31 or OPC-14597 or UNII-82VFR53I78):ti,ab,kw	537
#33	(Asenapine or Org 5222 or EINECS 265-829-4 or UNII-JKZ19V908O or Saphris or Sycrest):ti,ab,kw	

58
#34 [mh Clozapine] 424
#35 (Clozapine or "BRN 0764984" or CCRIS 9171 or Alemoxan or Azaleptin or Clopine or Clopsine or Clorazil or Clozapin or Clozapina or Clozapinum or Clozaril or Denzapine or Dorval or Dozapine or EINECS 227-313-7 or Elcrit or Fazaclo or HF 1854 or HF1854 or HSDB 6478 or Iprox or Lapenax or Leponex or Lozapin or Lozapine or LX 100-129 or Sizopin or UNII-J60AR2IKIC or Versacloz or W-801 or Zapen or Zaponex):ti,ab,kw 983
#36 (Lurasidone or Latuda or MK 3756 or MK3756 or SM-13496 or SM13496 or SMP-13496 or SMP13496 or UNII-22IC88528T):ti,ab,kw 47
#37 (Olanzapine or Anzatric or Lanopin or Lanzac or LY 170053 or LY170053 or Meltolan or Midax or Olace or Oladay or Olan or Olandus or Olanex or Olansek or Olapin or Olazax or Oleanz or Olexar or Oltal or Olzap or Onza or Ozapin or Psychozap or Relprevv or UNII-N7U69T4SZR or Zalasta or Zelta or Zypadhera or Zydis or Zyprexa*):ti,ab,kw 1977
#38 (Paliperidone or Invega or 9-hydroxyrisperidone or 9-hydroxy-risperidone or 9-OH-risperidone or R 76477 or RO76477 or UNII-838F01T721 or xeplion):ti,ab,kw 174
#39 (quetiapine or Seroquel or "ICI 204,636" or ICI 204636 or Co-Quetiapine or HSDB 7557 or Socalm or Tienapine or UNII-BGL0JSY5SI):ti,ab,kw 901
#40 [mh Risperidone] 916
#41 (Risperidone or Risperdal or Risperidal or Riperidon or "R-64,766" or R-64766 or Belivon or Consta or Neripros or Noprenia or Pexidone or RN 4891881 or HSDB 7580 or Psychodal or R 64 766 or "R 64,766" or R 64766 or Risolept or Rispen or Risperidona or Risperidonum or Risperin or Rispid or Rispolept or Rispolet or Rispolin or Rizodal or Sequinan or Spiron or UNII-L6UH7ZF8HC or Zargus or Zofredal):ti,ab,kw 2006
#42 (Ziprasidone or CP 88059 or CP 88059-01 or "CP-88,059" or "CP-88,059-01" or "CP-88,059-1" or Geodon or HSDB 7745 or UNII-6UKA5VEJ6X or Zeldox or Zeldrox or Ziprazidone or Zipsydon):ti,ab,kw 457
#43 {or #26-#42} 5752
#44 #25 and #43 Publication Year from 2009 to 2014 65
DSR – 6 (*did not download – RCT search only*)
DARE – 2 (*did not download – RCT search only*)
CENTRAL – 55
HTA – 2 (*did not download – RCT search only*)

Appendix B: Included Study List

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
De Deyn, 1999 (41)	**International:** 51 centers in **8 countries** *(unspecified)* (12 weeks)	"Elderly patients with dementia and behavioral symptoms"	**Setting unclear:** Patients were 'institutionalized'	**Dementia:** DSM-IV **BPSD:** Scores of ≥ 4 on FAST, >1 BEHAVE-AD global rating, and ≥8 on the BEHAVE-AD total score.	**N=344** **Placebo, oral solution:** n=114 **Risperidone, oral solution, 0.5-4 mg/d:** n=115 **Haloperidol, oral solution, 0.5-4 mg/d:** n=115	**Placebo, oral solution:** n=40/114 (35%) **Risperidone, oral solution, 0.5-4 mg/d:** n= 47/115 (41%) **Haloperidol, oral solution, 0.5-4 mg/d:** n=34/115 (30%)
Ballard, 2005 (49)	**National:** Care facilities in **North East of England** (26 weeks)	"Patients with dementia and agitation" aged > 60 years.	**Long term care:** Nursing homes	**Dementia:** NINCDS-ADRDA **BPSD:** "clinically significant agitation reported by a member of staff or a physician" CMAI total score >39	**N=93** **Placebo, route unspecified:** n=31 **Quetiapine, route unspecified, 50-100mg/day:** n=31 **Rivastigmine, route unspecified, 6 to ≥ 9mg/day:** n=31	**Placebo, route unspecified:** n=1/31 (3%) **Quetiapine, route unspecified, 50-100mg/d:** n=8/31 (26%) **Rivastigmine, route unspecified, 6 to ≥ 9mg/d:** n=10/31 (32%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Chan, 2001 (42)	**National:** 3 hospitals in **Hong Kong, China** (12 weeks)	"Chinese demented elderly"	**Hospital:** Inpatients from the Psychogeriatric Departments of three Hong Kong hospitals **Long-term care:** Nursing home residents **Community:** Outpatients from the Psychogeriatric Departments of three Hong Kong hospitals ***Note:*** *31 inpatients and 19 outpatients accounted for 88% of the total study population.*	**Dementia:** DSM-IV **BPSD:** "Active behavioral symptoms, as evidenced by a frequency score of at least 4 on one and at least 3 on another item of the CMAI" A total score of at least 8 on BEHAVE-AD	**Risperidone, oral tablet, 0.5-2mg/day:** n=29/58 **Haloperidol, oral tablet, 0.5-2mg/day** n= 29/58	**Risperidone, oral tablet, 0.5-2mg/day:** n=2/29 (7%) **Haloperidol, oral tablet, 0.5-2mg/day** n= 1/29 (3%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
De Deyn, 2004 (37)	**International:** 61 sites across **Europe, Australia, Israel, Lebanon,** and **South Africa** (10 weeks)	Patients aged 40 years and greater with "psychotic symptoms associated with AD"	**Long-term care:** Residents of nursing homes and **Hospital:** Inpatients of continuing-care hospitals	**Dementia diagnosed by:** NINCDS-ADRDA and DSM-IV-TR **BPSD Criteria for Inclusion:** "All exhibited clinically significant psychotic symptoms (delusions or hallucinations) due to AD".	**Placebo, oral capsule:** n=129/649 **Olanzapine, oral capsule, fixed dose 1.0mg/day:** n=129/649 **Olanzapine, oral capsule, fixed dose 2.5mg/day:** n=134/649 **Olanzapine, oral capsule, fixed dose 5.0mg/day:** n=125/649 **Olanzapine, oral capsule, fixed dose 7.5mg/day:** n=132/649 **Note: 652 patients were randomized; data for only 649 were reported*	**Placebo, oral capsule:** n=38/129 (29%) **Olanzapine, oral capsule, fixed dose 1.0mg/day:** n=44/129 (34%) **Olanzapine, oral capsule, fixed dose 2.5mg/day:** n=33/134 (25%) **Olanzapine, oral capsule, fixed dose 5.0mg/day:** n=31/125 (25%) **Olanzapine, oral capsule, fixed dose 7.5mg/day:** n=38/132 (29%)
Fontaine, 2003 (53)	**Location not defined:** Authors are based in the **United States** (2 weeks)	"Behavioral disturbance in elderly persons with dementia"	**Long-term care:** All subjects resided in long term care facilities.	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** ADCS agitation screening scale score ≥ 25 with 6 points on the delusions, hallucinations, physical aggression, or verbal aggression subscales.	**Risperidone (Risperdal), oral, 0.5-2mg/day:** n=19/39 **Olanzapine (Zyprexa), oral, 2.5-10mg/day:** n=20/39	**Risperidone (Risperdal), oral, 0.5-2mg/day:** n=19/39 (11%) **Olanzapine (Zyprexa), oral, 2.5-10mg/day:** n=20/39 (20%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Holmes, 2007 (28)	**Location not defined:** Authors are based in the **United Kingdom** and **Egypt** (6 weeks)	Patients (mean age 86 years) with "severe probable AD… and clinically significant agitation"	**Long-term care:** All participants resided in nursing homes	**Dementia diagnosed by:** NINCDS-ADRDA **BPSD Criteria for Inclusion:** CMAI score > 39 points for at least 6 weeks	**Risperidone, oral capsule, 1mg/day:** n=12/27 **Rivastigmine, oral capsule, 6mg/day:** n=15/27	Discontinuations were not reported
Katz, 1999 (43) ***Companion:*** **Grossman, 2004 (57)**	**National:** 40 sites in the **United States** (12 weeks)	Long term care patients, 55 years or older, with dementia, psychosis and aggression.	**Long-term care:** Residents of nursing homes and **Hospital:** Inpatients in a chronic disease hospital	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** BEHAVE-AD total score ≥ 8 and BEHAVE-AD global rating ≥ 1	**Placebo, oral tablet:** n=163/625 **Risperidone (Risperdal), oral tablet, 0.5 mg/day:** n=149/625 **Risperidone (Risperdal), oral tablet, 1.0 mg/day:** n=148/625 **Risperidone (Risperdal), oral tablet, 2.0 mg/day:** n=165/625	**Placebo, oral tablet:** n=44/163 (27%) **Risperidone (Risperdal), oral tablet, 0.5 mg/day:** n=32/149 (21%) **Risperidone (Risperdal), oral tablet, 1.0 mg/day:** n=45/148 (30%) **Risperidone (Risperdal), oral tablet, 2.0 mg/day:** n=69/165 (42%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Deberdt, 2005 (36)	**National:** 64 sites in the **United States** (10 weeks)	Patients ≥40 years old with "moderate-to-severe psychotic symptoms associated with dementia"	**Long-term care:** Residents of assisted-living centers **Community:** Outpatients ***Note:*** *All but two patients fell into the above categories*	**Dementia diagnosed by:** NINCDS-ADRDA or DSM-IV **BPSD Criteria for Inclusion:** "All patients exhibited clinically significant psychotic symptoms…" NPI or NPI/NH scores of ≥6 (severity x frequency) on Hallucinations + Delusions subscales	**Placebo, route unspecified:** n=94/494 **Risperidone, route unspecified, 0.5–2 mg/day:** n=196/494 **Olanzapine, route unspecified, 2.5- 10 mg/day:** n=204/494	**Placebo, route unspecified:** n=19/94 (20%) **Risperidone, route unspecified, 0.5–2 mg/day:** n=61/196 (31%) **Olanzapine, route unspecified, 2.5- 10 mg/day:** n=77/204 (38%)
Gareri, 2004 (34)	**Location not defined:** Authors are based in **Italy** (8 weeks)	Patients with "behavioral and psychological symptoms in dementia"	**Setting not defined**	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** A score of 24 or more on the NPI	**Risperidone, oral, 1-2mg/day:** n=20/60 **Olanzapine, oral, 5-10mg/day:** n=20/60 **Promazine, oral, 50-100mg/day:** n=20/60	Discontinuations were not reported
Meehan, 2002 (51) ***Companion:*** **Eli Lily, 2005 (58)**	**International:** 38 sites across the **United States** (n=33), **Russia** (n=2), and **Romania** (n=3) (24 hours; **NOTE:** *2 hours was treated as end of study period due to a change in study design (crossover) and how the data were reported)*	Inpatients aged 55 years or older with "acute dementia-related agitation"	**Long-term care:** Nursing home residents **Hospital:** Hospitalized inpatients	**Dementia diagnosed by:** NINCDS-ADRDA or DSM-IV **BPSD Criteria for Inclusion:** Score of ≥ 14 on the Excited Component of PANSS; at least one individual PANSS item score ≥ 4 on a scale of 1-7 A diagnosis of "clinically significant agitation for which treatment with a parenteral agent is indicated"	**Placebo, IM**: n=67/272 **Olanzapine, IM, Fixed 2.5mg (after 2 hrs):** n=71/272 **Olanzapine, IM, fixed dose 5.0mg (after 2 hrs):** n=66/272 **Lorazepam, IM, fixed dose 1.0mg (after 2 hrs):** n=68/272	Discontinuations were not reported separately by study period (hour 2 was end of period I)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Mintzer, 2006 (35)	**National:** 44 centres across the **United States** (8 weeks)	Patients aged ≥55 years "with psychosis of AD"	**Long-term care:** Residents of nursing home and long-term care facilities	**Dementia diagnosed by:** As specified in *Jeste and Finkel, 2008* (55) **BPSD Criteria for Inclusion:** Score of ≥ 2 on any item of BEHAVE-AD psychosis subscale	**Placebo, oral tablet:** n=238/473 **Risperidone, oral tablet, 0.5-1.5mg/day:** n=235/473	**Placebo, oral tablet:** n=59/238 (25%) **Risperidone, oral tablet, 0.5-1.5mg/day:** n=60/235 (26%)
Tariot, 2006 (38)	**National:** 47 sites across the **United States** (10 weeks)	Patients > 64 years of age "with AD complicated by psychosis"	**Long-term care:** Nursing home residents who were not bedridden	**Dementia diagnosed by:** NINCDS-ADRDA or DSM-IV **BPSD Criteria for Inclusion:** "The presence of psychosis was required, defined as BPRS scores ≥ 24 and CGI-S scores ≥4 at screening and baseline, scores of ≥3 on two or more of the following BPRS items: 4, conceptual disorganization; 11, suspiciousness; 12, hallucinatory behavior; 15, unusual thought content; and frequency scores of ≥3 on at least one of two psychosis items (delusions or hallucinations) of the NPI-NH"	**Placebo, oral capsule:** n=99/284 **Quetiapine, oral capsule, 25-600mg/day:** n=91/284 **Haloperidol, oral capsule, 0.5-12mg/day:** n=94/284	**Placebo, oral capsule:** n=36/99 (36%) **Quetiapine, oral capsule, 25-600mg/day:** n=29/91 (32%) **Haloperidol, oral capsule, 0.5-12mg/day:** n=39/94 (41%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Verhey, 2006 (47)	**National:** 6 centers across the **Netherlands** (5 weeks)	Elderly "out-patients with dementia and agitation"	**Long-term care:** Patients living in nursing homes and **Community:** Patients living in their own homes (out-patients)	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** "A level of agitation that was clinically judged to represent a clinical problem requiring antipsychotic treatment for a behavioral disorder" "A score of at least 45 on the CMAI"	**Olanzapine, oral capsule, 4.71mg/day (mean dose at start of study period II):** n=30/58 **Haloperidol, oral capsule, 1.75mg/day (mean dose at start of study period II):** n=28/58 ***Note:*** *59 patients were randomized; authors excluded one patient because of too many missing data but did not state which group to which they were randomized*	Nine (9) patients discontinued from the study prematurely (9/59=15%) N=4 patients discontinued because of severe aggressive behavior, n=2 because of severe motor behavior, and n=2 because of refusal. Authors do not advise which group(s) these patients were randomized to.

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Zhong, 2007 (39) ***Companion:*** **AstraZeneca, 2009 (22)**	**National:** 53 centers across the **United States** (10 weeks)	"Elderly institutionalized patients with dementia and agitation"	**Long-term care:** Residents of nursing homes and assisted living facilities	**Dementia diagnosed by:** NINCDS-ADRDA or DSM-IV **BPSD Criteria for Inclusion:** "Documented clinical symptoms of agitation that did not result directly from the participant's medical condition and required treatment with antipsychotic medication on in the opinion of the investigator" A score of ≥14 on the PANSS-EC and ≥4 on one of the 5 PANSS-EC items (hostility, tension, uncooperativeness, excitement, poor impulse control)	**Placebo, oral tablet:** n=92/333 **Quetiapine, oral tablet, fixed dose 100mg/d:** n=124/333 **Quetiapine, oral tablet, fixed dose 200mg/d:** n=117/333	**Placebo, oral tablet:** n=32/92 (35%) **Quetiapine, oral tablet, fixed dose 100mg/d:** n=43/124 (35%) **Quetiapine, oral tablet, fixed dose 200mg/d:** n=43/117 (37%)
Brodaty, 2003 (44) ***Companions:*** **Brodaty, 2005 (59)** **Frank, 2004 (60)**	**International:** 14 sites across **Australia** and **New Zealand** (12 weeks)	Elderly patients with dementia and "significant aggressive behaviors"	**Long-term care:** Nursing home residents	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** A minimum aggression score on CMAI "of ≥ 4 on at least 1 aggressive item, or a score of 3 on at least 2 aggressive items, or a score of 2 on at least 3 aggressive items, or 2 aggressive items occurring at a frequency of 2 and 1 at a frequency of 3"	**Placebo, oral liquid:** n=170/337 **Risperidone, oral liquid, 0.5-2ml/day:** n=167/337 ***Note:*** *345 patients were randomized; only 337 patients received a drug intervention.*	**Placebo, oral liquid:** n=56/170 (33%) **Risperidone, oral liquid, 0.5-2ml/day:** n=45/167 (27%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
De Deyn, 2005 (40)	**Location not defined:** Authors are based in **Belgium, United States,** and **Japan** (10 weeks)	Patients aged 55-95 year of age "with psychosis associated with Alzheimer's Disease (AD)"	**Long-term care:** Residents of assisted living facilities or adult communities **Community:** Patients living with a caregiver	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** "Symptoms of delusions or hallucinations present (at least intermittently) for 1 month or longer". A score of ≥ 6 on delusions or hallucinations items on the NPI	**Placebo, route unspecified:** n=102/208 **Aripiprazole, route unspecified, 2-15 mg/d:** n=106/208	**Placebo, route unspecified:** n=18/102 (18%) **Aripiprazole, route unspecified, 2-15 mg/d:** n= 18/106 (17%)
Mintzer, 2007 (30) ***Companion:*** **Breder, 2004 (61)**	**International:** 81 centres across the **United States, Australia, Canada, South Africa,** and **Argentina** (6 weeks, **NOTE**: this was the end of double-blind period for all patients)	Men and women aged 55-95 years of age, diagnosed with AD and "psychotic symptoms of delusions or hallucinations "	**Long-term care:** Residents of nursing homes and residential assisted-living facilities	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** Persistent or intermittent "delusions, hallucinations or both for at least one month"	**Placebo, unknown route:** n=121/487 **Aripiprazole, unknown route, Fixed Dose, 2mg/d:** n=118/487 **Aripiprazole, unknown route, Fixed Dose, 5mg/d:** n=122/487 **Aripiprazole, unknown route, Fixed Dose, 10mg/d:** n=126/487	**Placebo, unknown route:** n=56/121 (46%) **Aripiprazole, unknown route, Fixed Dose, 2mg/d:** n=41/118 (35%) **Aripiprazole, unknown route, Fixed Dose, 5mg/d:** n=49/122 (40%) **Aripiprazole, unknown route, Fixed Dose, 10mg/d:** n= 57/126 (45%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Mowla, 2010 (54)	**National:** The Abolfazl Clinic; affiliated with Bushehr University of Medical Sciences **(Iran)** (8 weeks)	Patients (mean age 75 years) with "Alzheimer dementia who presented with behavioral disturbances"	**Community:** Outpatients "referred to Abolfazl Clinic, affiliated with Bushehr University of Medical Sciences"	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** A "complaint of behavioral disturbances" A NPI Part 1 score of > 1 in delusions, hallucinations, agitation/aggression, and irritability/ liability subscales	**Risperidone, oral tablet, 0.5-2mg/day:** n=23/48 **Topiramate, oral tablet, 25-50 mg/day:** n=25/48	**Risperidone, oral tablet, 0.5-2mg/day:** n=3/23 (13%) **Topiramate, oral tablet, 25-50 mg/day:** n=4/25 (16%)
Paleacu, 2008 (26)	**Location not defined:** Authors are based in Israel (6 weeks)	"Elderly AD patients with BPSD"	**Setting unspecified**	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** A score of > 6 on any item included in the NPI	**Placebo, oral tablet:** n=20/40 **Quetiapine, oral tablet, 50-300mg/day:** n=20/40	**Placebo, oral tablet:** n= 5/20 (25%) **Quetiapine, oral tablet, 50-300mg/day:** n= 8/20 (40%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Pollock, 2007 (45) ***Companions:*** **Dombrovski, 2010 (62)** **Culo, 2010 (63)**	**National:** The University of Pittsburgh Medical Center **(United States)** (12 weeks)	Non-depressed patients (mean age 82 years) with "dementia hospitalized because of behavioral symptoms"	**Hospital:** "Participants were recruited upon admission to the gero-psychiatric unit of an academic hospital" **Long-term care:** If patients improved sufficiently, some were "discharged to nursing homes or… personal care homes… for continued treatment under double-blind conditions" **Community:** If patients improved sufficiently, some were discharged to "residential homes for continued treatment under double-blind conditions"	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** "Target symptoms had to be of moderate or higher severity as evidenced by the need for hospitalization and a rating of 3 or higher (moderate to severe) on at least one of the agitation items (aggression, agitation, hostility) or psychosis items (suspiciousness, hallucinations, or delusions)" on the NBRS.	**Risperidone, oral capsule, 0.5-2.0mg/day:** n=50/103 **Citalopram, oral capsule, 10-40mg/day:** n=53/103	**Risperidone, oral capsule, 0.5-2.0mg/day:** n=30/50 (60%) **Citalopram, oral capsule, 10-40mg/day:** n=28/53 (53%)
Rainer, 2007 (31)	**National:** 6 centers in **Austria**; however, one centre did not recruit any patients (8 weeks)	Patients aged 55-85 years, with Alzheimer's disease, and behavioral disturbances	**Community:** Patients lived with someone for the duration of the study (out-patients) or had substantial daily contact with a caregiver	**Dementia diagnosed by:** DSM-IV and ICD-10 **BPSD Criteria for Inclusion:** "Suffer from behavioral disturbances" A NPI Part 1 score in "delusions, hallucinations, agitation/aggression, disinhibition and aberrant motor behavior"	**Risperidone, oral, 0.5-4 mg/day:** n=34/72 **Quetiapine, oral, 50-400 mg/day:** n=38/72	**Risperidone, oral, 0.5-4 mg/day:** n=3/34 (9%) **Quetiapine, oral, 50-400 mg/day:** n=4/38 (11%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Rappaport, 2009 (52)	**National:** 16 centres across the **United States** (24 hours)	Patients aged 55 to 95 with AD, vascular, or mixed dementia, and moderate- to severe acute exacerbations of agitated behaviours.	**Setting unclear:** Patients resided in "healthcare facilities"	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** A PANSS-EC score "≥ 15 and ≤ 32 with ≥1 of the 5 items with a score ≥ 4"	**Placebo, IM:** n=26/129 **Aripiprazole, IM, Fixed dose 5mg/d:** n=12/129 **Aripiprazole, IM, Fixed dose 10mg/d:** n=78/129 **Aripiprazole, IM, Fixed dose 15mg/d:** n=13/129	One (n=1) discontinuation was recorded; treatment arm was unspecified.
Savaskan, 2006 (46)	**National:** A single centre in **Switzerland** (5 weeks)	Alzheimer's patients, aged 65 or older, with behavioral and cognitive symptoms	**Hospital:** Participants were inpatients; "hospitalized on the gerontopsychiatric ward"	**Dementia diagnosed by:** ICD-10 **BPSD Criteria for Inclusion:** "Behavioral symptoms (at least three of the following: aggression, psychotic symptoms, sleep wake cycle disturbances, agitation, restlessness or sundowning"	**Quetiapine, oral, 25-225mg/day:** n=11/30 **Haloperidol, oral, 0.5-4mg/day:** n=11/30 ***Note:*** *30 patients "entered the study"; # randomized not defined.*	Four (n=4) "patients dropped out in the course of the study"; treatment arm was unspecified

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Schneider, 2006 (50) ***Companions:*** **Schneider, 2001 (64)** **Sultzer, 2008 (65)** **Vigen, 2011 (66)** **Schneider, 2003 (67)** **Mohamed, 2012 (68)** **Zheng, 2009 (69)** **Schneider, 2009 (70)** **Schneider, 2006 (50)** **Schneider, 2009 (71)** **Sultzer, 2009 (70)**	**National:** 42 sites across the **United States** ***Note:*** *Trial was conducted at 45 sites, but 3 did not randomly assign patients* (36 weeks; end of Phase I. **Note:** *This was treated as the end of study period due to changes in study design and how the data were reported)*	Outpatients (mean age 78 years) with "Alzheimer's disease and psychosis, aggression, or agitation"	**Community:** Patients that were ambulatory and living at home **Long-term care:** Patients living in assisted-living facilities. Ten patients entered nursing homes during phase 1 of the study.	**Dementia diagnosed by:** NINCDS-ADRDA (72) or DSM-IV **BPSD Criteria for Inclusion:** Delusions, hallucinations, aggression, or agitation that developed after the onset of dementia and was severe enough to disrupt their functioning and, in the opinion of the study physicians, to justify treatment with antipsychotic drugs" At least a moderate rating for conceptual disorganization, suspiciousness, or hallucinatory behavior on the BPRS scale. Alternatively, "a frequency rating of 'often' or 'more frequently' and a severe rating of at least 'moderate' were required for delusions, hallucinations, agitation, or 'aberrant motor behavior'" in the NPI.	**Placebo. oral capsule:** n=142/421 **Risperidone (Risperdal), oral capsule, 0-2.5mg/day:** n=85/421 **Olanzapine (Zyprexa), oral capsule, 0-17.5mg/day:** n=100/421 **Quetiapine (Seroquel), oral capsule, 0-200mg/day:** n=94/421	**Placebo. oral capsule:** n=121/142 (85%) **Risperidone (Risperdal), oral capsule, 0-2.5mg/day:** n=66/85 (78%) **Olanzapine (Zyprexa), oral capsule, 0-17.5mg/day:** n=80/100 (80%) **Quetiapine (Seroquel), oral capsule, 0-200mg/day:** n=77/94 (82%) ***NOTE:*** *Phase I discontinuation rates only*

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Street, 2000 (27) ***Companions:*** **Cummings, 2002 (73)** **Kennedy, 2001 (74)** **Mintzer, 2001 (75)** **Clark, 2001 (76)** **Street, 2001 (77)**	**National:** 28 sites across the **United States** (6 weeks)	Elderly patients with AD, "psychosis and/or agitation/ aggression"	**Long-term care:** Residents of nursing care facilities	**Dementia diagnosed by:** NINCDS-ADRDA (72) **BPSD Criteria for Inclusion:** A score of "3 or higher on any of the Agitation/ Aggression, Hallucinations, or Delusions items" of the NPI-NH.	**Placebo, oral tablet:** n=47/206 **Olanzapine, oral tablet, fixed dose 5mg/d:** n=56/206 **Olanzapine, oral tablet, fixed dose 10mg/d:** n=50/206 **Olanzapine, oral tablet, fixed dose 15mg/d:** n=53/206	**Placebo, oral tablet:** n=11/47 (23%) **Olanzapine, oral tablet, fixed dose 5mg/d:** n=11/56 (20%) **Olanzapine, oral tablet, fixed dose 10mg/d:** n=14/50 (28%) **Olanzapine, oral tablet, fixed dose 15mg/d:** n=18/53 (34%)
Streim, 2008 (29) ***Companions:*** **Streim, 2004 (78)** **Paleacu, 2010 (79)**	**National:** 35 centers across the **United States** (6 weeks, **NOTE**: this was the end of double-blind period for all patients)	Institutionalized men and women, aged 55-95 years of age, with "psychosis of AD"	**Long-term care:** Patients residing in nursing homes and residential assisted-living facilities	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** "Psychotic symptoms of delusions or hallucinations (at least intermittently) for ≥ 1 month" A score of ≥ 6 on either the delusions or hallucinations items of the NPI-NH	**Placebo, route unspecified:** n=125/256 **Aripiprazole, route unspecified, 2-15 mg/day:** n=131/256	***Note:*** *due to the change in study design at Week 6 for some patients, and authors' style of reporting, only data to week 6 was extracted from this study. Number of discontinuations before or at week 6 could not be discerned.*

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Astra Zeneca Pharma-ceuticals, 2009 (22)	**Location not defined:** Study took place across 18 centres (6 weeks)	Patients "aged 65 years or more presenting with dementia and psychoses"	**Setting not defined**	**Dementia diagnosed by:** ICD-10 **BPSD Criteria for Inclusion:** "Presence of predominantly delusional or hallucinatory symptoms"	**Quetiapine (Seroquel), oral tablet, 50-300mg/day:** n=55/112 **Haloperidol, oral capsule and tablet, 1-6mg/day:** n=57/112	**Quetiapine (Seroquel), oral tablet, 50-300mg/day:** n=17/55 (31%) **Haloperidol, oral capsule and tablet, 1-6mg/day:** n=17/57 (30%)
Herz, 2002 *(Abstract only) (23)*	**Location not defined:** Primary author is based in the **United States** (6 weeks)	"Agitated male patients over age 65 with advanced Alzheimer's dementia"	**Setting not defined**	**Dementia diagnosed by:** Not reported **BPSD Criteria for Inclusion:** Baseline agitation: rating of Moderate on both CGS and one of ADAS agitation items or the BPRS Tension or Excitement scales.	**Placebo, route unspecified:** n=8/29 **Risperidone, route unspecified, 0.5-4mg/day:** n=14/29 **Olanzapine, route unspecified, 2.5-20mg/day:** n=7/29 ***Note:*** *29 patients are reported on; # randomized was not defined.*	**Placebo, route unspecified:** n=0/8 (0%) **Risperidone, route unspecified, 0.5-4mg/day:** n=0/14 (0%) **Olanzapine, route unspecified, 2.5-20mg/day:** n=1/7 (14%)
Barak, 2011 (24)	**National:** The Abarbanel Mental Health Center in **Israel** (6 weeks)	Inpatients (mean age 78 years) with AD, who had been "hospitalized because of behavioral symptoms"	**Hospital:** A psychiatric inpatient setting in Israel; "Patients were hospitalized for the duration of the study"	**Dementia diagnosed by:** DSM-IV **BPSD Criteria for Inclusion:** "Patients had to be admitted to our psychiatric center… because of signs and symptoms of psychosis, aggression or agitation that were severe enough to warrant hospitalization"	**Risperidone, oral tablet, 1mg/day:** n=20/40 **Escitalopram , oral tablet, 10mg/day:** n=20/40	**Risperidone, oral tablet, 1mg/day:** n=9/20 (45%) **Escitalopram , oral tablet, 10mg/day:** n=4/20 (20%)

Last Name of First Author, Year	Location and # of Centers (Treatment duration)	Indication for Treatment	Care Setting	Scale(s) Used for Dementia Diagnosis* and BPSD Criteria+ for Inclusion	Total No. Randomized, Group description and No. randomized to group	No. (%) Patients Discontinued by Treatment Arm
Teranishi, 2013 (33)	**National:** The Sato Psychiatric Hospital in **Japan** (8 weeks)	Elderly inpatients with dementia and BPSD	**Hospital:** Inpatients at Sato Psychiatric Hospital in Japan. *Patients entered hospital because their BPSD symptoms could no longer be managed by caregivers or nursing homes*	**Dementia diagnosed by:** DSM-IV; dementia subtypes were diagnosed based on NINCDS-ADRDA(72), NINDS-AIREN (80), Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy Bodies (81) **BPSD Criteria for Inclusion:** At least 1 symptom score of > 4 in NPI-NH subscales at trial start	**Risperidone, oral, flex dose, 0.5-2.0 mg/d:** n=27/55 **Fluvoxamine oral, flex dose, 25-200 mg/d:** n=28/55 ***Note:*** *The Yukukansan (herbal treatment) trial arm has been excluded from this study; n=55 were randomized to two of the three trial arms of interest.*	**Risperidone, oral, flex dose, 0.5-2.0 mg/d:** n=1/27 (4%) **Fluvoxamine oral, flex dose, 25-200 mg/d:** n=2/28 (7%)
De Deyn, 2012 (25)	**International:** 12 sites across **Belgium, Norway, Australia, Canada,** and **South Africa** (6 weeks)	"Patients with AD, aged ≥65 years…requiring antipsychotic medication for symptoms of psychosis and/or agitation"	**Long-term care:** Participants resided in "nursing homes or equivalent institutions"	**Dementia diagnosed by:** DSM-IV and ICD-10 revision Research Diagnostic Criteria **BPSD Criteria for Inclusion:** NPI (Part 1) score of ≥3 for any of: "agitation, delusions and hallucinations; stable general health appropriate for age; willingness and ability to comply with the safety monitoring guidelines and to adhere to the schedule of assessments"	**Quetiapine XR, oral tablet, 50-300 mg/day:** n=68/100 **Quetiapine IR, oral tablet, 50-300 mg/day:** n=32/100	**Quetiapine XR, oral tablet, 50-300 mg/day:** n=9/68 (13%) **Quetiapine IR, oral tablet, 50-300 mg/day:** n=1/32 (3%)
Shen, 2014 (48)	**National:** 1 centre in Shanghai, **China** (6 months)	Outpatients (mean age 73 years) with AD and psychological and behavioral symptoms	**Community:** Participants were outpatients	**Dementia diagnosed by:** NINCDS-ADRDA (72) or DSM-IV **BPSD Criteria for Inclusion:** Patients had daily or intermittent hallucinations, delusions, agitation, and aggression daily or intermittently for at least 4 weeks prior to visiting doctors	**Not taking Quetiapine:** n=25/51 **Quetiapine, oral, 25-400mg/day:** n=26/51	Discontinuations were not reported

Appendix C: Included Studies with No Extracted Data

Suh GH, Son HG, Ju YS, Jcho KH, Yeon BK, Shin YM, et al. A randomized, double-blind, crossover comparison of risperidone and haloperidol in Korean dementia patients with behavioral disturbances. Am J Geriatr Psychiatry. 2004;12(5):509-16 (17)

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Satterlee W, Reams S, Burns P, Hamilton S, Tran PV, GD T. A clinical update on olanzapine treatment in schizophrenia and in elderly Alzheimer's disease patients. Psychopharmacol Bulletin. 1995;31:534 (19)

Galeotti F, Vanacore N, Gainotti S, Izzicupo F, Menniti-Ippolito F, Petrini C, et al. How legislation on decisional capacity can negatively affect the feasibility of clinical trials in patients with dementia. Drugs and Aging. 2012;29(8):607-14 (20)

Mulsant BH, Gharabawi GM, Bossie CA, Mao L, Martinez RA, Tune LE, et al. Correlates of anticholinergic activity in patients with dementia and psychosis treated with risperidone or olanzapine. J Clin Psychiatry. 2004;65(12):1708-14 (21)

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