

Atypical antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia: systematic review

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Abstract

Objective To review the role of oral atypical antipsychotic drugs in the management of the behavioural and psychological symptoms of dementia (BPSD).

Data sources Medline, Embase, and the Cochrane Library. Reference lists were reviewed and experts were contacted to identify additional trials.

Study selection Double blind randomised controlled trials that evaluated the four oral atypical antipsychotic therapies for BPSD.

Review methods Two reviewers assessed trial validity independently.

Data extraction Demographics of patients, study duration, dose of antipsychotic, primary end points, adverse events.

Results 77 abstracts were reviewed. Five randomised trials (1570 patients) evaluating risperidone and olanzapine were identified. The quality of trials was generally good. Most participants were in an institution (>96%), elderly (weighted mean 82.3 years), and had Alzheimer's disease (76.3%). Trials lasted 6-12 weeks. Treatment with atypical antipsychotic drugs was superior to placebo for the primary end point in three of the five trials. Two trials comparing risperidone with haloperidol did not find any differences in the primary measures of efficacy. Adverse events were common and included extrapyramidal symptoms, somnolence, and abnormal gait.

Conclusions Although atypical antipsychotic drugs are being used with increasing frequency, few randomised trials have evaluated their use for BPSD. Limited evidence supports the perception of improved efficacy and adverse event profiles compared with typical antipsychotic drugs.

Introduction

The term "behavioural and psychological symptoms of dementia" (BPSD) has been proposed to describe the spectrum of non-cognitive manifestations of dementia that include verbal and physical aggression, agitation, psychotic symptoms (hallucinations and delusions), sleep disturbances, and wandering.¹ BPSD can

decrease quality of life for patients and caregivers and increase the likelihood of admission to an institution.²

Management of BPSD has not been standardised and currently entails various non-pharmacological and pharmacological approaches. For many years, typical antipsychotic (neuroleptic) drugs were the most common treatment. Although there has been extensive experience with their use, typical antipsychotics are only modestly effective and have potentially serious adverse effects that limit their usefulness in older adults.³

Recently, atypical antipsychotics have become available. These drugs have been widely adopted to treat psychotic disorders because they are perceived to have superior efficacy and safety compared with typical agents. Compared with typical antipsychotic agents, atypical antipsychotics are thought to be less likely to cause extrapyramidal symptoms such as parkinsonism and tardive dyskinesia.⁴⁻⁶ Data supporting the efficacy and safety of atypical antipsychotics need to be examined, especially in light of their high costs and newly identified adverse events.

While the use of atypical antipsychotic drugs has been well studied in younger adults with psychotic symptoms, less information is available regarding their use in older adults. To assess the benefits and risks of atypical antipsychotic drugs for BPSD, we performed a systematic review of the randomised trials in this field.

Methods

Search strategy—We carried out electronic searches of Medline (1966-September 2003), Embase (1980-September 2003), and the Cochrane library (issue 1, 2003). We used MeSH headings: dementia, antipsychotic agents, atypical, risperidone or risperdal, olanzapine or zyprexa, quetiapine or seroquel, and clozapine or clozaril, and searched for Enzyme Commission numbers assigned to new substances identified by the Chemical Abstracts Service registry. We also manually searched reference lists and contacted clinical experts to identify additional trials.

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Selection of eligible trials—We included all published double blind randomised controlled trials that evaluated the four oral atypical antipsychotic drugs used to treat BPSD available in Canada, the United States, and the United Kingdom (clozapine, risperidone, olanzapine, and quetiapine). Two geriatric medicine specialists (PEL and SSG) reviewed each abstract to select papers meeting inclusion criteria. The two reviewers independently appraised each trial using a standardised form to record data relating to demographics of patients, study duration, drug dose, and primary end points. We extracted data on the most common and serious reported adverse events. The two reviewers also independently scored the methodological quality of the trials.^{7 8}

Results

From the 77 abstracts reviewed, we identified five randomised trials (1570 patients).^{9–13} Of the remaining abstracts, 66 described articles that did not meet our inclusion criteria (for example, letters, review articles, observational studies), one study was an open label extension of a previously published trial, and four studies involved post hoc analyses of trial data. We also excluded a trial that evaluated intramuscular olanzapine¹⁴ because of the route of administration and short length of follow up (24 hours).

Four trials evaluated risperidone, and one evaluated olanzapine. All trials were sponsored by the pharmaceutical industry. Table 1 details the assessments of trial quality. In general, trials were of good quality, but only two adequately reported efforts to maintain concealment of allocation.⁸ Table 1 also gives characteristics of the participants. Most participants were in an institution (>96%). The Chan trial also enrolled some people who were living in the community.¹⁰

Table 2 outlines the main efficacy results. Several factors made interpretation of the efficacy outcomes in the trials complex. Firstly, several different measure-

ment scales were used to assess the benefits of atypical antipsychotics in managing BPSD. A second element of complexity arose from the fact that some trials defined a >30% reduction in scores as a “clinical response” while others used >50% reduction as their definition. Thirdly, the trials often reported changes on both total scores and several subscale scores. Finally, the use of multiple comparisons can inflate the type I error rate. Only three trials described statistical methods to compensate for making multiple comparisons.^{9 12 13}

Efficacy of atypical antipsychotics v placebo

Katz et al compared three fixed doses of risperidone (0.5, 1, and 2 mg/day) with placebo.¹² The BEHAVE-AD, CMAI, and CGI (clinical global impressions) scales were used to measure efficacy. Patients who received 1 or 2 mg/day of risperidone showed significant improvements compared with the placebo group on several outcome measures.

De Deyn et al compared risperidone with haloperidol and placebo.¹¹ The primary outcome was the proportion of participants achieving ≥30% reduction from baseline to end point in BEHAVE-AD total scores. For this outcome, risperidone was not found to be superior to haloperidol or placebo. The authors, however, reported significant differences between risperidone and placebo on multiple secondary end points.

Brodsky et al compared flexible doses of risperidone with placebo.⁹ The adjusted CMAI total aggression scores were significantly better with risperidone than with placebo. BEHAVE-AD total and subscale scores and CMAI scores were also better with risperidone.

The only published trial evaluating oral olanzapine was reported by Street et al.¹³ This trial randomised participants to placebo or one of three fixed doses of olanzapine. The primary end point was the NPI-NH¹⁵ core total score, which was used to classify patients as responders (≥50% reduction from baseline) or

Table 1 Characteristics and methodological quality of randomised trials in review

	Katz, 1999 ¹²	De Deyn, 1999 ¹¹	Chan, 2001 ¹⁰	Brodsky, 2003 ⁹	Street, 2000 ¹³
Interventions	Risperidone v placebo	Risperidone v haloperidol v placebo	Risperidone v haloperidol	Risperidone v placebo	Olanzapine v placebo
No of patients	625 (462 risperidone, 163 placebo)	344 (115 risperidone, 115 haloperidol, 114 placebo)	58 (29 risperidone, 29 haloperidol)	337 (167 risperidone, 170 placebo)	206 (159 olanzapine, 47 placebo)
Drug dose (per day)	Fixed: 0.5, 1, or 2 mg	Flexible: mean 1.1 mg risperidone, 1.2 mg haloperidol	Flexible: mean 0.85 mg risperidone, 0.9 mg haloperidol	Flexible: mean 0.95 mg	Fixed: 5, 10, or 15 mg
Duration (weeks)	12	12	12	12	6
Mean age (years)	82.6	81.3	80.5	83.0	82.8
Diagnosis	73% AD, 15% VaD, 11% mixed	67% AD, 26% VaD, 7% mixed	79% AD, 21% VaD	58% AD, 29% VaD, 13% mixed	100% AD
Mean MMSE (out of 30) ²¹	6.6	8.4	8.0	5.5	6.7
Assessment of quality:					
Randomisation*	1	2	1	1	2
Blinding†	2	2	1	2	2
Withdrawals/dropouts‡	1	1	1	1	1
Jadad quality score§	4	5	3	4	5
Concealment¶	0	1	0	0	1
Follow up**	2	2	2	2	2

AD=Alzheimer's disease; MMSE=Folstein mini-mental state examination; VaD=vascular dementia.

*0=not randomised or pseudo-randomised; 1=randomised, method not described; 2=randomised, appropriate method reported.

†0=no blinding or inappropriate method; 1=double blind, blinding not reported; 2=double blind, blinding appropriate.

‡0=not described for each group; 1=described by group.

§Score out of 5, based on scores for randomisation, blinding, and withdrawals/dropouts; does not consider concealment of allocation or adequacy of follow up.¹⁷

¶0=no concealment process described; 1=concealment process described.

**0=no or inadequate reporting of follow up; 1=reported, data not analysed according to intention to treat; 2=reported, data analysed according to intention to treat.

Table 2 Efficacy and safety results from included trials

	Katz, 1999 ¹²		De Deyn, 1999 ¹¹		Chan, 2001 ¹⁰		Brodaty, 2003 ⁹		Street, 2000 ¹³	
	Risperidone (1 mg/day) (n=148)	Placebo (n=163)	Risperidone (n=115)	Placebo (n=114)	Risperidone (n=29)	Haloperidol (n=29)	Risperidone (n=167)	Placebo (n=170)	Olanzapine (5 mg/day) (n=55)	Placebo (n=45)
Efficacy										
Clinical end point	≥50% reduction in BEHAVE-AD total score*		≥30% reduction in BEHAVE-AD total score*		Not specified		CMAI total aggression score*		≥50% reduction in NPI-NH core total score*	
No (%) who achieved end point	67 (45)	53 (33†)	62 (54)	54 (47)	—	—	—	—	36 (66)	16 (36†)
Change in total scores*:										
BEHAVE-AD	-6.5	-4.2†	-8.6	-6.2†	—	—	-6.8	-2.3†	—	—
CMAI	Raw data not provided†		-8.3	-4.9†	-8.1	-10.0‡	-7.5	-3.1†	—	—
NPI-NH	—	—	—	—	—	—	—	—	-7.6	-3.7†
No (%) with effect										
Extrapyramidal symptoms	19 (13)	12 (7‡)	17 (15)	13 (11‡)	Raw data not provided†		39 (23)	27 (16§)	Raw data not provided‡	
Any adverse event	121 (82)	138 (85)	88 (77)	83 (73)	NR		157 (94)	157 (92)	NR	
Serious adverse events	24 (16)	21 (13‡)	NR		NR		28 (17)	15 (9§)	NR	
Withdrawals	45 (30)	44 (27§)	47 (41)	40 (35§)	2 (7)	1 (3§)	45 (27)	56 (33‡)	11 (20)	11 (24‡)

BEHAVE-AD=behavioural pathology in Alzheimer's disease rating scale; CMAI=Cohen-Mansfield agitation inventory; NPI-NH=neuropsychiatric inventory-nursing home version; NR=not reported.

*From baseline to end point.

†Significant improvement with risperidone or olanzapine v control (haloperidol or placebo) (P<0.05 considered to be significant).

‡No significant difference.

§Significance not reported.

non-responders. On this measure, olanzapine 5 and 10 mg/day were superior to placebo.

Efficacy of atypical v typical antipsychotic therapy

Two trials compared risperidone with haloperidol. A post hoc analysis by De Deyn et al failed to show greater improvements with risperidone than with haloperidol on the BEHAVE-AD total scores but did show significant improvements with risperidone over haloperidol on aggressiveness subscales of BEHAVE-AD and CMAI.¹¹ Chan et al compared flexible doses of 0.5-2 mg/day of either risperidone or haloperidol.¹⁰ No significant differences were found. However, the small sample size of this trial limits the conclusions that can be drawn from these results.

Adverse events and withdrawals

Investigators used various scales to specifically assess for extrapyramidal symptoms, a common adverse effect of antipsychotics. Most symptoms examined were presumably due to parkinsonism because tardive dyskinesia would be unlikely to develop during these short trials (6-12 weeks). The trials of De Deyn et al¹¹ and Brodaty et al⁹ (both of which used mean doses of about 1 mg/day of risperidone) did not document significant differences in extrapyramidal symptoms associated with treatment rather than placebo. Katz et al found a dose dependent increase in extrapyramidal symptoms with risperidone that was significant for participants receiving 2 mg/day.¹² Street et al reported no differences with olanzapine compared with placebo.¹³ The two trials that compared risperidone and haloperidol both found that extrapyramidal symptoms were more common with haloperidol.^{10, 12}

Brodaty et al reported serious adverse events in 9% of participants receiving placebo and in 17% of those taking risperidone.⁹ In the risperidone group, six cerebrovascular adverse events were noted while none occurred in the placebo group.

Despite their short duration, most trials reported high withdrawal rates in the treatment and placebo groups. In two trials half of the withdrawals were due to adverse events.^{11, 12} Katz et al found that withdrawals

related to adverse events were dose dependent (12% of placebo subjects v 8%, 16%, and 24% of participants received 0.5, 1, and 2 mg/day of risperidone, respectively).¹² A similar dose dependent withdrawal rate was found with olanzapine in the trial of Street et al.¹¹ In the trial by Chan et al only three patients withdrew; one patient receiving risperidone withdrew because of a hip fracture.¹⁰

Discussion

Our review identified only five trials evaluating use of oral atypical antipsychotic drugs to treat the behavioural and psychological symptoms of dementia (BPSD). There have been no head to head trials comparing atypical antipsychotics. An independent review identified similar trials of atypical antipsychotic therapies and came to similar conclusions.¹⁶

Improvements in BPSD were commonly seen with atypical antipsychotics and with placebo. In the clinical course of BPSD symptoms often persist over periods as long as a year,¹⁷ and the improvements with placebo may result from non-pharmacological co-interventions received by all trial participants.

The trials reviewed were short, lasting only 6-12 weeks. In clinical practice, however, patients with BPSD are sometimes maintained on antipsychotic drugs for months, and symptoms may persist for over a year.¹⁷ Street et al presented open label follow up results of their trial to six months.¹⁸ Other authors have claimed that atypical antipsychotics may be safe for long term treatment of BPSD.¹⁹ Ideally, a longer duration of follow up should be incorporated into future trials.

When treatment of BPSD is indicated, the choice of atypical antipsychotic drug is often made on the basis of how likely it is that patient will experience an adverse event. Common adverse events include antipsychotic induced parkinsonism, somnolence, and abnormal gait. Adverse events seem to be dose related, supporting the practice of starting with a low dose and increasing slowly as tolerated.

What is already known on this topic

Antipsychotic drugs are commonly used to manage the behavioural and psychological symptoms of dementia (BPSD)

Newer "atypical" antipsychotic therapies are thought to have better efficacy and adverse event profiles than typical antipsychotic drugs

What this study adds

Only five published randomised trials have assessed the efficacy and safety of atypical antipsychotic drugs for BPSD

Evidence to support the perception of improved efficacy and adverse event rates is limited

Further evidence is required before such use of these drugs can be endorsed

There is increasing evidence that treatment with atypical antipsychotics may be associated with metabolic disturbances such as impaired glucose metabolism and hyperlipidaemia.²⁰ The trials we reviewed did not find evidence of such metabolic disturbances, but it is unlikely that these events would become apparent over only 6-12 weeks.

Conclusions

Although atypical antipsychotic drugs are being used with increasing frequency, only a few randomised trials have evaluated their use in BPSD. Additional evidence is required to support the perception of an improved efficacy and adverse event profile relative to typical antipsychotic agents. In light of concern regarding the potential adverse events associated with treatment with these drugs, further evidence is required before their use can be endorsed in the management of BPSD.

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Competing interests: MF has received honorariums from Janssen-Ortho for participating in an advisory board meeting, consulting, and chairing an educational session, and has been supported by Janssen-Ortho to attend conferences. He has also received honorariums from Pfizer and Novartis and has been supported by Pfizer and Novartis to attend conferences.

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Endpiece

Superiority

I believe there is no one principle which predominates in human nature so much in every stage of life, from the cradle to the grave, in males and females, old and young, black and white, rich and poor, high and low, as this passion for superiority.

McCullough D. *John Adams* [1777]. New York: Simon & Schuster, 2001:170

Jeremy Hugh Baron, honorary professorial lecturer, Mount Sinai School of Medicine