

Efficacy of Atypical Antipsychotics in Elderly Patients With Dementia

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Pharmacotherapy in patients with dementia aims to improve distressing behavioral and psychological signs of dementia after nonpharmacologic interventions fail, without causing unacceptable side effects or exacerbating underlying cognitive impairment. We review data describing risperidone (3 published placebo-controlled trials), olanzapine (1 abstract regarding a placebo-controlled trial and a published placebo-controlled trial), quetiapine (1 published open-label trial and an abstract regarding a placebo-controlled trial), and aripiprazole (1 abstract regarding a placebo-controlled trial). For example, a 12-week study of risperidone in patients with Alzheimer's disease showed a dose-related improvement in psychosis and agitation. The frequency of extrapyramidal symptoms (EPS) was also significantly greater in patients receiving the highest doses. A 6-week study of olanzapine showed greater improvement than placebo in agitation/aggression and psychosis with doses of 5 and 10 mg/day, but not 15 mg/day, with side effects including gait disturbance and sedation at all doses. A 52-week, open-label trial of quetiapine (median dose = 138 mg/day) in elderly patients with psychosis suggested good tolerability with apparent behavioral benefit; EPS improved or remained unchanged in most patients. Limited data describing aripiprazole have shown inconclusive evidence regarding relief of psychosis in elderly patients with Alzheimer's disease-related dementia, with apparently good tolerability over the short term. It appears that, in the aggregate, atypical antipsychotics are efficacious for treatment of agitation in dementia, with less clear impact on psychosis, but their tolerability profiles clearly differ. The National Institute of Mental Health-funded Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease project will provide the first head-to-head comparisons of atypicals in dementia and will examine possible drug-drug differences between efficacy and effectiveness.

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The goal of pharmacotherapy with psychotropics in patients with dementia is to relieve the behavioral and psychological signs and symptoms of dementia, which include psychotic features, anxious and depressive features, agitation and aggression, and apathy, without causing undue side effects or exacerbating underlying cognitive impairment. Antipsychotic use is reserved for

treatment of agitation and/or psychosis that is considered clinically significant and justifies somatic therapy.

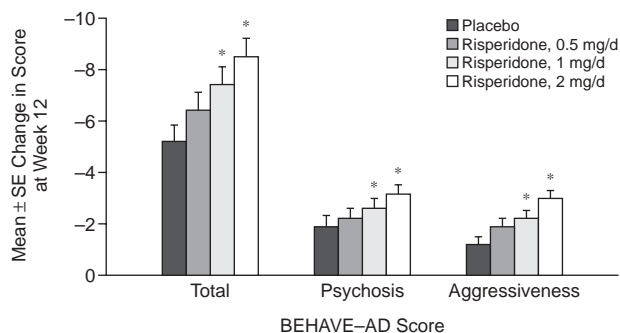
It has been estimated that only one third of patients with dementia show behavioral improvement with conventional antipsychotic treatment,¹ while the majority of patients treated with conventional antipsychotics will experience side effects such as akathisia, parkinsonism, tardive dyskinesia, sedation, peripheral and central anticholinergic effects, postural hypotension, and cardiac conduction defects.² These tolerability issues are not confined to the elderly; however, relative to nongeriatric populations, older patients appear to have heightened sensitivity and elevated susceptibility to these highly distressing side effects. It is clear that a need exists for more effective treatment strategies for dementia. Atypical antipsychotics are characterized by efficacy at least equivalent to that of conventional agents in younger populations and generally improved tolerability profiles compared with older agents. This article reviews progress in the field of treating dementia with the atypical antipsychotics risperidone, olanzapine, and quetiapine and considers emerging data describing aripiprazole.

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Figure 1. Changes From Baseline in Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) Scores Following a 12-Week, Double-Blind, Placebo-Controlled Study of Risperidone in Elderly Patients With Dementia^a



^aAdapted with permission from Katz et al.³

* $p = .05$ to $< .001$.

RISPERIDONE

Risperidone has been investigated, as well as used extensively, in patients with dementia. A 12-week, double-blind, placebo-controlled study of 625 nursing home residents with psychosis and/or agitation associated with Alzheimer's disease, vascular dementia, or a combination of both (mixed dementia) examined the efficacy and tolerability of 3 fixed doses of risperidone (0.5, 1, or 2 mg/day).³ Patients showed a dose-related response (defined as $\geq 50\%$ decline in the primary outcome measure, the Behavioral Pathology in Alzheimer's Disease rating scale [BEHAVE-AD] total score) to risperidone. Specifically, patients given 1 or 2 mg/day (but not 0.5 mg/day) of risperidone showed significant improvement compared with placebo ($p = .02$ and $p = .002$, respectively) (Figure 1). The most frequent adverse events (AEs) in patients receiving placebo or risperidone, 0.5, 1, or 2 mg/day, included reported injury (37%, 33%, 28%, and 32%, respectively), somnolence (8%, 10%, 17%, and 28%, respectively), fall (20%, 16%, 13%, and 25%, respectively), extrapyramidal disorder (7%, 7%, 13%, and 21%, respectively), and peripheral edema (6%, 16%, 13%, and 18%, respectively). The incidence of extrapyramidal disorder was the only AE that differed significantly between risperidone (2 mg/day) and placebo ($p < .001$), while some AEs that were not statistically significantly different from placebo are nonetheless seen clinically in some patients, e.g., edema and somnolence. The severity of parkinsonism and hypokinesia (Extrapyramidal Symptom Rating Scale scores) was significantly greater with 2 mg/day of risperidone compared with placebo ($p < .001$).

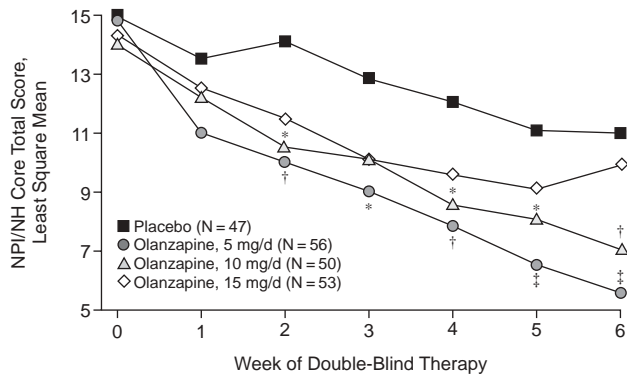
The efficacy of risperidone was less clear in a 13-week study of 344 nursing home residents with Alzheimer's disease, vascular dementia, or mixed dementia complicated

by psychosis and/or agitation.⁴ There was no evidence of difference in patient response (defined as $\geq 30\%$ decline in BEHAVE-AD total score at endpoint or week 12) to flexibly dosed risperidone or haloperidol compared with placebo (mean doses at endpoint were 1.1 mg/day and 1.2 mg/day, respectively). Specifically, response rates at endpoint were 47% for placebo, 54% for risperidone, and 63% for haloperidol. Conversely, planned analysis of a secondary parameter, change from baseline in Cohen-Mansfield Agitation Inventory (CMAI) total aggression scores, showed significant improvement in the risperidone group compared with the placebo group at week 12 and endpoint ($p = .02$ and $p = .01$, respectively). No significant difference was seen in AEs across the 3 groups, while rates of extrapyramidal symptoms (EPS) were greater in the patients treated with haloperidol ($p < .05$).

More recently, results from a 12-week, placebo-controlled study of risperidone in 345 nursing home residents with Alzheimer's disease, vascular dementia, or mixed dementia have been reported.⁵ Unlike the previous studies, this Australia- and New Zealand-based study focused on the treatment of aggression using the total aggression subscale score of the CMAI as its primary efficacy outcome. Patients were given placebo or flexibly dosed with risperidone up to a maximum of 2 mg/day and received a mean (SE) dose of risperidone at endpoint of 0.95 (0.03) mg/day. At endpoint, patients treated with risperidone showed a significant improvement in the CMAI total aggression score ($p < .01$) and Clinical Global Impressions of Change scale (CGI-C) score as rated by the investigator and the caregiver ($p < .001$). The results from the investigator-rated CGI-C assessments showed improvement in 63.3% of the risperidone group compared with 36.6% in the placebo group. The most common AEs in patients treated with placebo or risperidone were somnolence (25.3% and 36.5%, respectively), injury (37.1% and 35.9%, respectively), falls (27.1% and 25.1%, respectively), and urinary tract infection (14.7% and 23.4%, respectively). The most frequent serious AEs were injury, cerebrovascular disorder, pneumonia, and accidental overdose. Cerebrovascular AEs (CVAEs) were reported in 3 patients (1.8%) treated with placebo and 15 patients (9%) treated with risperidone, 5 of whom suffered a stroke and 1 of whom suffered a transient ischemic attack. Of these 6 patients (age range, 79–89 years), 5 had either vascular dementia or mixed dementia and 1 had Alzheimer's disease; all 6 patients had significant predisposing factors for cerebrovascular events (hypertension, atrial fibrillation, and diabetes mellitus).

The higher incidence of CVAEs in the risperidone group reported in the study by Brodaty et al.⁵ prompted an examination of CVAEs reported across 4 placebo-controlled dementia trials with risperidone.⁶ This overview of risperidone safety showed that risperidone led to twice as many reported CVAEs compared with placebo (4% and

Figure 2. Neuropsychiatric Inventory-Nursing Home Version (NPI/NH) Scores Following a 6-Week Study of Elderly Patients With Alzheimer's Disease Treated With Olanzapine^a



^aReprinted with permission from Street et al.¹⁰

* $p < .05$ vs. placebo.

† $p < .01$ vs. placebo.

‡ $p < .001$ vs. placebo.

2%, respectively). This perceived heightened risk precipitated an update of safety information that was issued to doctors and pharmacists in Canada and then in the United States describing the possible higher incidence of strokes or related events in elderly patients with dementia following treatment with risperidone.^{6,7} It should be noted that risperidone showed no increased risk of CVAEs in 2 of the 4 trials examined.

Treating physicians should make a measured judgment of the risk-benefit ratio when selecting any of the atypicals. They need to consider the likelihood that treatment will relieve morbid behavioral complications relative to any risk of causing harm. If an alternative agent is to be used, what is the extent of information regarding both its safety and efficacy?⁸

OLANZAPINE

A placebo-controlled, flexible-dose study in 238 outpatients with dementia complicated by agitation or psychosis showed no benefit of olanzapine therapy.⁹ Since the primary objective of this study was to characterize patient tolerability relative to dose, the perceived lack of efficacy of olanzapine was probably a result of suboptimal dosing (mean dose at end of study = 2.7 mg/day). Olanzapine was subsequently found to show benefit in a 6-week, double-blind, placebo-controlled study of 206 nursing home residents with Alzheimer's disease who exhibited psychosis and/or agitation.¹⁰ This study investigated the efficacy and tolerability of fixed doses of olanzapine (5, 10, or 15 mg/day) and found that the proportion of patients responding (defined as $\geq 50\%$ decline in Neuropsychiatric Inventory-Nursing Home version [NPI/NH] core total scores) to olanzapine, 5 or 10 mg/day, was significantly

different from placebo ($p = .005$ and $p = .04$, respectively). Further, patients receiving 5 or 10 mg/day showed significant improvements in the sum of the agitation/aggression, hallucinations, and delusions items (core total) of the NPI/NH compared with placebo ($p < .001$ and $p = .006$, respectively) (Figure 2).

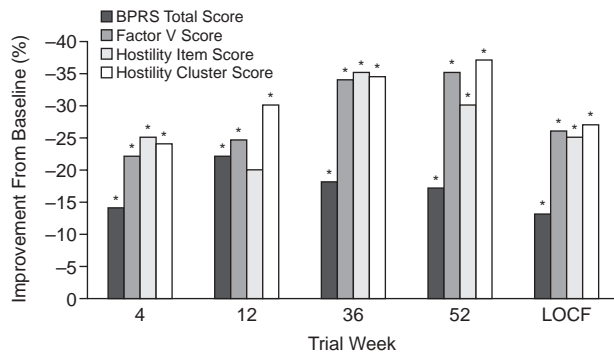
Adverse events associated with placebo or olanzapine at doses of 5, 10, or 15 mg/day in elderly patients included accidental injury (28%, 25%, 24%, or 38%, respectively), somnolence (6%, 25%, 26%, and 36%, respectively), pain (11%, 14%, 12%, and 25%, respectively), and abnormal gait (2%, 20%, 14%, and 17%, respectively).¹⁰ Somnolence and abnormal gait were the only AEs that had a significantly higher incidence in the olanzapine groups compared with placebo, and these were dose-related (5 mg/day [$p < .05$ and $p < .01$, respectively], 10 mg/day [$p < .05$, somnolence only], 15 mg/day [$p < .001$ and $p < .05$, respectively]). The incidence of pooled AEs that could be related to peripheral anticholinergic activity was significantly greater in the 15-mg/day olanzapine group compared with placebo ($p = .008$); there was no difference in the incidence of pooled AEs that could be related to central anticholinergic activity. The olanzapine data set is the second largest in dementia at present.

QUETIAPINE

The bulk of available data regarding use of quetiapine in dementia come from an open-label, 52-week study of 184 patients with various psychotic disorders (the majority of whom had dementia) conducted to explore dosing, titration, safety, and tolerability and to preliminarily assess efficacy.¹¹ The median dose at time of withdrawal was 150 mg/day, and quetiapine was well tolerated, with most reported AEs being of mild or moderate intensity. The most frequently reported AEs included somnolence (31%), dizziness (17%), and postural hypotension (15%), all of which were transient in the majority of patients, occurred in the first few weeks of treatment, and resolved over time. Accidental injuries (24%) were associated with neither any specific time in the study nor any specific dose of quetiapine. Agitation (16%) was also transient and occurred throughout the study. EPS, as assessed by mean total score on the Simpson-Angus Scale or Abnormal Involuntary Movement Scale, were either unchanged or improved from baseline for the duration of the study. The low rate of tardive dyskinesia (TD) was consistent with results previously reported by Jeste et al.¹²

Good clinical practice dictates that patients receive individualized pharmacotherapeutic dosing regimens initiated and modified relative to clinical efficacy and tolerability. In the open-label study,¹¹ quetiapine was administered in the range 12.5 to 800 mg/day; a dose of 800 mg/day was necessitated in 1 patient only as she was asymptomatic at this dose, had reemergence of psychotic symptoms at

Figure 3. Changes in Brief Psychiatric Rating Scale (BPRS) Total and Subscale Scores Following a 52-Week, Open-Label, Multicenter Trial of Quetiapine in Elderly Alzheimer's Disease Patients With Psychosis^a



^aAdapted with permission from Schneider et al.¹³ Median quetiapine dose was 100 mg/day.

* $p < .05$ vs. baseline.

Abbreviation: LOCF = last observation carried forward.

lower doses, experienced no undue tolerability issues, and had reversal of TD present at baseline. In the remainder of the study population, the highest daily doses of quetiapine on the last full day of treatment were within the range 100 to 300 mg.

Although open-label efficacy data must be interpreted with caution, improvements from baseline were shown in mean Brief Psychiatric Rating Scale (BPRS) total score and mean Clinical Global Impressions-Severity of Illness scale scores by week 2 (observed cases and last observation carried forward), improvements that were maintained throughout the study ($p < .001$ and $p < .002$, respectively).¹¹

Data from a subset of 78 patients diagnosed with Alzheimer's disease from this study were retrospectively analyzed to explore the potential for quetiapine (median dose = 100 mg/day; range, 25–800 mg/day) to improve symptoms of psychosis and hostility.¹³ Significant improvements in the BPRS factor V (mean of hostility, suspiciousness, uncooperativeness), the BPRS hostility item, and the BPRS hostility cluster (mean of anxiety, tension, hostility, suspiciousness, uncooperativeness, excitement) scores were seen by week 2 for some variables (BPRS total, hostility cluster, and positive symptoms) and week 4 for all variables and were sustained (with the exception of the hostility item at week 12 only) throughout the 52-week study period (Figure 3).

These results are generally consistent with more recent data, presented in abstract form, describing a 10-week, double-blind, placebo-controlled study of flexibly dosed quetiapine or haloperidol in 378 nursing home residents with various psychotic disorders.¹⁴ The a priori focus was on the subgroup of 284 patients with Alzheimer's disease and psychosis defined operationally. No difference

was seen on measures of psychosis across the 3 treatments, while both antipsychotics significantly improved the BPRS agitation factor compared with placebo ($p < .05$). At the same time, the BPRS anergia factor in the quetiapine group improved significantly compared with haloperidol or placebo ($p < .01$). Moreover, quetiapine was superior to haloperidol in terms of improved functional status, as assessed by the Physical Self-Maintenance Scale ($p = .004$) and the Multidimensional Observation Scale for Elderly Subjects ($p < .001$). Information regarding the non-Alzheimer's disease patients from this study is not currently available. Full results from this trial have yet to be published.

USE OF NEWER ANTIPSYCHOTICS IN THE ELDERLY

No geriatric-specific studies of ziprasidone have been conducted. Results have been reported recently in abstract form and describe the use of aripiprazole in outpatients with Alzheimer's disease complicated by psychosis.¹⁵ A 10-week, placebo-controlled study of 208 patients (mean age = 81.5 years) with baseline Mini-Mental State Examination scores of at least 14.2 and Neuropsychiatric Inventory scores of at least 6 were flexibly dosed with 2 to 15 mg/day of aripiprazole.¹⁵ The primary outcome, change from baseline to endpoint in caregiver-rated Neuropsychiatric Inventory Psychosis subscale, was similar in the aripiprazole and placebo groups. A secondary measure of behavior suggested benefit, although the precise details are not available. The most common AEs reported were urinary tract infection (8% vs. 12%, placebo), accidental injury (8% vs. 5%), somnolence (8% vs. 1%), bronchitis (6% vs. 3%), and EPS-related events (5% vs. 4%). In a small pilot, open-label, ascending-dose cohort study in 30 elderly patients with dementia, aripiprazole showed a dose-related association with somnolence.¹⁶

CONCLUSION

To optimize clinical effectiveness in the management of geriatric patients with dementia, it is essential to consider therapeutic efficacy as well as safety and tolerability in this vulnerable population. The available evidence varies in magnitude and quality for each of the atypicals, with the most extensive data available for risperidone. While each has some evidence indicative of efficacy for treatment of psychopathology in the elderly, shown most convincingly for risperidone, there are important differences in safety and tolerability among these agents. For instance, elderly patients are susceptible to dose-related increases in EPS, a feature associated with risperidone and, based on studies in patients with EPS disorders to begin with, olanzapine to a lesser extent. Sedation, which could be beneficial in some patients and detrimental in others, is seen to

varying degrees with all of these agents. A greater appreciation of these differences among the atypicals should enable clinicians to treat elderly patients more effectively.

The issue of limited data directly comparing atypicals in the elderly is being addressed in a 36-week, National Institute of Mental Health–sponsored study comparing placebo, risperidone, olanzapine, and quetiapine as treatments for patients with Alzheimer's disease complicated by delusions, hallucinations, and/or agitation.¹⁷ Inclusion criteria for this study specify that patients must not have benefited sufficiently from prior treatment with psychotropic medication. This is one of two Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), the goal of which is to provide clinicians with more definitive guidance concerning the most effective treatment for dementia associated with hallucinations, delusions, or agitation. The hypothesis is that efficacy will be equivalent across the agents but with clinically meaningful differences in clinical effectiveness measured by side effects, adherence, patient/caregiver satisfaction, and health utilization, among others.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, aripiprazole, haloperidol, olanzapine, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of agitation or psychosis in dementia.

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