Olanzapine, quetiapine, or risperidone did not differ from placebo for Alzheimer disease

Schneider LS, Tariot PN, Dagerman KS, et al. **Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease.** N Engl J Med. 2006;355:1525-38.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Geriatrics ★★★★★★☆ Neurology ★★★★★★☆

QUESTION

In patients with Alzheimer disease (AD) and psychosis, aggression, or agitation, are the atypical antipsychotic drugs olanzapine, quetiapine, or risperidone more effective than placebo?

METHODS

Design: Randomized placebo-controlled trial (Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease).
Allocation: Concealed.*
Blinding: Blinded (clinicians and patients).*
Follow-up period: Up to 36 weeks.
Setting: 42 sites in the United States.
Patients: 421 outpatients (mean age 78 y, 56% women) who had AD or probable AD. All patients had had psychosis, aggression, or agitation almost daily during the previous week or at least intermittently for 4 weeks. Exclusion criteria were a primary psychotic disorder, delirium, or other dementia; psychosis, aggression, or agitation better accounted for by another medical condition or medication or by substance abuse; psychiatric admission; suicidal trend; treatment with a cholinesterase inhibitor or antidepressant; previous treatment with ≥ 2 of 3 study drugs; or contraindications to any of the study drugs.
Intervention: Olanzapine, 2.5 or 5.0 mg daily (n = 100); quetiapine, 25 or 50 mg daily (n = 94); risperidone, 0.5 or 1.0 mg daily (n = 85); or placebo (n = 142). The study physicians determined the starting doses and adjusted the doses based on clinical judgment and patients' responses. A benzodiazepine or haloperidol could also be prescribed.
Outcomes: Time to discontinuation of treatment for any reason. Secondary outcomes included attainment of minimal or greater improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks; time to discontinuation of treatment because of lack of efficacy; time to discontinuation of treatment because of adverse events, intolerability, or death; and adverse events.
Patient follow-up: 98.8% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for time to discontinuation of treatment for any reason (Table). At 12 weeks, groups did not differ for improvement on the CGIC scale. Overall, 63% of patients discontinued treatment at 12 weeks. The median time to discontinuation of treatment because of lack of efficacy was longer with olanzapine or risperidone than with placebo (Table). More patients in the study-drug groups discontinued treatment because of adverse events, intolerability, or death than did those in the placebo group (Table).

CONCLUSION

In patients with Alzheimer disease and psychosis, aggression, or agitation, olanzapine, quetiapine, or risperidone did not differ from placebo for time to discontinuation of treatment.

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*See Glossary.

Olanzapine, quetiapine, or risperidone vs placebo in Alzheimer disease with psychosis, aggression, or agitation up to 36 weeks†

Outcomes	Hazard ratio (95% CI)		
	Olanzapine	Quetiapine	Risperidone
Discontinuation for any reason	0.83 (0.62 to 1.11)‡	1.01 (0.75 to 1.36)‡	0.88 (0.64 to 1.20)‡
Discontinuation because of lack of efficacy	0.51 (0.35 to 0.74)	0.81 (0.57 to 1.15)‡	0.61 (0.41 to 0.89)
Discontinuation because of adverse events, intolerability, or death	4.32 (1.84 to 10.12)	3.58 (1.44 to 8.91)	3.62 (1.45 to 9.04)

†CI defined in Glossary.
‡Not significant.

COMMENTARY

Psychosis, aggression, and agitation in AD are typically more disturbing and challenging for physicians and caregivers than are memory loss and other aspects of cognitive impairment that define the disease. The well-done study by Schneider and colleagues, with a primary endpoint being time to discontinuation of the medication, closely resembles clinical practice.

The bottom line is that these medications—thought by many to be superior to such first-generation agents as haloperidol—are not very effective for treating this challenging symptom complex. At best, about 1/4 to 1/3 of patients had at least minimal improvement with risperidone, quetiapine, or olanzapine compared with 1/5 with placebo. 82% of patients discontinued medication for any reason, most commonly because of "lack of efficacy," but 1/5 to 1/4 discontinued because of "intolerability, adverse effects or death." The most common adverse effects were parkinsonism and sedation.

The study adds to the evidence base in pharmacotherapeutics. To my knowledge, there is only 1 good clinical trial comparing medications (haloperidol and trazodone) with placebo and psychological treatment (1). Reductions in agitation levels were similar in all 4 groups, but fewer side effects occurred in the behavioral-management group. Thus, the evidence suggests that current antipsychotic drugs are not the answer to this difficult problem and supports the need for psychological treatments for disruptive behaviors (2).

What does work? Regular exercise and provision of so-called pleasant events seem to reduce frequency of disabling symptoms (3), as do treatments designed to reduce caregiver stress and to teach behavioral techniques focusing on problem solving factors associated with troublesome behaviors. In addition, helping patients and families connect with resources in the community that offer additional assistance, such as the local AD association, can be an invaluable adjunct to care.

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References

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