

Review: Atypical antipsychotic drugs modestly improve neuropsychiatric symptoms of dementia

Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA*. 2005;293:596-608.

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

QUESTION

What is the effectiveness of pharmacologic agents for neuropsychiatric symptoms of dementia?

METHODS

Data sources: MEDLINE (1966 to July 2004), Cochrane Database of Systematic Reviews, and reference lists of retrieved studies and reviews.

Study selection and assessment: English-language, randomized, double-blind, placebo-controlled trials (RCTs) or meta-analyses of RCTs that evaluated any drug therapy in patients with dementia, including Alzheimer disease, vascular dementia, mixed dementia, and dementia with Lewy bodies; and assessed outcomes for neuropsychiatric symptoms. {Study quality was assessed based on randomization procedure, allocation concealment, blinding, outcome assessment in all patients, and intention-to-treat analyses.}*
Outcomes: Neuropsychiatric symptoms (e.g., hallucinations, delusions, combativeness, verbal aggression, psychomotor agitation, and wandering).

Outcomes: Neuropsychiatric symptoms (e.g., hallucinations, delusions, combativeness, verbal aggression, psychomotor agitation, and wandering).

MAIN RESULTS

25 RCTs and 4 meta-analyses met the inclusion criteria. The results are summarized in the Table. *Typical antipsychotics (2 RCTs and 2 meta-analyses):* 1 meta-analysis of 7 RCTs showed a benefit from neuroleptics and 1 RCT showed thioridazine improved agita-

tion, but the trial was of poor quality. *Atypical antipsychotics (6 RCTs):* A modest benefit was seen with 5 to 10 mg/d of olanzapine (2 RCTs) and 1.0 mg/d of risperidone (2 RCTs). *Antidepressants (5 RCTs):* 1 RCT showed a 10-point improvement in the Neurobehavioral Rating Scale with citalopram. *Mood stabilizers (5 RCTs):* 1 of 2 RCTs of carbamazepine showed a benefit. *Cholinesterase inhibitors (6 RCTs and 2 meta-analyses):* 1 RCT and 1 meta-analysis of 2 RCTs showed a benefit of galantamine. 2 RCTs showed a benefit of donepezil. 1 meta-analysis of 16 RCTs showed modest improvement in Neuropsychiatric Inventory (NPI) scores with cholinesterase inhibitors (1.72-point improvement vs placebo on a scale of 0 to 120). *Memantine (2 RCTs):* 1 of

2 RCTs of memantine, 20 mg/d, showed improvement on NPI scores and behavioral outcomes.

CONCLUSIONS

Among several classes of pharmacologic agents, improvement in neuropsychiatric symptoms of dementia is only consistently seen with atypical antipsychotics (risperidone and olanzapine) and cholinesterase inhibitors. The magnitude of benefit is small and of questionable clinical significance, especially for cholinesterase inhibitors.

Sources of funding: National Institute on Aging and Paul Beeson Faculty Scholars in Aging Research.

For correspondence: Dr. K.M. Sink, Wake Forest University School of Medicine, Winston-Salem, NC, USA. E-mail kmsink@wfuwmc.edu. ■

*Information provided by author.

Pharmacologic agents for neuropsychiatric symptoms of dementia†

Drugs	Number of RCTs/ meta-analyses (n)	Follow-up	Number of RCTs/meta-analyses showing significant improvement (drugs)
Typical antipsychotics	2 RCTs, 2 meta-analyses (1237)	17 d to 16 wk	2 (haloperidol, thioridazine)
Atypical antipsychotics	6 (2261)	24 h to 12 wk	4 (risperidone, olanzapine)
Antidepressants	5 (429)	17 d to 16 wk	1 (citalopram)
Mood stabilizers	5 (342)	3 to 6 wk	1 (carbamazepine)
Cholinesterase inhibitors	6 RCTs, 2 meta-analyses (8764)	6 wk to 4 y	5 (donepezil, galantamine)
Memantine	2 (656)	24 to 28 wk	1

†Typical antipsychotics: haloperidol, thioridazine, thiothixene, chlorpromazine, trifluoperazine, acetophenazine, perphenazine. Atypical antipsychotics: risperidone, olanzapine. Antidepressants: fluoxetine, trazodone, citalopram, sertraline. Mood stabilizers: carbamazepine, divalproex sodium, sodium valproate. Cholinesterase inhibitors: rivastigmine, donepezil, galantamine, metrifonate, tacrine, velnacrine, physostigmine. RCTs = randomized controlled trials.

COMMENTARY

Neuropsychiatric symptoms are common in dementia and may precipitate a plea from a family member or nursing staff for physicians to “do something.” Although the risks associated with the use of psychotropic drugs in frail elderly patients have been well documented, patients are regularly placed on psychotropic drugs, often indefinitely. The benefits of these agents in management of behavioral disturbances related to dementia are not well understood.

Sink and colleagues’ systematic review showed statistically significant improvements on neuropsychiatric and behavioral scales for some drugs, but improvements were small and unlikely to be clinically important. Overall, the authors found little evidence that pharmacologic therapy is clinically effective. This is consistent with observations of drug-use patterns following the Nursing Home Reform Amendment (OBRA-87), in which antipsychotic medicines were discontinued in nursing home patients without apparent ill effects (1).

Direct comparisons between older and newer antipsychotic drugs in demented elderly persons are scarce. Newer agents have the theoretical advantage of a lower incidence of tardive dyskinesia but may cause

weight gain, impaired glycemic control, and increased risk for stroke. The authors note that studies of risperidone and olanzapine offer the best evidence of efficacy compared with placebo. Risperidone, olanzapine, and quatrains will be compared in the upcoming placebo-controlled Clinical Antipsychotic Trials of Intervention Effectiveness (2). Until such data are available, these agents should be used with caution in demented elderly persons, with frequent monitoring for side effects and a low threshold for discontinuing use. Indeed, the Food and Drug Administration has recently released an advisory about these medications outlining the risk for increased mortality (3).

Kathryn M. Ryder, MD, MS

Ronald I. Shorr, MD, MS

University of Tennessee and Methodist University Hospital
Memphis, Tennessee, USA

References

- Shorr RI, Fought RL, Ray WA. *JAMA*. 1994;271:358-62.
- Schneider LS, Ismail MS, Dagerman K, et al. *Schizophr Bull*. 2003;29:57-72.
- Deaths with antipsychotics in elderly patients with behavioral disturbances. www.fda.gov/cder/drug/advisory/antipsychotics.htm.