Cochrane for Clinicians

Putting Evidence into Practice

Antidepressants for Agitation and Psychosis in Patients with Dementia

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The Cochrane Abstract on the next page is a summary of a review from the Cochrane Library. It is accompanied by an interpretation that will help clinicians put evidence into practice. Dr. Bui presents a clinical scenario and question based on the Cochrane Abstract, followed by an evidence-based answer and a critique of the review. The practice recommendations in this activity are available at http://www2.cochrane.org/reviews/en/ab008191.html.

EB CME

This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). See CME Quiz on page 15.

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Clinical Scenario

An 85-year-old man with advanced dementia presents to your office accompanied by his daughter. She is upset because he has been increasingly agitated and combative in the evenings. He sometimes behaves as if he were hallucinating. You wonder if antidepressants can improve his symptoms.

Clinical Question

Are antidepressants effective in managing neuropsychiatric symptoms, such as psychosis or agitation, in patients with dementia?

Evidence-Based Answer

There are few high-quality studies examining the effectiveness of antidepressants for treating the neuropsychiatric symptoms of dementia. Although there is some evidence to support the use of the selective serotonin reuptake inhibitors (SSRIs) sertraline (Zoloft) and citalopram (Celexa), they should be used only if nonpharmacologic interventions are unsuccessful. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Dementia affects 5 percent of adults older than 65 years and up to 30 percent of persons older than 85 years. Between 80 and 90 percent of persons with dementia experience psychosis, agitation, or disordered mood, which collectively are referred to as neuropsychiatric symptoms.[1,2] In addition, 20 percent of community-dwelling persons with Alzheimer disease and 40 to 60 percent of those with Alzheimer disease living in long-term care facilities experience agitation.[1] About 15 percent of community-dwelling persons with Alzheimer disease experience delusions, visual hallucinations, or auditory hallucinations, and 20 percent experience clinical depression.[2] Neuropsychiatric symptoms often result in decreased quality of life or distress in patients, as well as increased stress and depression in caregivers. Persons with these symptoms may require institutional care and pose a considerable treatment challenge for physicians.[3,4]

Persons with dementia who exhibit symptoms of psychosis or agitation are commonly treated with antipsychotic medications.[1-3,5,6] However, in 2005 the U.S. Food and Drug Administration issued a boxed warning for atypical antipsychotic medications in the treatment of neuropsychiatric symptoms because of evidence of increased risk of stroke and death.[2-4] In 18 short-term randomized controlled trials, atypical antipsychotic medications used for the treatment of neuropsychiatric symptoms were associated with three times the risk of stroke and almost twice the risk of death compared with placebo.[2,3,5] Treatment with haloperidol has been associated with a greater risk of mortality than treatment with atypical antipsychotics.[6] Typical and atypical antipsychotics have been associated with an increased rate of cognitive decline compared with placebo.[2]

This Cochrane review included nine randomized controlled trials that compared antidepressants with placebo or with atypical antipsychotics for the treatment of neuropsychiatric symptoms. All the trials included SSRIs or trazodone. Four trials compared SSRIs with placebo, three trials compared SSRIs with typical antipsychotics, and one trial compared the SSRI citalopram with the atypical antipsychotic risperidone (Risperdal). Of the three trials that included trazodone, one trial compared trazodone

Cochrane Abstract

Background: Agitation and psychosis are common among older adults with dementia and are challenging to manage. At the present time, little is known about the effectiveness and safety of antidepressant medications when used to treat these symptoms.

Objectives: To assess the safety and effectiveness of antidepressants in treating psychosis and agitation in older adults with Alzheimer disease or vascular or mixed dementia.

Search Strategy: We searched the Cochrane Dementia and Cognitive Improvement Group's Specialized Register, which included Cochrane Central Register of Controlled Trials (The Cochrane Library 2009, Issue 3), Medline (January 1950 to October 2009), EMBASE (1980 to October 2009), CINAHL (all dates to October 2009), and PsycINFO (1806 to October 2009).

Selection Criteria: Randomized controlled trials of antidepressants (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants, trazodone, and other antidepressants), compared with placebo or comparator medications (typical or atypical antipsychotics, anticonvulsants, benzodiazepines, cholinesterase inhibitors, memantine, or other medications) for treatment of agitation or psychosis in older adults with dementia.

Data Collection and Analysis: Two authors independently assessed trial quality and extracted trial data. We collected information on effectiveness as measured by dementia neuropsychiatric symptom rating scales and adverse effects. Study authors were contacted for additional information.

Main Results: Nine trials involving a total of 692 persons were included in the review. Five studies compared SSRIs with placebo, and two studies were combined in a meta-analysis for the outcome of change in Cohen-Mansfield Agitation Inventory (CMAI) scores. There was a significant difference between antidepressants and placebo on measures of agitation as reported on the change in CMAI total score (mean difference [MD] = −0.89; 95% confidence interval [CI], −1.22 to −0.57), although the results were heavily weighted by one large study. There were no significant differences in change in behavioral symptoms of dementia for SSRIs compared with placebo in the one study that reported on changes in the Neuropsychiatric Inventory and Behavioral Pathology in Dementia scales. One study comparing citalopram with placebo found a significant difference in neuropsychiatric symptoms as measured on the Neurobehavioral Rating Scale (NBRS) after controlling for baseline severity NBRS score, although the unadjusted mean difference was not statistically significant (MD = −7.70; 95% CI, −16.57 to 1.17). There was no difference in the rates of trial withdrawals from adverse events for SSRIs compared with placebo for four studies reporting this outcome (relative risk [RR] = 1.07; 95% CI, 0.55 to 2.11) or in the number of trial withdrawals from any cause in the three studies reporting this outcome (RR = 0.91; 95% CI, 0.65 to 1.26). One study compared the SSRI citalopram with the atypical antipsychotic risperidone and found no difference in NBRS scores, trial withdrawals from any cause, or trial withdrawals from adverse events, although the rates of adverse events as measured on the Udvalg for Kliniske Undersogelser Side Effect Rating Scale were lower for citalopram (MD = −2.82; 95% CI, −4.94 to −0.70). Three studies compared SSRIs with typical antipsychotics. In meta-analysis of two studies there was no statistically significant difference in changes in CMAI total scores (MD = 4.66; 95% CI, −3.58 to 12.90). There also was no difference in trial withdrawals from any cause or from adverse events for SSRIs compared with typical antipsychotics. One study of trazodone compared with placebo did not find any significant difference in change in CMAI total scores (MD = 5.18; 95% CI, −2.86 to 13.22) or trial withdrawals from any cause (RR = 1.06; 95% CI, 0.54 to 2.09). Two studies comparing trazodone with haloperidol did not detect any difference in change in CMAI total scores (MD = 3.28; 95% CI, −3.28 to 9.85) or trial withdrawals from any cause (RR = 0.79; 95% CI, 0.43 to 1.46).

Authors' Conclusions: Currently, there are relatively few studies of antidepressants for the treatment of agitation and psychosis in dementia. The SSRIs sertraline and citalopram were associated with a reduction in symptoms of agitation when compared with placebo in two studies. SSRIs and trazodone appear to be tolerated reasonably well when compared with placebo, typical antipsychotics, and atypical antipsychotics. Future studies involving more participants are required to determine if SSRIs, trazodone, or other antidepressants are safe and effective treatments for agitation and psychosis in dementia.

with placebo, and two trials compared trazodone with haloperidol. None of the trials were free of bias, and many did not report sufficient information to assess their potential bias completely.[3]

In two trials, sertraline and citalopram were associated with modest improvement of psychosis and agitation compared with placebo.[7,8] There was no statistically significant difference in effectiveness between SSRIs and atypical or typical antipsychotics.[3,7,9] However, SSRIs were no better than placebo in another trial.[3] Trazodone was not significantly different from placebo, and it was about as effective as haloperidol.[3]

Management of neuropsychiatric symptoms of dementia should begin with an evaluation for potential causes, including a medication review.[2,4] The physician should perform a complete neurologic examination and an assessment of mental status, cognitive function, activities of daily living, overall well-being, and mental health. Pain, loneliness, depression, and boredom have been associated with neuropsychiatric symptoms. Additionally, visual or auditory impairment and occult infections (e.g., urinary tract, pulmonary, or dental infections) can trigger neuropsychiatric symptoms.[2,4]

Nonpharmacologic interventions for neuropsychiatric symptoms include music therapy, physical activity, behavioral modification techniques, reminiscence therapy, socialization with pet therapy, family interaction or family videos, and aromatherapy.[2,4,10] If available, caregivers should be referred to training and support programs. These programs have been found to reduce agitation in patients as well as stress and depression in caregivers.[5]

SSRIs may cause serious adverse effects, including gastrointestinal bleeding, hyponatremia, falls, and fractures.[3] SSRIs were not significantly different from antipsychotic medications in trial withdrawals related to

adverse effects—an important measure of overall tolerability—although citalopram resulted in fewer adverse effects than risperidone.[9] There is insufficient evidence on the long-term safety of antidepressant use for neuropsychiatric symptoms in patients with dementia.

If pharmacologic intervention is considered, the risks and benefits should be discussed with the caregiver, and consent should be documented in the medical record.[4,5] After drug therapy has started, the physician should monitor the patient closely for adverse effects, changes in medical condition, and functional status.[4,5] Because of their limited benefits and considerable risks, antidepressants should be used only if all other nonpharmacologic interventions for neuropsychiatric symptoms are unsuccessful.

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