Q/ Which drugs are best when aggressive Alzheimer's patients need medication?

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Atypical antipsychotics are an effective short-term treatment for aggressive behavior.

EVIDENCE-BASED ANSWER

A/ **ATYPICAL ANTIPSYCHOTICS ARE EFFECTIVE;** so are selective serotonin reuptake inhibitors (SSRIs), and they may be safer. Atypical antipsychotics are an effective short-term (6-12 weeks) treatment for aggressive behavior in patients with Alzheimer's disease because they consistently decrease aggression scores (strength of recommendation [SOR]: **A,** multiple randomized controlled trials [RCTs]). However, evidence of drug-related deaths in patients taking these drugs mandates weighing the benefits against the risks. SSRIs may be a safer, effective alternative (SOR: **B,** limited studies).

Evidence for the efficacy of antiepileptic agents is conflicting (SOR: **C,** inconsistent patient-oriented evidence). Valproate is ineffective for treating aggression (SOR: **C,** very small RCT).

No data exist to guide long-term medication use. All available studies lasted no longer than 12 weeks.

Nonpharmacologic therapy should be the first-line treatment for aggression in patients with Alzheimer's disease. Consider drug therapy for patients who pose an imminent threat to themselves or others.

Evidence summary

Psychotic symptoms, including aggression, in patients with dementia are a leading cause of nursing home placement and pharmacologic treatment. RCTs have demonstrated the efficacy of atypical antipsychotics in aggressive nursing home patients.

Risperidone significantly reduces aggression

An RCT comparing risperidone with placebo in 345 patients found that low-dose risperidone (mean 0.95 mg/d) significantly improved aggression scores (number needed to treat [NNT]=4; $P<.001$). Serious adverse events included injury, cerebrovascular events, pneumonia, and accidental overdose (number needed to harm [NNH]=13).[1] Other RCTs also have found risperidone to be effective in reducing aggressive behavior.[2,3]

Olanzapine is effective and well tolerated

Researchers have also studied olanzapine, another atypical antipsychotic. A 6-week RCT of 206 elderly nursing home patients with Alzheimer's disease and psychotic or behavioral symptoms found that low-dose olanzapine (5 or 10 mg/d) decreased agitation and aggression scores (olanzapine 5 mg: NNT=5; olanzapine 10 mg: NNT=6) compared with placebo. Commonly reported adverse effects included somnolence (5 mg: NNH=5; 10 mg: NNH=5) and gait disturbance (5 mg: NNH=6; 10 mg: NNH=8).[4] An open-label follow-up study also found low-dose olanzapine to be well tolerated and effective in decreasing agitation and aggression scores.[5]

Weigh the benefits against the risks

The US Food and Drug Administration issued a public health advisory regarding increased mortality risk after reviewing RCTs that evaluated atypical antipsychotics in patients with dementia.[6] A meta-analysis of

SSRIs may be a safer, effective alternative to antipsychotics.

15 RCTs (N=5110) that studied olanzapine, aripiprazole, risperidone, and quetiapine in patients with dementia demonstrated a small, but increased risk of death associated with their use when compared with placebo (3.5% vs 2.3%; odds ratio=1.54; 95% confidence interval [CI], 1.06-2.23; *P*=.02; NNH= 83).[7]

A population-based (community and long-term care facilities), retrospective cohort study of atypical and conventional antipsychotics involving 27,259 matched pairs also suggested an increased risk of death. Thirty days after beginning an atypical antipsychotic medication, increased mortality was noted when compared with no antipsychotic use in both the community cohort (adjusted hazard ratio [AHR]=1.31 [95% CI, 1.02-1.70]; NNH=500) and the long-term care cohort (AHR=1.55 [95% CI, 1.15-2.07]; absolute risk difference=1.2 percentage points; NNH=83). Conventional antipsychotics were associated with higher rates of death than atypical antipsychotics (absolute risk difference= 2.6 percentage points in the community group [NNH=38] and 2.2 percentage points in the long-term care groups [NNH=45]).[8]

SSRIs may be an alternative

An RCT comparing citalopram and risperidone over 12 weeks in 103 patients with dementia demonstrated similar efficacy for the 2 drugs in treating agitation. Patients receiving citalopram experienced fewer adverse effects than those receiving risperidone.[9] The study suggests that SSRIs may be an alternative to atypical antipsychotics.

Carbamazepine helps, valproate doesn't

Evidence regarding the use of antiepileptic medications is conflicting. One RCT of 51 patients found carbamazepine 300 mg daily to be efficacious for short-term control of agitation with good safety and tolerability. Six weeks after beginning the study, Overt Aggression Scale scores decreased 6.7 points for carbamazepine compared with 1.9 points for placebo (*P*=.008). Adverse effects, including ataxia, drowsiness, postural instability, rash, weakness, and disorientation, were more common in the carbamazepine group than the placebo group (absolute risk increase=30%; NNH=3).[10]

When compared with placebo, 480 mg daily of sodium valproate for 8 weeks showed no differences in controlling aggressive behavior.[11] In an open-label follow-up study, aggressive behavior improved from 10.52 on the Social Dysfunction and Aggression Scale to 6.31 (*P*<.001), but no improvement was observed using the Clinical Global Impression Scale for aggressive behavior. Seven deaths that authors couldn't attribute to the drug occurred. Three patients experienced drowsiness. No other adverse events were noted.[12]

A very small, double-blind crossover RCT (N=14) evaluated 250 to 1500 mg sodium valproate daily for 6 weeks compared with placebo. A 2-week period separated the valproate and placebo regimens. Neuropsychiatric Inventory agitation and aggression scores worsened significantly with valproate (increase of 1.43 points compared with a decrease of 2.08 points with placebo; *P*=.04). Adverse events related to valproate included falls, sedation, loss of appetite, thrombocytopenia, and loose stools (NNH=3).[13]

Recommendations

The Expert Consensus Guideline for the Treatment of Agitation in Older Persons with Dementia[14] and treatment guidelines for Alzheimer's disease and other dementias from the American Psychiatric Association (APA)[15] offer different recommendations for first-line treatment.

The Expert Consensus Guideline recommends divalproate, risperidone, and conventional high-potency antipsychotics for patients with severe anger and physical aggression. Alternative treatments include olanzapine, carbamazepine, trazodone, and SSRIs.[14]

The APA recommends antipsychotics to treat agitation based on available evidence. If treatment fails, consider anticonvulsants, lithium, or beta-blockers. The APA notes that although evidence for SSRIs is limited, they may be appropriate for agitated nonpsychotic patients.[15] JFP

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No data exist to guide long-term medication use for aggressive behavior in patients with Alzheimer's disease.

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