Q/ How best to treat agitation in patients with irreversible dementia?

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EVIDENCE-BASED ANSWER

A/ **ATYPICAL ANTIPSYCHOTICS** modestly reduce agitation compared with placebo but have significant adverse effects (strength of recommendation [SOR]: **A,** systematic reviews of randomized controlled trials [RCTs]).

Haloperidol doesn't reduce symptoms and has serious adverse effects (SOR: **A,** systematic reviews of RCTs).

Selective serotonin reuptake inhibitors (SSRIs) and melatonin—although well tolerated—don't reduce agitation (SOR: **B,** extrapolated data from systematic reviews of RCTs).

Evidence summary

A meta-analysis by the Agency for Healthcare Research and Quality of 37 RCTs examined off-label use of atypical antipsychotics in a total of 5364 patients.[1] Pooled results from 17 RCTs showed a statistically significant but clinically modest difference between atypical antipsychotics and placebo for agitation; the standard mean difference was 0.22 (95% confidence interval [CI], 0.09-0.35). Investigators found statistically significant but small effect sizes for aripiprazole, olanzapine, and risperidone.

Atypical antipsychotics are associated with serious adverse cerebrovascular events and extrapyramidal symptoms. A meta-analysis of 17 RCTs (N= 5106) demonstrated that patients who received antipsychotics had higher mortality than patients who received placebo (3.5% vs 2.3%).[2]

Haloperidol has significant adverse effects without significant results

A systematic review of 5 RCTs compared haloperidol with placebo over 3 to 16 weeks in 856 patients ages 72 to 81 years with dementia and agitation.[3] When investigators pooled results from 3 RCTs (N=690) using an intention-to-treat analysis and 3 assessment tools, they found that haloperidol produced a statistically significant, but not clinically meaningful, standard mean difference in aggression.

Adverse effects included extrapyramidal symptoms (odds ratio [OR]=2.34; 95% CI, 1.25-4.38; number needed to harm [NNH]=6), somnolence (OR=4.20; 95% CI, 1.78-9.91; NNH=8), and fatigue (OR=5.39; 95% CI, 2.04-14.22; NNH=3). Most studies were underpowered, didn't document randomization, and had dropout rates as high as 20%.

Antidepressants have no effect

A systematic review of 9 RCTs involving 692 patients with dementia compared antidepressants with placebo, other antidepressants, and antipsychotics using various neuropsychiatric symptom scales.[4] Investigators performed meta-analyses for numerous outcomes but found none of clinical or statistical significance.

Pooled analysis of 2 RCTs that examined a total of 250 outpatients with Alzheimer's disease found that sertraline and fluoxetine produced a statistically, but not clinically, significant difference in the Cohen Mansfield Agitation Inventory total score. One RCT (N=52) demonstrated that citalopram improved the Neurobehavioral Rating Scale total score after adjusting for baseline severity.

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Investigators found no difference in withdrawal rates between SSRIs and placebo (relative risk=1.07; 95% CI, 0.55-2.11). All studies had multiple methodological limitations.

Melatonin has no adverse effects, but no benefit either

A systematic review that included 2 RCTs compared melatonin with placebo for agitation in 121 patients ages 77 to 79 years with dementia.[5] Investigators prescribed melatonin for periods of 4 to 7 weeks and found reductions in agitation that were statistically significant, but not clinically meaningful. They reported no adverse events. The studies had a low risk of bias.

Recommendations

The American Psychiatric Association (APA) advocates evaluating and treating secondary causes of agitation and using environmental and behavioral measures to reduce agitation.[6] The APA advocates using the lowest effective dosages of antipsychotics after considering adverse effect profiles and the risks of not treating.

The APA recommends benzodiazepines to treat prominent anxiety or infrequent agitation, preferably lorazepam and oxazepam rather than diazepam or clonazepam and suggests trazodone or SSRIs as alternative therapy for agitation in patients without psychosis or those who are intolerant to antipsychotics.[6] JFP

References

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