FPIN's Clinical Inquiries

Pharmacologic Management of Agitation in Patients with Dementia

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Clinical Question

Which medications are effective at decreasing agitation in patients with dementia?

Evidence-Based Answer

Selective serotonin reuptake inhibitors (SSRIs) and risperidone (Risperdal) are moderately effective at decreasing agitation in all types of dementia. (Strength of Recommendation [SOR]: A, based on meta-analysis.) Olanzapine (Zyprexa) and risperidone reduce dementia-related agitation much longer than placebo. (SOR: B, based on one high-quality randomized controlled trial [RCT].) Dextromethorphan/quinidine (Nuedexta) may be effective at reducing agitation in patients with dementia. (SOR: B, based on one high-quality RCT cited in meta-analysis.)[1]

Evidence Summary

A 2018 meta-analysis examining medications used to alleviate agitation in all types of dementia included 36 RCTs with a total of 5,585 participants (mean age = 81.8 years ± 4.9 years; 69.1% female).[1] The primary outcome was a 50% reduction in baseline agitation at eight weeks. Twenty individual medications and one combination medication were included in the analyses. Risperidone (odds ratio [OR] = 1.96; 95% CI, 1.49 to 2.59; number needed to treat [NNT] = 6) and SSRIs as a class (OR = 1.61; 95% CI, 1.02 to 2.53; NNT = 25) were more effective than placebo, although no individual SSRI reached statistical significance. Dextromethorphan/quinidine was also more effective than placebo (OR = 3.04; 95% CI, 1.63 to 5.66; NNT = 5), but it was evaluated in only one RCT.

A 2011 Cochrane review assessed the safety and effectiveness of antidepressants for agitation in adults who had one of several different types of dementia, analyzing nine RCTs with a total of 692 patients.[2] Five trials compared SSRIs (i.e., sertraline [Zoloft], citalopram [Celexa], fluoxetine [Prozac], and fluvoxamine) with placebo over periods of 17 days to 12 weeks. SSRIs were more effective than placebo and no less safe than placebo or antipsychotics. (SOR = A, based on meta-analysis.) Two trials measured changes in Cohen-Mansfield Agitation Inventory scores (assessing 29 behaviors, each scored by an observer as 1 point [never] to 7 points [multiple occurrences per hour]) and found a slight yet statistically significant improvement with SSRIs compared with placebo (mean difference of improvement = −0.89 points across all behaviors; 95% CI, −1.22 to −0.57). Four trials assessed the rates of withdrawal because of adverse effects from SSRIs vs. placebo. They showed no difference (relative risk = 1.07; 95% CI, 0.55 to 2.11). One trial comparing citalopram and risperidone measured change on the Neurobehavioral Rating Scale (a 28-item observer-rated scale using seven gradations ranging from not present [1 point] to extremely severe [7 points]) and showed similar effectiveness (mean difference = −0.53 points; 95% CI, −2.37 to 1.31) and no significant difference in withdrawal because of adverse effects.

A 2017 RCT with 75 nursing home residents who had Alzheimer-type dementia and were 60

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years or older at diagnosis measured the effectiveness and safety of citalopram (30 ± 5.8 mg per day) relative to quetiapine (Seroquel) and olanzapine, with 25 patients per group.[3] The interventions were equally effective in treating agitation in patients with Alzheimer-type dementia and citalopram was associated with fewer adverse outcomes than quetiapine and olanzapine. (SOR = B, based on one medium-quality RCT.) At 24 weeks, there were no significant improvements in agitation between citalopram and quetiapine as measured by two agitation scales (i.e., the Neuropsychiatric Inventory [NPI] scale: regression coefficient = 0.022; 95% CI, −0.093 to 0.137; *P* = .882 and the modified Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change [mADCS-CGIC] scale: OR = 1.00; 95% CI, 0.92 to 1.07; *P* = .935), or between citalopram and olanzapine (NPI scale: regression coefficient = −0.041; 95% CI, −0.068 to 0.036; *P* = .409 and mADCS-CGIC scale: OR = 0.98; 95% CI, 0.86 to 1.20; *P* = .849). The NPI scale assesses 12 items, each with a score of 0 to 12, with higher scores indicating worsening agitation. At baseline, NPI mean subscale scores for the trial participants in the citalopram, quetiapine, and olanzapine arms were 9.7 ± 2.1, 9.6 ± 2.0, and 9.7 ± 2.2, respectively; at 24 weeks, mean subscale scores improved by −6.5 ± 2.5, −6.6 ± 2.4, and −6.0 ± 2.0, respectively. The mADCS-CGIC score ranges from 1 to 7, with higher numbers correlating with worsening function. Improvement was defined as a mADCS-CGIC score of 1 or 2 at week 24; for the citalopram, quetiapine, and olanzapine arms, improvement was noted for 88.0%, 87.0%, and 91.3% of participants, respectively. Patients treated with citalopram had fewer falls than those treated with olanzapine (OR = 0.81; 95% CI, 0.68 to 0.91; *P* = .012), less orthostatic hypotension than those taking quetiapine (OR = 0.81; 95% CI, 0.68 to 0.97; *P* = .032) and olanzapine (OR = 0.80; 95% CI, 0.66 to 0.95; *P* = .020), and fewer hospitalizations than those who were given quetiapine (OR = 0.92; 95% CI, 0.88 to 0.95; *P* = .016) and olanzapine (OR = 0.78; 95% CI, 0.64 to 0.92; *P* = .004).

A 2006 double-blind RCT examined 421 outpatients (median age = 77.9 years ± 7.5 years; 56% female) with Alzheimer dementia and psychosis, aggression, or agitation who were randomly assigned to receive olanzapine, quetiapine, risperidone, or placebo.[4] Effectiveness was approximated by time to drug discontinuation. Olanzapine (22.1 weeks; hazard ratio [HR] = 0.51; 95% CI, 0.35 to 0.74) and risperidone (26.7 weeks; HR = 0.61; 95% CI, 0.41 to 0.89) had a longer median time to discontinuation than placebo (9.0 weeks; *P* = .002), whereas quetiapine was no different than placebo (9.1 weeks; HR = 0.81; 95% CI, 0.57 to 1.15; *P* = .24).

Recommendations from Others

The American Psychiatric Association supports the use of nonemergency antipsychotic treatment for behavioral/psychological symptoms of dementia (including agitation) after assessing for pain and exhausting nonpharmacologic options, and when symptoms are severe, dangerous, or cause significant distress to the patient. They recommend starting at a low dosage and discontinuing therapy for severe adverse effects or lack of improvement at four weeks. Even if treatment is effective, an attempt to taper should be made at four months.[5]

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