A Review of Treatment Options for Agitation and Psychosis Related to Dementia

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Approximately 5.8 million Americans are living with Alzheimer disease (AD).[1] Dementia has various etiologies, many of them reversable. The irreversible causes of dementia are AD, Lewy body dementia (LBD), frontotemporal dementia (FTD), and vascular dementia (VD).[2] At any time throughout the course of the neurodegenerative process, aggression and agitation can manifest. In fact, 75% of persons with dementia will demonstrate symptoms of aggression, agitation, and psychosis (eg, paranoia, delusions, hallucinations), which can interfere with quality of life for the person and his or her family.[3]

To date, no treatment has been approved by the Food and Drug Administration (FDA) for symptoms of psychosis or agitation in patients with dementia. For this reason, medications are being used off-label, and specific antipsychotic medications can cause significant adverse effects such as an increased risk of falls, sedation, heart rhythm abnormalities, and an overall increased risk of mortality.[4] Based on the risks of long-term antipsychotic use, experts in the United States and Canada suggest limiting their use.[5,6] Several studies have been conducted to identify a safer option to treat the disruptive symptoms of agitation in patients with dementia.

CITALOPRAM

A large randomized controlled clinical trial looked at 186 patients who were randomly assigned to receive psychosocial intervention plus either the selective serotonin-reuptake inhibitor (SSRI) citalopram or placebo.[7] In the Citalopram for Agitation in Alzheimer Disease Study (CitAD), Porsteinsson and colleagues worked with 8 academic centers in the United States and Canada from August 2009 to January 2013. In this study, agitation was defined as moderate or marked severity on the agitation/aggression domain of the Neuropsychiatric Inventory (NPI). Participants' probable AD was determined with a Mini-Mental State Examination (MMSE) score from 5 to 28. Cholinesterase inhibitors and memantine were allowed. Citalopram was titrated from 10 mg to 30 mg over 3 weeks with the use of lorazepam, 0.5 mg daily, and trazodone, up to 50 mg daily, as rescue medications. The patients were followed for 9 weeks. After data analysis, citalopram was found significant in reducing agitation in up to 40% of the patients, compared with 26% for placebo. The downside of these study results is that there was evidence of cognitive worsening and prolonged QT interval in the treatment group, which may negate the potential benefits of citalopram administration in this population. In fact, the FDA has suggested that the maximum dose of citalopram be limited to 20 mg based on concerns for elongated QT interval.[4] Due to insufficient data, it is unclear whether a lower dose of citalopram would be as efficacious.

ESCITALOPRAM AND RISPERIDONE

Another study compared the SSRI escitalopram with the atypical neuroleptic agent risperidone.[8] In the 6-week trial, escitalopram was titrated from 5 mg to 10 mg over 1 week, and risperidone was titrated from 0.5 mg to 1 mg over 1 week. All 40 patients met criteria for AD according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, with an MMSE score of 5 to 24. Agitation was defined as being severe enough to warrant hospitalization. Dementia medications were allowed. Agitation was measured using the NPI. The researchers discovered that both groups had a significant decline in NPI score after 6 weeks, although no significant difference was found between the treatment groups. Two individuals receiving risperidone sustained falls, which were likely related to the adverse effect of parkinsonism from risperidone.

FLUVOXAMINE AND RISPERIDONE

Another study compared the SSRI fluvoxamine to risperidone and to yokukansan, a traditional Japanese medication that affects

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the glutamatergic system.[9] All 76 participants met criteria for dementia with an MMSE score of less than 19. Patients were included if they were hospitalized for agitation. The NPI for Nursing Homes (NPI-NH) was used to measure treatment. There was no predetermined fixed dose for these medications; the dose was determined by the principal investigator (PI) depending on the patient's clinical course. The mean dose of risperidone was 1.10 mg daily, the mean dose of fluvoxamine was 83.02 mg daily, and the mean dose of yokukansan was 7.02 g daily. All medications were found effective in reducing patients' agitation score on the NPI-NH, with fluvoxamine leading to the most significant improvement. No statistically significant difference was found between the 3 medications. An encouraging result was the discovery of no significant change in MMSE score, unlike in the CitAD study.[7] In the escitalopram–risperidone study,[8] the MMSE was not checked at the last visit. Falls were documented with all 3 medications. Other adverse events were oversedation, swallowing difficulty, stridor, muscle rigidity, parkinsonian symptoms (consistent in this class), and sudden death in the risperidone group; head injury and fracture in the yokukansan group; and hallucinations, delusions, and refusal to eat in the fluvoxamine group.

LITHIUM

Lithium is of interest in treating agitation in patients with AD, based on previous studies suggesting that it has cognition-enhancing effects.[10] Lithium has been found to have inhibitory effects on tau phosphorylation, which has raised interest in lithium being possibly neuroprotective for AD.[5] Lithium is FDA-approved to treat bipolar disorder and other psychiatric disorders, but there have only been weak trials assessing its positive effect on agitation in patients with AD.[10] Currently, a phase 2 clinical trial is studying lithium for agitation for patients with AD at 4 university-affiliated centers.[10] The researchers report that their study design is unique and will be able to assess whether lithium is effective as monotherapy vs add-on therapy with a neuroleptic agent. Included patients have MMSE scores of 5 to 26 and a diagnosis of AD based on National Institute on Aging criteria. The NPI is used as the rating tool for agitation, and persons with a previous diagnosis of bipolar disorder or other psychiatric disorder were excluded. The goal is to enroll 80 patients for 12 weeks of treatment. The treatment groups are compared with placebo. In the treatment group, patients will be prescribed lithium, 150 mg daily, with close follow-up of blood lithium levels. Based on response to the low dose and blood levels, participants' dose will be titrated to 300 mg daily. Lithium levels are kept at lower levels than typically accepted for bipolar disorder. At week 4 and 6, the dose is increased to 450 mg and 600 mg pending the clinical course and blood levels.[10] The placebo group receives sham lithium levels determined by unblinded, independent physicians in order to keep the study PI-blinded. The 3 aims of this study are to see whether lithium is efficacious in treating agitation in patients with AD, to assess for negative side effects, and to explore associations between improvement on lithium and serum brain-derived neurotrophic factor levels.[10] Pending the results of this phase 2 trial, it will move on to phase 3 and potentially provide enough positive evidence for FDA approval for a treatment option for agitation in patients with AD.

Devanand and colleagues also published a case series of 6 patients with a diagnosis of dementia (AD, FTD-behavioral variant, FTD-semantic variant–primary progressive aphasia) treated successfully with lithium as add-on therapy for agitation.[5] The dosages varied between 300 mg and 600 mg daily, with serum levels of 0.2 to 0.6 mmol/L in 5 cases and 0.8 mmol/L in 1 case. Adverse effects were noted only when a lithium dose exceeded 600 mg. Serum lithium levels remained low with low dosages. These case reports were positive and spring-boarded the current phase 2 clinical trial by the research team led by Devanand, testing lithium as monotherapy rather than add-on therapy.[10]

PIMAVANSERIN

Like persons with AD, persons with Parkinson disease (PD) are at increased risk of developing psychosis, which until recently had been difficult to treat based on a lack of FDA-approved treatments.[11] A unique antipsychotic, pimavanserin, recently has been FDA-approved to treat PD psychosis, Pimavanserin is a serotonin inverse agonist that targets serotonin 2A receptors and, to a lesser extent, serotonin 2C receptors.[11] The selective engagement decreases potential adverse effects seen with the typical and atypical antipsychotics that have been used for treating psychosis and agitation in patients with dementia. Even though the clinical trials enrolled patients over the age of 40 with PD psychosis, pimavanserin contains a black box warning about the risk of increased mortality in elderly patients (65 or older). Pimavanserin has been found to prolong the QT interval; therefore, caution should be used, and regular electrocardiographic monitoring should take place.[11]

Pimavanserin was again studied in the phase-3 HARMONY trial to test its use for delusions and hallucinations associated with all dementia related psychosis.[12,13] Many types of dementia are represented, such as AD, LBD, VD, and FTD. Based on the results of an interim analysis, the study was stopped due to evidence of highly statistically significant longer time to relapse of psychosis compared with placebo.[13] The patients were to have been brought in for final visits, and a full analysis is to be conducted. If the final analysis continues to reveal significant benefit, pimavanserin may be an option for treating dementia related psychosis.

OTHER CONSIDERATIONS

Dementia with psychosis can be problematic not only for the patient but also for caregivers and family members. Agitation

often can be managed with behavior modification such as distraction and reorientation. Assessing for infection, such as urinary tract infection or pneumonia, is necessary in the acute presentation of agitation. Also, assessing for pain, discomfort from constipation, boredom, insomnia, and hunger is important to keep in mind.

If nonpharmacologic therapy is not effective, medication will be necessary. In the elderly population, who often have multiple comorbidities, polypharmacy can be problematic. It is the responsibility of the health care provider to be cautious when treating agitation and remember to always use the lowest dose for the shortest amount of time. In fact, the American Psychiatric Association (APA) recommends that if antipsychotics are necessary for treatment of agitation, they "should be initiated at a low dose to be titrated up to the minimum effective dose as tolerated."[14] The APA also recommends that the provider "attempt to taper and withdraw the drug … within 4 months of initiation, unless the patient experienced a recurrence of symptoms with prior attempts at tapering of antipsychotic medication."[14] An antipsychotic should only be given a 4-week trial of an adequate dose to assess for positive response before discontinuing its use.[14]

Hopefully in the future, better options will be available for treating dementia-related psychosis and agitation that are associated with less significant adverse effects.[5,10] ■

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