Medscape

September 28, 2017

Final Frontier: Managing Acute Delirium in Last Days of Life

By Kristin Jenkins

Delirium at the end of life is common, and many patients with delirium become agitated and restless, causing distress for the patient as well as the patient's family and caregivers. The main treatment options are neuroleptics and benzodiazepines, but use of the latter is controversial.

Now, there is evidence from a placebo-controlled trial that the addition of the benzodiazepine lorazepam (*Ativan*, Pfizer) to the neuroleptic haloperidol (*Haldol*, Ortho-McNeil) may control agitation better than haloperidol alone. The study was conducted in 90 hospitalized patients with advanced cancer and persistent delirium.

"Patients in the lorazepam plus haloperidol group required fewer rescue medications, were perceived to be more comfortable by both caregivers and nurses blinded to treatment assignment, and had no difference in adverse events, respiratory depression, or survival," report the study authors, led by David Hui, MD, of the Department of Palliative Care, Rehabilitation and Integrative Medicine at the University of Texas MD Anderson Cancer Center, in Houston.

"Taken together, this study supports the judicious use of single-dose lorazepam plus haloperidol for patients with persistent agitated delirium after a trial of scheduled haloperidol," they conclude.

The findings were published online September 19 in *JAMA*.

The study was conducted in patients with advanced cancer who experienced agitation and delirium. The patients, who had been prescribed haloperidol at an acute palliative care unit at MD Anderson Cancer Center, were enrolled from February 11, 2014, to June 30, 2016.

Of the 90 patients who were enrolled, 52 (58%) completed the study. The mean age of the patients was 62 years, 42 (47%) were women, and 58 (64%) received the study medication.

Patients were routinely treated for any potentially reversible causes of delirium, such as opioid neurotoxicity, polypharmacy, infections, hypercalcemia, and other metabolic disorders. Caregivers were provided with education, and patients were given orientation cues and were provided with window light. Intensive symptom management was provided, and unnecessary stimuli were reduced.

The addition of intravenous lorazepam (3 mg) to intravenous haloperidol (2 mg) resulted in a significantly greater reduction in scores on the 10-point Richmond Agitation Sedation Scale (RASS) at 8 hours than placebo plus haloperidol (-4.1, indicating deep sedation, vs -2.3 points, indicating light sedation; $P < .001$), the study authors report. Adding lorazepam to haloperidol also reduced the need for median rescue neuroleptics (2.0 mg) more than haloperidol (4.0 mg) plus placebo ($P = .009$).

In addition, 84% of blinded caregivers and 77% of blinded nurses perceived that patients were more comfortable after they had received the lorazepam plus haloperidol regimen. By comparison, 37% of blinded caregivers and 30% of blinded

nurses thought the patients who had been given haloperidol alone were more comfortable after receiving the medication.

No significant differences were observed between the two groups with respect to delirium-related distress and survival. Hypokinesia was the most common adverse effect, seen in three of the patients given lorazepam and haloperidol (19%) and in four of the patients given haloperidol alone (27%).

In the control group, a single 2-mg dose of haloperidol resulted in a rapid decrease in agitation level, but its effect was highly variable and nonsustained. This underscores "the need to identify better options to manage persistent agitation," they point out.

"There has been much debate on the role of benzodiazepines for delirium," Dr. Hui told *Medscape Medical News.* "We found it interesting that even in the persistent agitated delirium setting, a single dose of intravenous haloperidol alone was able to reduce agitation within 30 minutes for many patients, albeit inconsistently. Reassuringly, the lorazepam plus haloperidol group had a more consistent and robust effect."

The addition of lorazepam to haloperidol as rescue for patients with persistent agitation may be justified when patients fail to respond to haloperidol alone, said Dr. Hui. Typically, the survival time for these patients is short, and controlling agitation is critical for families who prefer that the patient not be overly sedated if possible, he explained.

On the basis of eligibility criteria of the current study, however, "we could only recommend the addition of lorazepam for patients in the palliative care setting with delirium and persistent agitation despite scheduled haloperidol," Dr. Hui emphasized.

He noted that many of the study participants were no longer lucid even without sedation, so more research is needed "to determine what caregivers see as a trade-off and a realistic expectation for the RASS score at the very end of life," he said. "Different dosing and other treatment strategies may also strike a balance and need to be investigated."

The research team is now examining the effect of other neuroleptics, benzodiazepines, and drug combinations on agitation to identify optimal treatment strategies.

Use Lowest Possible Dose

In an accompanying editorial, Pratik P. Pandharipande, MD, of Vanderbilt University Medical Center, and E. Wesley Ely, MD, MPH, of Vanderbilt University School of Medicine, Nashville, Tennessee, emphasize that "the lowest-possible doses of targeted antipsychotic medications or benzodiazepines" should be used only when delirium persists.

Individualized treatments, such as managing infections and dehydration, and supportive care, such as providing aids for vision, hearing aids, and having family members present, have been shown to reduce the severity and duration of symptoms of delirium, the editorialists write, but they acknowledge that there is limited evidence to guide clinicians in symptom management.

"In this fast-paced world of medicine, the challenge for clinicians is to show patience and balance in seeking to reduce distressing symptoms, such as those involving severe pain or hyperactive delirium," they write.

The use of psychoactive medications to shut down the symptoms of hyperactive delirium robs dying patients and their families of precious time to talk to each other and can have adverse effects, Dr. Pandharipande and Dr. Ely point out. The current study's findings "may reveal more about the desire to treat the distress experienced by caregivers and the health care team than actually being a patient-centered intervention," they suggest.

To make the end of life meaningful for patients and their families — whether for the last few days or hours — clinicians

must "focus on the humanness of medicine" rather than automatically reaching for a pharmacologic restraint, the editorialists say. Patients need to be as awake and aware as they want to be until pain or other severe symptoms need to be alleviated.

"Thus, the priorities of care are to ensure that the dying person's physical, medical, psychological, and spiritual needs are met, that medication needs are considered, that the family is supported, and that the views of team members with respect to decision making and intervention are considered. If hyperactive delirium persists after these important initial care steps, psychoactive medications remain a consideration."

Dr. Pandharipande and Dr. Ely warn that the findings of the current study are not generalizable to other patients, including those receiving intensive care. "If clinicians use this study...to justify treating delirious patients with benzodiazepines in contexts other than those in which death is imminent and treatment goals are palliative, it could result in harm to patients," they say.

When asked to comment, Maureen A. Malin, MD, PhD, medical director of the Cognitive Neuropsychiatry Program at **McLean Hospital** and instructor in psychiatry at Harvard Medical School in Boston, said she has found that low-dose lorazepam is helpful in treating some cases of agitated delirium in the palliative care setting.

"Sometimes two can be better than one," she said. "By staying at lower doses, you don't get quite the same side effects." It is important to be aware of the risks and benefits, she added, and to "be sure the family is aware too. There has to be a balance."

If delirium can be treated, "there can still be some quality time," Dr. Malin told *Medscape Medical News.* Preparing for the end of life needs to come early, she said, and she estimated that about two thirds of cancer patients receive consultation about this with respect to palliative care.

"I find it's much better if you can be as open and honest in a caring way about what patients can expect to see and feel and the options for treatment," she explained. "We look at diagnosis, prognosis, and the trajectory, and talk about the goals of care at every stage, telling patients that many of the side effects of treatment can be anticipated. If anything, patients feel better when they know what's going to happen."

Prevention of delirium is critical and involves behavioral interventions that orient the patient—whether in the hospital or at home—by keeping them active, following schedules, having a calendar and clock nearby, and providing them with proper lighting. When patients are dying, it's important to think outside the box, Dr. Malin said. "You try to be creative about what helps. Massage, aromatherapy, and music therapy all help calm a patient, and you don't need as much medication."

Some patients still develop active delirium, however, which must be treated aggressively with medication, said Dr. Malin.

"Every patient dies differently, and it's a one-time show. But nobody wants to be agitated or feel frightened, looking at the anguished faces of their family. Patients want to be comfortable when they're living and peaceful when they're dying. We have to do our best to deliver that, to maximize the time patients have but also to make sure that patients and families don't suffer unduly."

This study was supported by the National Cancer Institute, the American Cancer Society, the Andrew Sabin Family Foundation, and the National Institutes of Health Cancer Center. The study authors report no relevant financial relationships. The editorialists received funding from the National Institutes of Health, the Veterans Affairs Clinical Science Research and Development Service, and the Veterans Affairs Tennessee Valley Geriatric Research, Education, and Clinical Center. Dr. Pandharipande has a relationship with Hospira, and Dr. Ely has relationships with Abbott, Orion, and Pfizer. Dr. Malin has disclosed no relevant financial relationships.