CLINICAL VIGNETTE

Use of Modafinil in Two Patients with Hypoactive Delirium

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Case One

An 85-year-old man with three-vessel coronary artery disease, systolic heart failure, severe aortic regurgitation and moderate aortic stenosis, was admitted to the hospital with an upper gastrointestinal bleed four days before a planned aortic valve replacement. During the initial part of the hospitalization, esophagogastroduodenoscopy found gastric ulcers, and after transfusions of packed red blood cells, had no further melena. He subsequently underwent transcatheter aortic valve replacement (TAVR). After the procedure, he developed daytime somnolence and lethargy, as well as restlessness and agitated behaviors at night. Oral intake was minimal.

Geriatric consultant initially recommended evening trazodone and melatonin to help with sleep, as well as removal of his urinary catheter. After one day, there was no noticeable improvements in his mental status, and the consulting team then recommended the use of daytime modafinil at 100 mg daily to improve daytime alertness, and the stoppage of nighttime olanzapine, which had been prescribed to treat nocturnal agitated behavior.

The patient's daytime alertness and nighttime sleep improved slightly, and the dose of modafinil was increased to 200 mg through the remainder of the hospitalization. His alertness and oral intake improved. Modafinil was stopped before discharge, to a skilled nursing facility.

Case Two

An 86-year-old woman with moderate-to-advanced Alzheimer's dementia was admitted to the hospital after a fall in her home with head trauma. Head CT revealed a large subdural hematoma, which was evacuated by neurosurgery, though she required a second surgical evacuation three days later. Her postoperative course was most notable for hypoactive delirium in the daytime, with somnolence and poor appetite. She also showed agitated behaviors in the evenings. Her hospital team managed these symptoms with as-needed oral evening trazodone and quetiapine. Her oral intake remained poor and she required intravenous fluids to maintain hydration and renal function. At a goals of care discussion, her daughter expressed preference for no feeding tubes.

In the three days before discharge, she was started on methylphenidate as a stimulant to help with alertness and appetite, which was increased to 10 mg twice a day. Over three days her daytime alertness improved, and she was eating a few bites of food per day before discharge.

She was discharged to a skilled nursing facility. Her daughter requested change in her methylphenidate, which she felt was making her mother jittery and anxious. Daily Modafinil 100 mg daily was substituted and her daughter also agreed to treatment with escitalopram for anxiety and depression. By the time of her discharge to home from the skilled nursing facility, the patient's oral intake improved to around 25-50% of meals. The patient's physician discontinued modafinil before hospital discharge, and she continued taking escitalopram at home.

Case Discussion

Delirium is an acute confusional state characterized by fluctuation in mental status, alteration in consciousness, and lack of attention. Delirium has been divided into subtypes based on the degree of alertness and motor behavior. Hyperactive delirium is characterized by restlessness and aggression, while hypoactive delirium commonly involves lethargy and apathy.[1] Mixed delirium constitutes symptoms of both hypo- and hyperactive delirium. Data suggest that about 50% of delirium is hypoactive, and that the mixed subtype accounts for 80% of all cases of delirium.[2] Prior studies also suggest that hypoactive delirium may be more commonly associated with metabolic disorders and organ failure, whereas hyperactive delirium is more common in substance intoxication or withdrawal. Hypoactive patients are also more likely to develop pressure ulcers or hospital-acquired infection. Mortality reports have been contradictory.[3]

Antipsychotics have been thoroughly studied in management of hyperactive delirium, and mixed data as to effectiveness and safety in the treatment of agitated behaviors. They are often used for these behaviors at night, but they may not address daytime lethargy. There is no consensus on the management of hypoactive delirium, other than addressing predisposing and precipitating factors for the delirium, like infection, polypharmacy, or electrolyte and fluid abnormalities. Once these factors have been addressed, or if there are only irreversible factors presenting such as cancer or dementia, there may be need for additional treatments.

There is rationale for use of stimulants in hypoactive delirium. They could increase daytime wakefulness and help normalize

the sleep-wake cycle. However, there is some concern because side effects could include worsening agitation or psychosis. Data on use of stimulants in hypoactive delirium are limited, to a few case reviews and a single small prospective studies. Gagnon et al prospectively studied 14 patients in an intensive care unit (ICU) with hypoactive delirium, and initially treated identifiable causes. They then treated the patients with methylphenidate. All 14 patients showed improvement in their mental status assessed by the Mini-Mental Status Examination (MMSE).[4]

Modafinil is a stimulant medication approved for narcolepsy, obstructive sleep apnea, and shift-work sleep disorder. Its action has been attributed to the catecholamine pathway like other stimulants. In comparison to other medications in this category like methylphenidate, it has lower sympathomimetic effects, especially on the cardiovascular system. It is not associated with the interruption of normal nighttime sleep, or with high abuse potential. There are limited case reports on modafinil use in the ICU for patients with daytime somnolence. One studied three patients with daytime somnolence and fatigue in ICU, and showed improvement in symptoms with 200 mg of daily modafinil.[5] Finally, there is an active randomized controlled trial of modafinil in hypoactive delirium. Because "modafinil restores sleep cycle synchrony in the ICU, it measures delirium free days and ICU outcomes". The study started in 2014, in patients 18 to 76 years of age.[6]

We observed two patients with mixed forms of delirium in whom the use of a stimulant was associated with increased day-time alertness, improved oral intake, and a decrease in agitated nighttime behaviors. The evidence is still too scant to recommend the use of stimulants in patients with hypoactive or mixed delirium, but more studies are forthcoming to help clarify their utility in this population.

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