PALLIATIVE CARE
CASE OF THE MONTH

"Quetiapine for Off-Label Use in Anxiety – What is the evidence?"

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Case:
Mrs. O is an 80-year-old woman with COPD and CHF who was admitted to the hospital with small bowel obstruction. Her course was complicated by severe acute respiratory distress syndrome requiring prolonged intubation and eventual trach placement. Six weeks after admission, she remained ventilator-dependent with inability to tolerate greater than three hours of spontaneous breathing trials in the setting of significant anxiety. Per staff, she would repeatedly ask whether the ventilator was working despite O2 saturation in the high 90s.

Prior to the hospitalization, she had no history of psychiatric disorders. In the setting of her prolonged stay, however, she reported new-onset anxiety exacerbated in moments she was alone, along with restlessness and "jitteriness." She endorsed associated symptoms of insomnia, feelings of guilt and hopelessness, and intermittent passive death wish. She did have mixed hyper/hypoactive delirium earlier in her hospitalization for which she received three doses of haloperidol 2.5mg IV over a week. Behavioral medicine was consulted for management of her anxiety.

Discussion:
Patients older than 65 who receive mechanical ventilation experience high rates of anxiety.[1] One study from Columbia University examining this population found anxiety in 36% of patients the week prior to hospital discharge and over 40% one month after discharge.[1] In this same study, patients who met criteria for frailty had an even higher prevalence of anxiety.[1] Proposed triggers of anxiety in mechanically-ventilated patients include breathing discomfort on the ventilator, inability to communicate with caregivers, inadequate rest, and delirium.[2-4]

Anxiety in intubated patients is associated with poor outcomes. One study examining the dysfunctional ventilator weaning response (DVWR) found that anxiety was the only factor consistently associated with difficulty weaning; the odds ratio for having DVWR was 20-40 in patients who experienced anxiety.[5] In addition, anxiety has been identified as a significant barrier to high-quality care upon discharge from intensive care.[6]

Despite its impact on patients, there is little data to guide the treatment of anxiety for elderly patients in the intensive care unit (ICU).[2, 6] Using short-acting agents for anxiety or breathlessness such as benzodiazepines or opioids are unproven and may have significant adverse effects including worsened delirium and paradoxical agitation.[3] In the setting of medical uncertainty, quetiapine has been increasingly utilized for anxiety associated with ventilatory support in the ICU.

Quetiapine was initially synthesized in 1985 from the combination of perlapin and fluperlapin, two benzodiazepine-derived components, and was FDA-approved in 1997 for the treatment of schizophrenia.[7] It has a relatively higher affinity for serotonergic receptors than dopaminergic receptors which is thought to contribute to its relatively low risk of extrapyramidal side-effects compared to other atypical antipsychotics. However, its high affinity for histaminergic receptors underlies its tendency for precipitating sedation and orthostatic hypotension in patients.[7]

The concept of using quetiapine for anxiety arose in the early 2000s.[8] Early, small-scale, open-label studies showed significant decreases in the Hamilton Rating Scale for Anxiety (HAM-A).[8-14] In 2007, the first double-blind, placebo-controlled trial of quetiapine as an adjunct to selective serotonin reuptake inhibitors or venlafaxine for patients with major depressive disorder and comorbid anxiety was published. This study randomized 58 patients to either quetiapine or placebo for up to eight weeks.[15] The average dose by completion of the study was nearly 200mg/day. Results showed a significant decrease in the HAM-A score in the intervention group compared to the placebo group by the end of week one, and this difference was maintained for the duration of the study. However, there was an attrition rate of 38% in the treatment arm due to side effects including sedation and weight gain.[15]

At present, the greatest evidence for off-label use of quetiapine is as a short-term anxiolytic in outpatients with generalized anxiety disorder (GAD).[16] In a systematic review of atypical antipsychotic medications, the pooled result of three large trials totaling 2,437 participants demonstrated a 26% chance of a favorable response to quetiapine at eight weeks.[16] However, conclusions are limited by significant heterogeneity between trials, dosing variation from 50mg/day to 300mg/day, and lack of evidence for maintenance therapy.

The efficacy of quetiapine in GAD has led to its usage in other settings, including the ICU. In 2007, quetiapine was used for a patient at the University of Pennsylvania with anxiety-associated DVWR.[17] In this case, a 39 year-old woman with multiple myeloma who had undergone a bone marrow transplant developed hypoxic respiratory failure from pneumonia. For three weeks, she failed to tolerate >1 hour off ventilation despite clinical resolution of the pneumonia and aggressive diuresis. She had an outpatient diagnosis of depression for which she was on escitalopram. Psychiatry was consulted for anxiety and she was treated with quetiapine 50mg qam, qnoon, and 100mg qhs. This was increased to 100mg q8h with immediate symptomatic improvement per nursing, and she was weaned off the ventilator within one day.[17]

(Discussion Continued)

While this case report is striking, it remains the only published evidence to support quetiapine for anxiolysis in prolonged weaning. As such, numerous concerns about its use in anxiety-associated DVWR remain. While short-term administration may not pose significant risk, studies demonstrate that antipsychotics started in the ICU are often continued to discharge where they are associated with cognitive deterioration, hip fracture, and pneumonia.[18-19]

In summary, while quetiapine is increasingly prescribed for anxiety in the ICU, evidence to support this practice is limited. Although it may appear safer than benzodiazepines, its use is limited by its antihistaminergic properties and the potential long-term complications when not discontinued following acute treatment.

Resolution of the Case:

In the absence of prior psychiatric disorders, Mrs. O was diagnosed with adjustment disorder with anxiety. Given the severity of her anxiety preventing weaning from the ventilator and her recent delirium, behavioral medicine started scheduled quetiapine 50mg qhs along with 25mg prn with nursing recommendation to administer 30 minutes prior to weaning trial. With the scheduled and morning prn doses of quetiapine, she tolerated significantly longer spontaneous breathing trials, increasing from three hours to over eight hours within two days after starting the quetiapine. However, she continued to have difficulty weaning from the ventilator for another month, and the quetiapine was discontinued due to lack of efficacy.

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