

Use of Quetiapine in Delirium

Case Reports

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Delirium is an acute confusional state with cognitive impairment, sleep-wake cycle disturbance, perceptual disturbances, affective lability, language and thought disorder, delusions, and psychomotor disturbances.^{1,2} A diminution in cholinergic function; an excess of dopamine, norepinephrine, and glutamate; and disturbances in serotonergic and γ -aminobutyric acid activities have been implicated in its pathogenesis.³⁻⁵

Haloperidol is considered by many clinicians as the gold standard in delirium treatment. It is mainly a dopamine D₂-receptor antagonist, has negligible anticholinergic side effects, has a high safety profile, and can be administered through oral, intramuscular, or intravenous routes.^{6,7} However the use of conventional high-potency neuroleptics such as haloperidol have been associated with significant side effects such as extrapyramidal symptoms (EPS).⁸ Intravenous use of haloperidol has been associated with torsade de pointe.^{9,10}

Novel antipsychotics have an advantage, in terms of side effects, over conventional antipsychotics for the treatment of psychotic disorders and may offer a viable option for the treatment of delirium. There are reports on the use of atypical neuroleptics such as risperidone and olanzapine in the management of delirium.^{11,12} Both drugs have been found to be safe and effective alternatives to haloperidol.

To our knowledge, there have been no large control studies examining the efficacy and safety of the atypical neuroleptic quetiapine in the management of delirium. Schwartz and Masand¹³ published a retrospective chart review of 11 patients treated with quetiapine for delirium. Mean quetiapine dose was 211.4 mg/day and 10 of the 11 patients showed more than 50% improvement in Delirium Rating Scale scores (DRS).

The case reports below show, albeit anecdotally, that quetiapine can be effectively and safely used in treating delirium at lower doses.

Case Report

Case 1. Mr. G. was a 63-year-old white man admitted for surgical management of squamous cell carcinoma of the larynx and for work up for a colorectal mass. Mr. G. underwent a total laryngectomy, and a psychiatry consultation was sought 5 days postsurgery because of an acute change in his mental status. Mr. G. was increasingly restless, confused, disoriented, and agitated. He had a psychiatric history significant for generalized anxiety disorder for which he was in outpatient treatment. Mr. G.'s regimen included thioridazine (15 mg tid), doxepin (50 mg hs), and clordiazepoxide (25 mg tid prn). He was maintained on this regimen for over 10 years with adequate symptom control.

On evaluation, Mr. G. had waxing and waning levels of consciousness characterized by episodes of lethargy and wakefulness. On initial assessment, he was restless, trying to get out of restraints, and trying to pull out his nasogastric tube (NGT) and intravenous lines. He was disoriented, had problems with delayed recall, and had difficulty sustaining attention. Mr. G. was able to follow simple commands but was unable to cooperate in a formal mental status examination. He had mood lability characterized by angry outbursts and psychomotor agitation. Mr. G. did not express any delusional ideation nor did he appear to be responding to auditory or visual hallucinations. His Mini-Mental State Exam (Folstein; MMSE) score was 5/30; his DRS score was 20; and his Delirium Rating Scale-R-98 (DRS-98) score was 23.

Laboratory tests revealed elevated glucose (124 mg/dl), decreased hemoglobin (11.7 d/dl), and hematocrit (39.4%). Electrolytes, BUN, creatinine, WBC, and platelets were within normal limits. Urine was cloudy but was negative for glucose,

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protein, nitrate, and leukocyte esterase. During admission, vital signs ranged from BP of 98/48 mmHg to 164/74 mmHg, and temperature of 95.7°–99.6°.

At the time of evaluation, Mr. G. was receiving the following medications: thioridazine (15 mg qid), chlorthalidone (25 mg qid), temazepam (15 mg hs), lorazepam (2 mg im q 4 h prn), and morphine (50 mg iv via pca pump). Doxepin was tapered off before surgery and no cholinergic rebound symptoms were noted. Temazepam and lorazepam were initiated to control Mr. G.'s restlessness and sleep disturbance postsurgery.

Mr. G. was diagnosed with substance-induced delirium (benzodiazepine/opiate/anticholinergic). Polypharmacy was minimized. Thioridazine, chlorthalidone, temazepam, and lorazepam were discontinued. However, Mr. G. continued to be confused, disoriented, and agitated. He was then started on a trial of quetiapine (25 mg bid via NGT). Mr. G. showed gradual improvement of behavioral and cognitive functioning. There were no symptoms of benzodiazepine withdrawal, cholinergic rebound, nor EPS. Five days after discontinuation of thioridazine and benzodiazepines and initiation of quetiapine, Mr. G. showed marked improvement in behavior, attention, concentration, and memory. He was considered at baseline functioning, and quetiapine was discontinued. Mr. G. was discharged after being gradually titrated back to his regular outpatient regimen. On follow-up evaluation 1 week after discharge, Mr. G. continued to do well with no behavioral or cognitive sequelae. He has undergone radiation therapy and was able to actively participate in speech therapy. His MMSE score improved to 24/30. His DRS and DRS-R-98 scores on follow-up were 3 and 6, respectively.

Case 2. Ms. H. was a 37-year-old woman admitted to the brain injury unit. She was involved in a motor vehicle accident as an unrestrained driver and was ejected from her vehicle. Her Glasgow Coma Scale (GCS) on admission to the university emergency room was 7. Her head CT revealed a right frontal contusion. She also suffered multiple fractures but required no neurosurgical or orthopedic intervention during her stay at the university hospital. She was on a ventilator for 15 days before a tracheostomy was placed. Ms. H. was started on diprivan for sedation. This was weaned, with her being started on lorazepam and diazepam for agitation. She was transferred to the brain injury rehabilitation unit after a 27-day acute hospitalization. There she became progressively more agitated, despite benzodiazepines being tapered and stopped. Psychiatry was consulted to assist with management of her agitation.

Ms. H. had no prior psychiatric history. She denied any symptoms of major depression, mania, or psychosis. Her family noted her to have mood lability but confirmed that there were no prolonged depressive symptoms nor any symptoms of mania.

Ms. H.'s medical history was unremarkable prior to her accident. At the time of psychiatry consultation, her medications were prednisone (30 mg/day), bisacodyl (10 mg pr every other night), diphenhydramine cream, calomoseptine ointment, hydroxyzine (25 mg every 6 h), sliding scale insulin, ranitidine (15 mg twice a day), and senna (187 mg twice a day). She used tobacco regularly and alcohol occasionally. CBC and chem7 were unremarkable, as were liver function tests. HIV, hepatitis screen, and RPR were negative. TSH was normal. Urine preg-

nancy test was negative. Urinalysis revealed 3+ blood, and urine cultures showed gram-positive cocci.

On examination, Ms. H. was pleasant and cooperative. Her speech showed normal tone and pressure. Her mood was "bad," and her affect was dysthymic but mildly labile. Her thought processes were tangential to loose unless the interviewer interceded to maintain the train of conversation. Her thought content was negative for suicidal/homicidal ideation, audio/visual hallucinations, or delusions. Her MMSE score was 11 of 30. Her DRS score was 18, and her DRS-R-98 was 21. Her neurological examination revealed a mild tremulousness but no other evidence of cerebellar dysfunction; the rest of the examination was within normal limits. At that time, Ms. H. was diagnosed with delirium due to traumatic brain injury, possibly complicated by urinary tract infection. Recommendations were to start her on quetiapine (25 mg at night) on a scheduled basis for agitation. Additionally, haloperidol (1 mg po/im every 6 h) could be used for breakthrough agitation. With quetiapine started, Ms. H. had normalization of her sleep/wake cycle. By the next day, she was noticeably calmer, which persisted throughout the week. She required no supplemental haloperidol for control of agitation at any time. Follow-up rating scales one week after consultation showed DRS score of 7 and DRS-R-98 score of 4. At that time, her quetiapine was discontinued, and her agitation remained under control. Ms. H. was discharged from the brain injury unit 2 weeks later, still with no agitation and requiring no antipsychotics.

Discussion

Conventional high-potency neuroleptic medications such as haloperidol have been the drug of choice in the treatment of delirium.⁷ However, these drugs are associated with adverse events such as EPS and neuroleptic malignant syndrome. Patients with delirium have an increased risk for EPS partly because delirium is more common in the elderly and severely medically ill, and these are the population that are more prone to EPS.⁸

The atypical neuroleptics risperidone and olanzapine have been used in the treatment of delirium with relative efficacy and safety. The use of quetiapine has been reported in 11 patients with delirium at doses ranging from 25 to 750 mg/day.

Quetiapine fumarate, is a dopamine D₁-, D₂-, and serotonin 5HT-1A, 5HT-2 receptors antagonist.^{6,14–16} It also has histamine H₁ and α -1 and α -2 adrenergic blocker properties. Quetiapine has the least incidence of extrapyramidal side effects among the currently available antipsychotics and has negligible affinity for cholinergic and muscarinic receptors. Furthermore, quetiapine's relatively short half-life (3–6 h) may be an advantage should rapid discontinuation be indicated because of adverse effects.

Quetiapine, like risperidone and olanzapine, has both dopaminergic and serotonergic activities and has negligible cholinergic and muscarinic activities, which may account for its efficacy in the treatment of delirium with low incidence of side effects such as EPS.

The two cases presented here indicate that quetiapine fumarate can be safely and effectively used at low doses for the management of delirium. As indicated by the reduction in the DRS scores and improvement of MMSE scores, both patients showed significant clinical improvement after the initiation of quetiapine. Neither patients experienced adverse events such as EPS during the course of treatment.

Although it may be argued that symptom resolution was a result of the natural course of the delirium and the treatment of the underlying cause (i.e., minimizing poly-

pharmacy), it is our impression that quetiapine played an integral part in the remission of delirium in these patients. The temporal association of quetiapine administration and clinical improvement of the neuropsychiatric symptoms bolsters this tenet.

Although quetiapine seems to be effective and safe anecdotally, further observational data and controlled studies are needed to prove its efficacy and safety for the treatment of delirium. A major practical issue in the use of quetiapine for delirium is its wide range of dosing and the probable need for dose titration. Therefore a controlled randomized study is necessary to determine recommended dosing and titration schedules. Nevertheless, quetiapine may prove to be a viable treatment option for the management of neurobehavioral symptoms of delirium.

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