Review Article

The Role of Atypical Antipsychotics in the Treatment of Delirium

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Delirium exemplifies the interface between medicine and psychiatry. It is generally characterized by acute disturbances of consciousness, cognition, and perception that are precipitated by an underlying medical condition. The gold standard of psychiatric treatment is to treat the underlying medical cause and use high-potency antipsychotics to treat the clinical manifestations of delirium. In the early 1990s, a new generation of novel antipsychotics was developed. Their mechanism of action, preferential serotonergic ($5HT_{2a}$) blockade, results in a markedly lower rate of extrapyramidal side effects, an advantage over the typical, older antipsychotic medications. These agents have been shown to be effective and well tolerated in common psychotic disorders (e.g., schizophrenia or bipolar disorder), but few studies have evaluated them in the treatment of delirium. This paper reviews the pertinent literature and summarizes tentative guidelines for novel antipsychotic use in delirium. (Psychosomatics 2002; 43:171–174)

Delirium is a syndrome that develops acutely (hours to days), and its symptoms tend to fluctuate throughout its course. It usually involves a disturbance of consciousness and an inability to maintain attention. Cognitive deficits and perceptual changes are common. These symptoms are not attributable to a preexisting psychiatric illness or substance-induced state, for which specific treatments are needed (antipsychotic agent or benzodiazapine). Symptom onset is acute or subacute, which helps differentiate delirium from dementia and other chronic psychotic illness.[1] Often, ample evidence from patient history, physical examination, and laboratory or diagnostic testing indicates an underlying medical or physiologic etiology.

Delirium occurs in 10%–18% of hospitalized medical and surgical patients[2,3] and is often accompanied by a high morbidity and mortality rate.[4] Elderly patients are at high risk for developing delirium (14%–56%).[5] Other populations at risk include postoperative, burn, and sensory-deprived patients and patients with HIV, head injury, seizure, renal failure, hepatic failure, or cardiac failure.

Diagnosing delirium may be easy when the patient exhibits florid, acute symptoms but is more difficult when symptoms are mild and slowly fluctuating with psychomotor retardation (quiet or hypoactive delirium). The first step is a clinical evaluation that uses a medical and psychiatric approach. Administration of the Mini-Mental Status Examination[6] or the Delirium Rating Scale (DRS/DRS-98)[7,8] helps confirm the clinical diagnosis. Electroencephalography (EEG) may be helpful when the differential diagnosis is complex.[9]

The American Psychiatric Association has developed a practice guideline for the treatment of patients with delirium.[3] Psychiatric consultation and management are preferred, with communication among the primary treating

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team, other consultants, nurses, and family members. Psychiatrists may also make environmental suggestions to increase or decrease sensory input or improve orientation. The treatment of choice is to diagnose and treat the underlying medical condition suspected of causing the delirium. Once this has begun, an antipsychotic is usually the somatic treatment of choice. Haloperidol is most often used because it has few anticholinergic side effects, few active metabolites, and few sedating side effects. It is also available for oral, intramuscular, and intravenous (not FDA approved) administration. Haloperidol should be started at 1–2 mg every 2–4 hours as needed, with dose increases for agitated patients. ECGs should be monitored because the QT_c interval may be prolonged, particularly with intravenous haloperidol. Benzodiazepine monotherapy should be avoided unless the delirium is attributable to sedative or alcohol withdrawal.

Despite these concise and comprehensive guidelines, little information is available on the safety and efficacy of the novel antipsychotics in the treatment of patients with delirium. Because most dopamine antagonist antipsychotics are effective in treating delirium, the newer atypical antipsychotics would be expected to provide similar efficacy and better tolerability, consistent with the common findings for treating psychosis. This paper reviews the literature on risperidone, olanzapine, and quetiapine, the available novel antipsychotics in the United States, in treating the symptoms of delirium. Of note is that the literature is scarce and devoid of randomized and controlled studies. Statistical results may also be confounded by the fact that, as underlying medical conditions are being treated, delirium symptoms improve. This confounding variable makes it difficult to study delirium in a formal setting, because withholding medical treatment in these individuals would be unethical. Finally, we offer some suggestions for the use of atypical antipsychotic agents in medically ill patients with delirium.

RISPERIDONE

In 1997, Sipahimalani and Masand[10] published a retrospective case report on successful treatment of delirium in two patients. One, a 60-year-old man, suffered cardiac arrest after admission to a hospital emergency room for sepsis and pneumonia. After resuscitation, the patient was withdrawn, apathetic, and disoriented. Several weeks later, delirium precipitated by hypoxic brain injury and hypernatremia was diagnosed. He was treated with 0.5 mg of risperidone twice daily and showed improvement by day 3. The delirium cleared by day 14 with 1.0 mg of risperidone twice daily, and risperidone was ultimately discontinued. In the second case, symptoms of delirium developed in a 14-year-old hospitalized boy who had hypoxic brain injury after a suicide attempt. He was treated with 1.0 mg/day of risperidone and improved considerably over the next 10 days. Three weeks later, he was released from the hospital and was instructed to take 1.0 mg of risperidone twice daily on a short-term basis. The authors reported that both patients tolerated treatment well with minimal side effects.

In another retrospective follow-up of 11 consecutive patients, age range 14–74 years, with delirium of multifactorial etiology,[11] eight patients improved clinically, with a reduction in delirium as measured by the Clinical Global Impression Scale.[12] The mean dose of risperidone was 1.59 ± 0.8 mg/day, and the patients' best clinical response occurred at 5.1 ± 4.3 days.

Advanced age is a risk factor for the development of delirium. In three elderly patients age 71–83 years, polypharmacy, including risperidone, was administered. Several hours to days later, delirium developed. All medications were stopped, and the delirium remitted. The authors could not acknowledge a risk of delirium with risperidone, especially in elderly patients who were taking other medications.[13]

A case series exists in which risperidone was used to treat psychotic delirious symptoms in seven hospitalized patients.[14] Concomitant medical conditions in these patients included brain surgery, anticardiolipin syndrome, renal failure, epilepsy, lupus, and metastatic carcinoma. In all seven patients, psychotic delirious symptoms remitted as measured by the Brief Psychiatric Rating Scale. It appeared that risperidone could be used to effectively treat psychotic symptoms due to various medical conditions (delirium).

OLANZAPINE

Olanzapine has been evaluated in a similar retrospective study.[15] Eleven delirious elderly patients with multiple medical illnesses received a mean dose of olanzapine of 8.2 ± 3.4 mg/day. The olanzapine group was compared with a cohort group of 11 patients with delirium who had received a mean of 5.1 ± 3.5 mg/day of haloperidol. According to the DRS, 5 of 11 olanzapine-treated patients and 6 of 11 haloperidol-treated patients experienced a >50% reduction in delirium severity. The peak clinical response occurred in 6.8 ± 3.5 days with olanzapine and

in 7.2 ± 4.9 days with haloperidol. These between-group differences in efficacy were not significant. Haloperidol, however, was more poorly tolerated: five patients taking haloperidol versus none of those taking olanzapine developed extrapyramidal symptoms, side effects that are common with conventional antipsychotics.

A case of delirium had been reported elsewhere in a woman with leukemia and pain of unknown origin.[16] The delirium continued and developed with moderate to severe extrapyramidal symptoms when her pain medications were increased. Changing her opioid analgesic and administering haloperidol (0.5–2.0 mg) were not effective. The patient was started on olanzapine with initial improvement but residual confusion in the evenings and at night. The olanzapine dose was increased to 10 mg nightly with 2 mg as needed during the day. After 3 days on this regimen, the patient's mental status was normal, and she was discharged from the hospital. In this case, the authors note that the combined use of haloperidol and olanzapine may have led to symptom resolution.

QUETIAPINE

In a retrospective study, Schwartz and Masand compared quetiapine with haloperidol in patients with delirium (11 patients in each group, age range 19–91 years).[17] Mean doses were 211.4 mg/day of quetiapine and 3.4 mg/day of haloperidol. Ten of 11 patients in each group showed improvement in DRS scores, with a reduction of >50% in global delirium symptoms. The peak clinical response occurred in 6.5 days with quetiapine and in 7.6 days with haloperidol. Treatment was discontinued in one patient who was taking quetiapine because of sedation and in two patients who were taking haloperidol because of parkinsonism.

ZIPRASIDONE

There is only one case report in press[18] regarding the newest atypical antipsychotic in delirium. Ziprasidone effectively cleared a delirium in a patient with HIV and cryptococcal meningitis but was fraught with mild to moderate QT_c prolongation when the patient's amphotericin treatment caused hypokalemia and hypomagnesemia.

DISCUSSION

Diagnosis and treatment of a delirious patient is often a complex and difficult situation. There is often severe comorbid medical illness with clear risk of mortality. Multiple medical specialties, nurses, care providers, and family members are often involved in treatment and decision making. Often, delirious patients are deemed to lack the capacity to make decisions because of their delirium symptoms. If there is an urgent need to treat with an antipsychotic agent (extreme agitation or dangerousness), patients are often medicated or restrained under emergency care statutes. In less urgent situations, next of kin are consulted for substitutive judgment with regard to medical decision making. If there is no next of kin (no close relatives or patient is a ward of the state), a court-appointed guardian is often sought to make decisions. These scenarios make it difficult to randomize or control prospective delirium studies.

Once an accurate diagnosis is made, several pharmacological treatment issues should be considered. If an oral or feeding tube route is not available because of the patient's medical condition, agitation, or refusal to take oral medications, atypical antipsychotics may not be used (without addressing medico-legal concerns) because they are not yet available in a parenteral form. Intramuscular or intravenous haloperidol may be a more reasonable choice in these circumstances.

If an oral or feeding tube route is available, 0.25–0.5 mg of risperidone twice daily (mild to severe agitation) is a reasonable starting dose. This may be increased up to 4 mg/day if symptoms initially fail to clear. ''As-needed'' risperidone may also be effective. We suggest a 0.25–0.5 mg every 4 hours as needed for agitation or increased delirium symptoms.

For olanzapine, 2.5–5 mg at bedtime (mild to severe agitation) is a reasonable starting dose. This may be increased to 20 mg/day if symptoms fail to clear. As-needed olanzapine may also be used; however, in our experience, it has not provided greater efficacy at higher doses.

For quetiapine, 25–50 mg twice a day is a reasonable starting dose. This may be increased every 1–2 days to 100 mg twice a day if it is well tolerated. Up to 600 mg/day may be used. As-needed quetiapine may also be effective. We suggest 25–50 mg every 4 hours as needed for agitation or increased delirium symptoms.

Risperidone, olanzapine, or quetiapine medication may be discontinued without difficulty 7–10 days after patients return to baseline, with cleared sensorium and alleviation of delirium symptoms, particularly after reorganization of the sleep-wake cycle. It has been reported,

however, that delirium developed with severe agitation and psychotic symptoms in three patients after the atypical antipsychotic clozapine was withdrawn.[19]

In summary of our experience, the use of an atypical antipsychotic is a reasonable first-line approach to the drug treatment of delirium. In clinical practice, our attending and resident psychiatrists use risperidone as the agent of choice. If this or any other atypical antipsychotic fails to treat delirium according to these guidelines, the medical and psychiatric (delirium) diagnosis is reevaluated and haloperidol instituted per American Psychiatric Association guidelines.

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