Atypical Antipsychotics for the Treatment of Delirious Elders

Lauren B. Ozbolt, MD, Miguel A. Paniagua, MD, and Robert M. Kaiser, MD, MHSc

Background: Delirium occurs frequently in hospitalized patients and is reported to occur at a rate of 10% to 40% in hospitalized elderly patients. The gold standard of treatment is to treat the underlying cause of delirium and use high-potency antipsychotics such as haloperidol to target the behavioral disturbances. Since the development of atypical antipsychotics, many psychiatric conditions that were previously only treatable using high-potency antipsychotics may now be managed with the atypical agents. This review will examine the current literature on atypical antipsychotics and summarize the results from published trials in order to evaluate the efficacy and potential benefits of atypical antipsychotics for the treatment of delirium in the elderly population.

Methods: A search of the published literature was conducted using MEDLINE and PubMed. The PubMed search was limited to articles that were (1) written in the English language, (2) focused on human subjects above age 65, and (3) were in the format of review articles, randomized controlled trials (RCTs), clinical trials, or meta-analyses. The initial PubMed search was conducted in March 2006 with follow-up investigations in April 2006 and July 2007.

Results: Risperidone, the most thoroughly studied atypical antipsychotic, was found to be approximately 80% to 85% effective in treating the behavioral disturbances of delirium at a dosage of 0.5 to 4 mg daily. Studies of olanzapine indicated that it was approximately 70% to 76% effective in treating delirium at doses of 2.5 to 11.6 mg daily. Very few studies have been conducted using quetiapine; it also appears to be a safe and effective alternative to high-potency antipsychotics. In comparison to haloperidol, the frequency of adverse reactions and side effects was found to be much lower with the use of atypical antipsychotic medications. In the limited number of trials comparing atypical antipsychotics to haloperidol, haloperidol consistently produced a higher rate (an additional 10% to 13%) of extrapyramidal side effects.

Conclusions: A review of current literature supports the conclusion that atypical antipsychotic medications demonstrate similar rates of efficacy as haloperidol for the treatment of delirium in the elderly patient, with a lower rate of extrapyramidal side effects. There is limited evidence of true efficacy, since no double-blind placebo trials exist. **(J Am Med Dir Assoc 2008; 9: 18–28)**

Keywords: Atypical antipsychotics; delirium; elderly

Delirium is a neuropsychiatric syndrome characterized by a disturbance of consciousness, cognition, attention, or perception that develops acutely over a brief period of time. These changes typically occur over hours to days and represent a significant decline from the patient's previous level of functioning (Table 1).

As illustrated in Table 2, the manifestations of delirium must be caused by the direct physiological consequences of a general medical condition or substance-induced state and cannot be attributable to a preexisting psychiatric illness.[1] Numerous psychiatric and neurological abnormalities can be seen in delirium, including dramatic changes in mood and behavior, tremors, nystagmus, incoordination, asterixis, and urinary incontinence.[2] Classically, delirium begins abruptly, has a brief and fluctuating course, and rapidly improves with identification and treatment of the underlying cause. As indicated in Table 2, the causes of delirium are numerous; the most common causes are central nervous system (CNS) disease, systemic disease, anticholinergic medications, and intoxication/withdrawal from pharmacologic or toxic substances.[3] Other risk factors include advanced age, cognitive impairment, sensory deprivation, and trauma.

The pathophysiology of delirium is not well understood. The clinical manifestations of delirium appear to represent a diffuse, reversible impairment of cerebral oxidative metabolism and neurotransmission.[4] The major neurotransmitter associated with delirium is hypothesized to be acetylcholine, and the major neuroanatomical area is thought to be the reticular formation.[2] Several studies have reported the rela-

Department of Psychiatry and Behavioral Sciences, Mental Health Hospital Center, University of Miami Miller School of Medicine, Miami, FL (L.B.O.); Division of Gerontology and Geriatric Medicine, St. Louis University Department of Medicine, St Louis, MO (M.A.P.); University of Miami Miller School of Medicine, Miami VA Geriatric Research Education and Clinical Center, Miami, FL (R.M.K.).

Address correspondence to Lauren Ozbolt, MD, University of Miami, Miller School of Medicine, Psychiatric Residency Training, Jackson Memorial Hospital, 1695 NW 9th Ave #2101, Miami, FL 33136. E-mail: lauren.ozbolt@gmail.com

DOI: 10.1016/j.jamda.2007.08.007

Table 1. *DSM-IV Criteria for Delirium*

- Disturbed consciousness with reduced ability to focus, sustain or shift attention
- Cognitive change such as memory deficit, disorientation or language disturbance, that is not better accounted for by dementia
- Perceptual disturbance (ie, hallucinations or visual illusions) not better accounted for by dementia
- Rapid onset (hours to days) and fluctuating daily course
- Evidence of a causal medical condition/substance intoxication/withdrawal

Adapted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. 1994.

tionship between delirium and decreased acetylcholine activity in the brain. In fact, many medications with anticholinergic side effects can worsen or induce delirium. The reticular formation in the brain stem is the principal area regulating attention and arousal. A decrease in acetylcholine in the reticular formation, specifically the dorsal tegmental pathway, appears to be strongly linked with delirium.[2] Researchers have also suggested another pathophysiological mechanism for delirium. Delirium occurring with alcohol withdrawal appears to be associated with hyperactivity of the locus ceruleus and its noradrenergic neurons. Dopaminergic excess and alterations in serotonin and glutamate have also been linked to the clinical manifestations of delirium. Cytokines such as interleukin-1, -2, and -6; interferon; and tumor necrosis factor alpha may also contribute to delirium by increasing the permeability of the blood-brain barrier and altering neurotransmission.[5] Chronic stress has been associated with the development of delirium, by activating the sympathetic nervous system and hypothalamic-pituitary-adrenocortical axis, which in turn increases cytokine and cortisol levels. Chronic hypercortisolism has harmful effects on the hippocampal serotonin 5-HT 1A receptors, which has been postulated to contribute to the symptoms of delirium.[5]

Delirium is a common condition seen in hospitalized patients. Approximately 10% to 15% of patients on general surgical wards and 15% to 25% of patients on general medical wards experience delirium at some time during their hospital stay.[2] The rate of delirium in the medically ill geriatric patient is thought to be much higher, because delirium is often exacerbated by sensory deficits and social isolation.[6] Mittal et al[7] reported that 14% to 24% of older patients at hospital admission and 6% to 56% of older patients during hospitalization experience delirium. Han and Kim[8] found a similar prevalence of delirium in the elderly hospitalized patient, with rates ranging from 10% to 40%. Further studies now report that 15% to 53% of older postoperative patients and 70% to 87% of elderly intensive care patients experience an episode of delirium while hospitalized.[5] Delirium in the elderly patient is associated with increased mortality, longer hospital stays, and increased risk of institutional placement. Inouye[5] reported that $6.9 billion (value of US dollars in 2004) of Medicare hospital expenditures were attributed to the treatment of delirium. A longer duration of symptoms results in a poorer functional outcome for the patient.[7] The identification and treatment of delirium in the geriatric patient is not only important because it is highly prevalent, but also because of the increase in morbidity and mortality. Recent studies indicate that mortality rates among hospitalized patients with delirium range from 22% to 76%. The severity of this problem becomes plainly evident when noting that mortality rates for patients with delirium are equivalent to mortality rates of patients with acute myocardial infarction or sepsis.[5]

Delirium is also a problem in patients presenting from long-term care facilities. Levkoff el al[9] found that 24% of elderly patients from the community and 64% of those presenting from nursing homes were delirious upon hospital admission. Delirium may persist much longer than previously believed. Recent studies suggest that symptoms of delirium can last months to years, thereby blurring the boundaries between delirium and dementia.[5] Levkoff and coworkers[10] reported that fewer than 20% of delirious patients had achieved full resolution of symptoms 6 months after hospital discharge. Jackson[11] also identified persistent cognitive impairment in nearly 1 in 3 patients with delirium at 6 months following hospitalization. The diagnosis of persistent delirium in patients being discharged from the hospital to home or to long-term care facilities is important in improving patient outcomes. A 2005 study by Rathier and McElhaney[12] found that patients who are diagnosed with delirium on admission to rehabilitation hospitals and skilled nursing facilities had a fivefold increase in 6-month mortality.

Delirium is usually diagnosed at the bedside and is easy to detect when symptoms are acute and florid. Cognitive impairment is typically demonstrated through administration of the Mini-Mental Status Examination or the Delirium Rating Scale (DRS).[13] A thorough history and physical should be conducted to look for the underlying etiology of the delirium. The patient's environment should be altered in a way that decreases sensory input and increases orientation. Standard laboratory testing such as blood chemistries, complete blood

Table 2. *Risk Factors for Delirium*

- Advanced age
- Cardiopulmonary disorders (myocardial infarction, hypotension, hypoxia)
- Central nervous system disease
- Electrolyte abnormalities (hypernatremia)
- Gastrointestinal or genitourinary disorders (ulcer, bleeding, constipation, urinary retention)
- Hypoalbuminemia
- Infections (urinary tract, lung, human immunodeficiency virus)
- Polypharmacy (anticholinergics, opioids, sedative hypnotics, withdrawal, intoxication)
- Sensory deprivation, overstimulation, environmental changes
- Trauma (falls, fractures, pain)
- Multiple medical morbities
- Pre-existing cognitive decline (dementia)

Adapted from: Katz et al 2002.

count, thyroid function test, serological test for syphilis, HIV antibody testing, urinalysis, electrocardiogram, chest x-ray, and blood/urine drug screens should be ordered to assist in determining the etiology. An electroencephalography (EEG) may also be helpful if the diagnosis is unclear. In delirium, the EEG will typically show a generalized slowing of activity. It may also reveal focal areas of hyperactivity but this latter finding is nonspecific and variable.[2]

Delirium is a multifactorial disorder and represents one of the most common preventable conditions among older persons during hospitalization.[5] Delirium is common among the hospitalized elderly, is frequently iatrogenic, and is closely linked to the process of care. Because of the incidence of delirium, it has been proposed that mental status be included as the sixth vital sign in large health care systems such as the Veterans Health Administration. Flaherty el al[14] proposed that fostering the frequent and consistent documentation of mental status (particularly attention and alertness) may lead to the early identification of serious medical conditions and the prevention of delirium.

Since the elderly patient is at an increased risk for delirium, preventive measures are now used for primary prevention. Several interventions have proven to significantly reduce the risk of delirium in the older hospitalized patient. Elderly patients should be provided with an optimum level of sensory stimulation. Sleep deprivation, dehydration, and immobilization should be avoided. Hearing aids and eyeglasses should be used to reduce sensory deprivation and improve orientation. Physical restraints and unnecessary medications should not be used and pain should be adequately assessed and addressed. As illustrated by Table 3, many risk factors for delirium can be targeted using specific interventions that focus on the source of the delirium.[9,42]

The primary treatment of delirium requires identifying and treating the underlying etiology. Pharmacological management with typical and atypical antipsychotic agents should be reserved for patients with severe agitation in which the symptoms of delirium would threaten their own safety, the safety of others, or would interrupt essential medical therapy. The criteria for use of antipsychotic medications include the management of behavioral disturbances and the treatment of overt psychotic symptoms (ie, hallucinations and delusions).[10]

Haloperidol is the agent most often used to treat the psychotic symptoms of delirium because of its infrequent anticholinergic side effects and few active metabolites and sedating effects.[13] Haloperidol has the advantage of being available in oral, intramuscular, and intravenous formulations. It is used in the treatment of 67% of delirium patients and is the first-line drug for delirium in 97% of medical institutions.[15] Despite its universal acceptance, a systematic review conducted by Lacasse et al[16] found no rigorous scientific data to support the use of haloperidol for the treatment of delirium. According to the study, clinical experience, theoretical benefit, and extrapolation from other patient populations have led to the widely accepted practice of ordering haloperidol as a first-line medication, despite no clearly defined clinical benefit.[16] Haloperidol does have significant disadvantages, including an increased incidence of cardiac arrhythmias and an increased risk of extrapyramidal side effects. Patients receiving haloperidol must be monitored for EKG (electrocardiogram) changes such as prolongation of the QT interval, which can cause fatal heart arrhythmias such as torsades de pointes and ventricular fibrillation. Extrapyramidal side effects such as parkinsonism, neuroleptic malignant syndrome, dystonia, akathisia, and tardive dyskinesia are other risks of haloperidol. Since the development of the atypical antipsychotics in the 1990s, many psychiatric conditions that were previously treatable only with high-potency antipsychotics can now be managed with less risky alternatives.

Atypical antipsychotics have similar rates of efficacy and a lower risk of extrapyramidal side effects. The current literature on atypical antipsychotics for the treatment of delirium is lacking in randomized, controlled trials. The few studies available may be confounded by the active treatment of the underlying cause of the delirium; resolution of symptoms may be attributable to the medical treatment, rather than the administration of antipsychotics. This article will review the current literature, summarize the results from published trials, and evaluate the efficacy and potential benefit of atypical antipsychotics for the treatment of delirium in the elderly population.

METHODS

The articles used for this review were obtained by performing MEDLINE and PubMed searches using the following keywords: "atypical antipsychotics," "delirium," "elderly," "risperidone," "olanzapine," and "quetiapine." After an initial

Table 3. *Risk Factors for Delirium*

Risk Factor	Intervention Protocol
Cognitive impairment	• Reorientation techniques (verbal reassurance, introduction to team members, patient schedules) • Early mobilization, minimize restraints, equipments • Environmental cues (visible clocks and calendars)
Psychoactive medications	• Restrict PRN sleep and psychoactives, non-drug protocols for sleep and anxiety
Sleep impairment	• Noise reduction, scheduling HS meds, nursing, procedures
Vision impairment	• Provide visual aids
Hearing impairment	• Amplifying devices, staff instruction on communication
Dehydration	• Maintenance of hydration

Adapted from: Inouye SK et al 1999.

search, additional articles pertaining to the topic were obtained using the bibliographies acquired in the initial search. Articles were selected from a database from the period of 1997 to 2005. The initial literature search was conducted in March 2006 and a follow-up investigation using the same key words was conducted in April 2006 and July 2007.

RESULTS

What is the effectiveness of risperidone, olanzapine, and quetiapine for the treatment of delirious elders as compared to haloperidol?

Risperidone

Risperidone Case Reports

The use of risperidone in the treatment of delirium has been sparsely studied, with only 6 case reports published to date (Table 4). Of these 6 reports, 3 demonstrate the effectiveness of risperidone in the treatment of delirium, while 3 suggested that risperidone might induce delirium in elderly adults.

In 1997, Sipahimalani and Masand[17] published 2 case reports that showed risperidone was successfully used to treat delirium. One case report described a 60-year-old man who suffered cardiac arrest after admission to the hospital for sepsis and pneumonia. He was diagnosed with delirium several weeks later, after sustaining a hypoxic brain injury and developing hyponatremia. The patient was treated with risperidone 0.5 mg by mouth twice a day and showed improvement by day 3. Risperidone was then increased to 1 mg in the morning and 2 mg at bedtime. The patient gradually improved but began to develop some extrapyramidal side effects. The risperidone was decreased to 1 mg twice a day and the delirium cleared by day 14. The risperidone was discontinued and the patient was discharged from the hospital 4 days later.[17]

In 2005, Bourgeois and Hilty published a case report of a 57-year-old man with multifactorial delirium, caused in part by alcohol withdrawal, who presented after sustaining multiple traumatic injuries. He later developed medical complications including muscular rigidity and pneumonia. After replacing haloperidol with risperidone, and tapering the benzodiazepine, the patient's cognition normalized and his rigidity resolved. The author suggested that atypical antipsychotics should be used to treat delirium, particularly since side effects are seen with typical agents.[18]

Risperidone Clinical Trials

Seven reviews have been published on the effectiveness of risperidone for the treatment of delirium in the elderly (Table 5). Two prospective studies found that risperidone was a safe and effective alternative to haloperidol and 1 study found no difference between haloperidol and risperidone. All 3 of these studies, however, involved a small sample size and enrolled fewer than 28 patients. These prospective studies were conducted as open-label trials and occurred without randomization or control groups. Four retrospective studies were conducted to examine the effectiveness of risperidone. All 4 of these studies found risperidone to be a safe and effective alternative to haloperidol for elderly patients with delirium or other associated psychiatric conditions.

In 2003, Horikawa et al[20] published a prospective open trial in which risperidone was used to treat 10 patients with delirium. The patients were medical or surgical inpatients who met the DSM-IV criteria for delirium at the Tokyo Women's Medical University between the dates of July and December 2001. The average age of patients in the study was 56.8 years. Horikawa et al[20] found that risperidone was effective in 80% of patients at an average dose of 1.7 mg/day (SD = 0.9, range 0.5–3.0). One patient in the study responded to a dose of 0.5 mg a day. They concluded that risperidone can be useful and effective in the treatment of delirium and has a rapid onset of action. They recommended that risperidone be started at a low dose (ie, 0.5 mg daily) and be increased slowly and gradually.[20]

In 2004, Han and Kim[8] conducted a randomized, double-blind comparative study of haloperidol and risperidone for the treatment of delirium. Twenty-eight patients from medical, intensive care unit (ICU), and oncology wards who met the criteria for diagnosis of delirium were randomly assigned to

Table 4. *Risperidone Case Reports*

Case #	Author	Year	Patient Age	Medical Diagnosis	Dose	Result
1	Sipahimalani and Masand	1997	60	Delirium secondary to hypoxic brain injury and hyponatremia	1 mg BID	Resolution of delirium
2	Sipahimalani and Masand	1997	14	Delirium secondary to hypoxic brain injury	1 mg/day	Resolution of delirium
3	Bourgeois and Hilty	2005	57	Multifactorial delirium, alcohol withdrawal	8 mg/day, tapered to 1 mg/day	Resolution of delirium
4	Ravona-Springer et al	1998	83	Major depression with psychotic features	1.5 mg/day	Induced delirium
5	Ravona-Springer et al	1998	71	Major depression with psychotic features	1 mg/day	Induced delirium
6	Ravona-Springer et al	1998	83	Major depression with psychotic features	1 mg/day	Induced delirium

Table 5. *Risperidone Clinical Trials—Summary of Reviews*

Study Type	Author	Year	# Patients in Study	Population	Mean Age (yrs)	Mean Dose (mg/day)	Result
Prospective							
1)	Horikawa et al	2003	10	Tokyo Women's Medical University	56.8	1.7	80% effective
2)	Han and Kim	2004	28	Korean University Medical Center ICU/Oncology	65.6/66.5	1.02	No observed difference between risperidone and haloperidol; both
3)	Mittal et al	2004	10	University of Mississippi Medical Center and Dept. of Veterans Affairs Hospital (Jackson, MS)	64.7	0.75	Effective in all patients
Retrospective							
1)	Zarate et al	1997	122	Hospitalized psychogeriatric patients	65+	1.6 ± 1.1	85% effective
2)	Schwartz and Masand	2002	NA	NA—collective review and summary of 3 prior studies	Varies	Varies	General effectiveness noted
3)	Gupta et al	2005	7	NA—demographics not provided	32	1.14	Effective in all patients
4)	Shingo et al	2007	266	Japanese inpatients at Kitasato University Hospital	72.5	1.0	Effective

receive a flexible dose regimen of haloperidol or risperidone. The mean dose of haloperidol was 1.71 mg a day and the mean dose of risperidone was 1.02 mg a day. The study found no significant difference in the DRS score or the mean Memorial Delirium Assessment Scale (MDAS) score between the 2 groups. The average period before response was 4.22 days in the haloperidol group and 4.17 days in the risperidone group; the difference was not statistically significant. The study ultimately found no significant difference in the efficacy or response rate between haloperidol and risperidone in the treatment of delirium.

Mittal et al[7] conducted a prospective open-label trial of risperidone in the treatment of delirium. The study enrolled 10 patients aged 18 to 90 years (mean age 64.7 years) who (1) had delirium according to the Confusion Assessment Method (CAM), (2) met DSM-IV criteria, and (3) had a score of 13 or higher on the DRS. After enrollment, the patients were treated with risperidone at a starting dosage of 0.5 mg twice daily, with medication adjustments made until the patients' DRS score decreased to 12 or under. The patients were treated for a total of 6 days. The trial demonstrated that the treatment of hospitalized patients with low-dose risperidone for 6 days is associated with a decrease in symptoms of delirium and an improvement in patient functioning. Risperidone was found to be safe in this population, with no evidence of newly emergent movement disorders. The study supported the use of atypical antipsychotics as an effective alternative to conventional antipsychotics in patients with delirium.

In 1997, Zarate et al[21] conducted a retrospective chart review of 122 hospitalized psychogeriatric patients age 65 years and older and who were newly treated with risperidone. Fifty-three percent of the patients in the study were started on risperidone for agitation or psychosis associated with dementia. Delirium was not specifically addressed. Eighteen percent of the participants were treated with risperidone for "other disorders." The charts were reviewed for indications, doses, and effects of the medication. The study found that risperidone appeared to be effective for 85% of individuals. The average daily dose was 1.6 ± 1.1 mg. The authors concluded that risperidone appeared to be effective and safe for many elderly psychiatric patients with comorbid medical conditions, provided that the initial dose was low and subsequently increased gradually.

Schwartz and Masand[13] published a review article in June of 2002, which summarized several trials involving atypical antipsychotics for the treatment of delirium. From the results of their literature review, they recommended starting risperidone as a first-line drug for the treatment of delirium if the patient could take the medication orally. The authors recommended that risperidone be started at a dose of 0.25 to 0.5 mg twice daily and increased to a maximum dose of 4 mg a day if symptoms of delirium persisted.

Gupta et al[22] published a small, open-label, retrospective case series in 2005 that demonstrated that risperidone in low doses is effective and safe for treating delirium. The study included 7 patients with an average age of 32 years. The patients had a mean duration of delirium for 5.29 days before treatment was begun. The average starting dose of risperidone was 1.14 mg daily, with the average dose during the treatment period averaging 1.07 mg daily. No patient developed significant side effects. The effectiveness of risperidone at low doses, and a lack of extrapyramidal side effects, led the authors to conclude that risperidone had certain advantages over haloperidol for the treatment of delirium.

Table 6. *Olanzapine Case Reports*

Case #	Author	Year	Medical Diagnosis	Dose	Result
1)	Passik and Cooper	1999	Leukemia and pain of unknown origin	10 mg/day	Resolution of delirium
2)	Lim et al	2006	Dementia of mixed etiology	5 mg/day	Induced delerium

Shingo et al[15] published a retrospective study of 266 Japanese delirium inpatients in 2007 in which risperidone was compared to oral haloperidol and intravenous and intramuscular haloperidol. The study included 266 patients with an average age of 72.5 years (range 65–78) and compared the risk of adverse events in delirium patients treated with risperidone versus haloperidol. The study found no statistically significant difference in the duration of hospitalization or delirium between the 3 groups. The incidence of adverse events was 6.5% for risperidone, 31.4% for oral haloperidol, and 32.8% for haloperidol injection. The incidence of death during delirium was 3.2% for risperidone, 2.1% for oral haloperidol, and 13.1% for haloperidol injection. The incidence of adverse events was lowest for risperidone, and the incidence of death during delirium was highest for intravenous/intramuscular haloperidol. The study had several limitations. The concomitant use of other antipsychotic drugs and benzodiazepines was permitted and may have biased the results. The severity of the underlying delirium as well as the underlying disease was not sufficiently characterized. The study also defined "adverse events" as any potential side effect listed in the medication package insert. Many such listed side effects (including excessive sedation and sleep disorders) may also be symptoms of the underlying disease itself and not necessarily drug induced.

Olanzapine

Olanzapine Case Study

A case of delirium in a woman with leukemia and pain of unknown origin was reported by Passik and Cooper (Table 6).[13] Extrapyramidal symptoms later developed when her opioid analgesic medication was increased. Haloperidol and changes in the pain medication regimen did not affect the delirium. Olanzapine was started at an unspecified dose and slowly titrated to 10 mg at bedtime and 2 mg as needed during the day. The delirium abated after 3 days and the patient was discharged from the hospital. The authors suggest that the combination of haloperidol and olanzapine may have led to the resolution of symptoms.[13]

In another case report, a 74-year-old white male with a diagnosis of dementia of mixed etiology was admitted to a teaching hospital for increasing agitation and worsening dementia. Olanzapine 2.5 mg was started and titrated up to 5 mg at bedtime. The patient developed delirium on hospital day 4. Discontinuation of the olanzapine resulted in resolution of the delirium.[23] The author postulated that the central anticholinergic properties of olanzapine might be related to the development of delirium.

Olanzapine Clinical Trials

Four trials have been published on the use of olanzapine for the treatment of delirium in the elderly patient (Table 7). All 4 studies had serious methodological problems. Control groups were not used and participants were not blinded. Two of the studies had sample sizes of 20 patients or less. The only prospective randomized trial comparing haloperidol with olanzapine was conducted by Skrobik et al[24] and included ICU patients aged 18 to 75 years (average age 65 years). This study used a method of randomization that produced an

Table 7. *Olanzapine Clinical Trials—Summary of Reviews*

Study Type	Author	Year	# Patients in Study	Population	Mean Age (yrs)	Dose (mg/day)	Result
Prospective							
1)	Sipahimalani and Masand	1998	22	NA	NA	8.2 ± 3.4	5 of 11 in olanzapine group showed significant improvement in DRS score (compared to 6/11 in haloperidol group)
2)	Kim et al	2001	20	Korean (unspecified)	45.8	5.9 ± 1.5	70% significant improvement in DRS scores
3)	Breitbart et al	2000	79	Hospitalized cancer patients	60.6	3-6.3	76 of 79 patients had complete resolution of delirium
4)	Skrobik et al	2001	73	Medical and surgical ICU, Montreal, Canada	63/67	2.5	Both groups (olanzapine and haloperidol) exhibited significant improvement

Table 8. *Quetiapine Clinical Trials—Summary of Reviews*

Study Type	Author	Year	# Patients in Study	Mean Age (yrs)	Mean Dose (mg/day)	Result
Prospective						
1)	Kim et al	2003	12	74	93.75 ± 23.31	100% exhibited significant improvement on NMSE, DRS, CDT, CGI-S tests
2)	Sasaki et al	2003	12	67.3	44.9 ± 31	100% remission of delirium
Retrospective						
1)	Schwartz and Masand	2002	22	Unknown—age range 19-91	211.4	10/11 patients showed significant improvement on DRS score

uneven distribution between the 2 comparison groups, with more patients randomized to the haloperidol group. Another study examined 79 cancer patients aged 19 to 89 years (average age 60.6 years) and showed a poor response to olanzapine in patients older than 70.[25] A study of olanzapine in 20 Korean patients ages 19 to 74 (average age 46) found that olanzapine administered at lower doses than in comparable studies (mean dosage of 5.9 mg/day versus 8.2 mg/day) was effective for the treatment of delirium.[26]

In 1998 Sipahimalani and Masand[27] first performed a small, open controlled study of olanzapine. Eleven elderly patients diagnosed with delirium received a mean dose of 8.2 ± 3.4 mg of olanzapine daily. The olanzapine group was compared with a cohort group of 11 patients with delirium who had received 5.1 ± 3.5 mg of haloperidol. The study showed that 5 of the 11 patients treated with olanzapine showed significant improvement on the scores of DRS, with no observable side effects. This was in contrast with 6 of the 11 haloperidol-treated subjects, who showed improvement on the scores of DRS, but 45% of these patients had significant extrapyramidal side effects or excessive sedation. The study concluded that olanzapine may be a useful alternative to haloperidol for the treatment of delirium in hospitalized patients.

Kim et al[26] performed an open trial of olanzapine in 20 Korean subjects (average age 45.8 ± 18.3 years) with delirium. The patients were given olanzapine with doses of 5.9 ± 1.5 mg a day. The average duration of treatment was 8.8 ± 2.2 days. Delirium was measured using the DRS. Fourteen of the 20 patients (70%) showed significant improvement (>50% score reduction) of DRS scores. The study concluded that olanzapine is effective in reducing behavioral disturbances and symptoms in delirium. Eleven of the 20 delirious patients in this study also had leukemia, which may have affected the results (all 11 leukemia patients showed 50% or more reduction in DRS scores).

In 2000, Breitbart et al[25] conducted an open, prospective trial of olanzapine for the treatment of delirium in 79 hospitalized cancer patients. The mean age of patients was 60.6 years and all met the criteria for delirium based on the DSM-IV and Memorial Delirium Assessment Scale. The mean starting dose of olanzapine was 3.0 mg a day and, at the end of the study, the mean dosage had increased to 6.3 mg daily. Seventy-six patients had complete resolution of their delirium on olanzapine therapy, and no patients experienced extrapyramidal side effects. The study also found that patients older than 70 had a poorer response to olanzapine treatment. The study concluded that olanzapine appears to be clinically effective and safe for the treatment of delirium in the medically ill hospitalized patient.

Skrobik et al[24] conducted a prospective, randomized trial of 73 patients between the ages of 18 and 75 years who were admitted to the medical and surgical ICU in Montreal, Canada, from June 2000 to September 2001. All patients enrolled in the study had the diagnosis of delirium using the DSM-IV criteria. Patients were randomized to receive either enteral olanzapine or haloperidol. Haloperidol was initiated at a dose of 2.5 to 5.0 mg every 8 hours and olanzapine was started at 5.0 mg daily. Patients older than 60 received haloperidol 0.5 to 1.0 mg or olanzapine 2.5 mg. Patients' delirium severity and benzodiazepine use were monitored over a 5-day period. The Delirium Index was noted to decrease significantly in both groups, as did the administration of benzodiazepines. Clinical improvement was similar in both groups. The olanzapine group reported no side effects, but 6 patients in the group receiving haloperidol exhibited extrapyramidal side effects. The study concluded that olanzapine was a safe alternative to haloperidol in the critically ill, delirious patient.

Quetiapine

Quetiapine Clinical Trials

Three trials have been published regarding the use of quetiapine for the treatment of delirium in the elderly patient (Table 8). All 3 studies involved a small sample size of 22 patients or less. In addition, 2 of the 3 were prospective studies conducted as open trials without randomization or a control group. The patients examined were typically older, with nearly all patients in the age range of 52.5 to 82.1 years.

Kim et al[28] conducted a study in which 12 patients (ages 64 to 88 years) who were diagnosed with delirium received quetiapine at a mean dose of 93.75 mg ± 23.31 mg daily. None of the 12 patients developed side effects and all patients experienced significant improvement in symptoms as manifested by Mini-Mental State Examination (MMSE), DRS, Clock Drawing Test (CDT), and Clinical Global Impression-Severity (CGI-S). The study concluded that quetiapine was a

safe and effective treatment in older hospitalized patients with delirium.

Saski et al[29] conducted an open-label, flexible-dose study of 12 patients using quetiapine. The participants had a mean age of 67.3 ± 14.8 years and all carried the DSM-IV diagnosis of delirium. The mean dose of quetiapine was 44.9 ± 31.0 mg daily. All patients in the study showed remission from delirium in 4.8 ± 3.5 days. The quetiapine treatment was well tolerated and no extrapyramidal side effects (EPS) were noted. The researchers concluded that quetiapine may be a useful alternative to conventional neuroleptics in the treatment of delirium.

In a retrospective study conducted by Schwartz and Masand,[13] 11 delirious patients (age 19 to 91 years) received quetiapine at a mean dose of 211.4 mg a day. This group was compared to a cohort of 11 delirious patients who received haloperidol at a dosage of 3.4 mg daily. Ten of the 11 patients in each group showed improvement in delirium, as measured by improvement in DRS scores and a reduction in global delirium symptoms. Treatment was discontinued in 2 patients on haloperidol, who developed parkinsonism, and in 1 patient taking quetiapine who experienced sedation. The study suggested that quetiapine may be a suitable alternative to haloperidol in the treatment of delirium.[13]

What are the frequency and type of adverse reactions and side effects of risperidone, olanzapine, and quetiapine as compared to haloperidol?

Risperidone

In the 6 case studies and 7 trials of risperidone, a low incidence of EPS was noted. One case study reported the presence of extrapyramidal side effects with higher doses of risperidone (3 mg or more daily). A prospective trial of 10 patients aged 22 to 81 years detected the presence of mild parkinsonism in 1 patient who was administered risperidone. A retrospective study involving 122 psychogeriatric patients demonstrated a 32% incidence of adverse effects in the elderly population. This included an 11% incidence of EPS and a 29% incidence of hypotension. However, this study did not specify whether risperidone was being used to treat delirium or to treat other psychiatric disorders; 76.2% of the patients were receiving another psychotropic agent. Three case reports have been published describing the presence of risperidone-induced delirium in elderly patients suffering from major depression with psychotic features.

In the case study of a 60-year-old male with delirium, Sipahimalani and Masand[17] reported that risperidone at a dose of 3 mg daily produced EPS such as upper extremity weakness and cogwheeling. The EPS resolved when the risperidone was reduced to 2 mg daily.

Ravona-Springer et al[19] reported on 3 cases in which elderly patients who carried the DSM-IV diagnosis of depression with psychotic features were treated with risperidone to control psychotic symptoms. In all 3 cases, risperidone was initiated at a dose of between 1 and 2 mg daily. Ravona-Springer and colleagues[19] noted that delirium began shortly after the administration of risperidone. The case study concluded that risperidone might increase the risk of delirium in elderly patients, in particular those receiving other medications or having other disorders affecting the central nervous system.

Horikawa et al[20] noted that sedation and parkinsonism occurred in some patients in a prospective, open trial of 10 patients with delirium treated with risperidone. Thirty percent of participants reported sedation and 10% reported drug-induced parkinsonism.

In Han and Kim's[8] double blind trial of risperidone and haloperidol, no adverse reactions were seen in the risperidone group. One patient in the haloperidol group experienced mild akathisia but was able to tolerate the medication throughout the treatment.

In Zarate et al's[21] retrospective study of 122 hospitalized psychogeriatric patients treated with risperidone for delirium, adverse effects occurred in 32% of the patients. The adverse effects noted were hypotension (29%), symptomatic orthostasis (10%), cardiac arrest (1.6%), extrapyramidal side effects (11%), and delirium (1.6%). These adverse effects were most closely associated with cardiovascular disease and its treatment, selective serotonin reuptake inhibitor (SSRI) antidepressants, valproate, and relatively rapid dose increment adjustments. The study concluded that risperidone appears to be effective and safe in treating delirium in the elderly, but caution was advised in patients being treated with other psychotropic agents or those with cardiovascular disease.

Olanzapine

At dosages used to treat delirium, olanzapine did not cause extrapyramidal side effects in the elderly population. The main side effect reported was sedation in 10% to 30% of patients. One case report found that olanzapine induced delirium in an elderly man with preexisting dementia. Other minor side effects were noted, but with a frequency of less than 5%.

In an open trial of olanzapine for the treatment of delirium in hospitalized cancer patients, conducted by Breitbart et al,[25] all 79 patients studied had no extrapyramidal side effects. Thirty percent of participants experienced sedation. One patient in the olanzapine group appeared to experience a worsening of delirium. An additional 4 patients experienced a variety of other side effects including rash, pruritus, nausea, stomachache, dizziness, light-headedness, blurring of vision, and headache. In a prospective, randomized trial of olanzapine verses haloperidol, the group receiving olanzapine reported no extrapyramidal side effects. Only 6 of the 45 patients randomized to the haloperidol group, however, reported low scores on extrapyramidal symptom testing.[24]

Quetiapine

In the 3 trials examining the effectiveness of quetiapine, no trial reported extrapyramidal side effects. One study reported that 10% of patients experienced sedation but this effect was otherwise well tolerated. Vivid dreams were also reported in 1 patient.

Results from Kim et al[27] and Saski et al[29] reported no EPS

associated with the use of quetiapine for the treatment of delirium in the elderly.

DISCUSSION

Mechanism of Action of Antipsychotic Medication

As described by Neil et al,[30] the brain has 3 primary dopaminergic tracts: the mesolimbic tract, the nigrostriatal tract, and the tuberoinfundibular tract. The mesolimbic tract encompasses the ventral tegmental area to the amygdala, pyriform cortex, lateral septal nuclei, nucleus accumbens, frontal cortex, and septohippocampal regions. The nigrostriatal tract includes the substantia nigra to the caudate nucleus and putamen. The tuberoinfundibular tract encompasses the arcuate nuclueus to the median eminence. Antagonism of dopamine at all these sites gives rise to the neuroleptic's antipsychotic effects, extrapyramidal side effects, and endocrine effects.

All medications designated as "antipsychotics" have clinically relevant antagonism for the D2 receptor (most with a mixture of D1 and D2). This affinity combined with varying degrees of nondopaminergic involvement (adrenergic, serotoninergic, histamine, and muscarinic) is what gives the antipsychotic medications their distinct pharmacologic profile. The atypical antipsychotics also display antagonism at the D3 and D4 receptors. Although not well understood, it may be the unique antagonism at these additional receptors that accounts for the low rates of EPS seen with atypical antipsychotics.[30] Haloperidol, a butyrophenone, has a high affinity for the D2 receptors and thus is associated with a high prevalence of EPS.

Pharmacologic Profile of Risperidone

Risperidone, a benzisoxazole, is a potent antagonist of the 5-HT receptor as well as the D2, D3, and D4 receptors. This drug has a high affinity for the alpha-1 receptors and H-1 histamine receptors, which accounts for its side effects of orthostatic hypotension, sedation, fatigue, and palpations.[31] Risperidone has relatively low affinity at the D1, B1, B2, and muscarinic receptors, which accounts for its low incidence of anticholinergic side effects.[30]

Pharmacologic Profile of Olanzapine

Olanzapine is an antipsychotic medication that belongs to the thienobenzodiazepine class. The drug has a strong affinity for the 5-HT 2a /2c, D2, D3, D4, H1, alpha-1 adrenergic, and muscarinic receptors, which give it unique properties.[32] Sedation is common with use of the medication because of its effect on the H1 receptors. The weak affinity at alpha-1 receptors may explain the presence of orthostatic hypotension in some patients. Despite its strong affinity for the muscarinic receptors M1-M5, few anticholinergic side effects have been reported in clinical practice.

Pharmacologic Profile of Quetiapine

Quetiapine is a dibenzothiazepine derivative that has a unique and novel pharmacologic profile. This medication has a higher affinity for the serotonin 5-HT 2A receptor than for the dopamine D2 receptors and also displays only transient D2 receptor occupancy. Quetiapine also demonstrates a high affinity for histamine H1 receptors and alpha-1 adrenergic receptors, which explains its side-effect profile of sedation and orthostatic hypotension. Upon chronic administration of quetiapine, the drug begins to demonstrate selectivity for the limbic system by producing a depolarization block of the A10 mesolimbic dopamine-containing neurons.[29] Since hyperactivity of the dopaminergic neurons in the limbic system is believed to be one of the pathophysiologies of delirium, quetiapine might work in the treatment of delirium by specifically blocking the mesolimbic D2 receptors.[29] Additionally, because of the sedative effect that quetiapine has through its affinity with H1 receptors, this drug is preferable to benzodiazepine hypnotics for the treatment of delirium.

Safety of Atypical Antipsychotics

Risperidone, like typical antipsychotic medications, can produce extrapyramidal side effects, dizziness, hyperactivity, sedation, and nausea. In the first week or two of treatment, risperidone can produce orthostatic hypotension. Caution is advised when risperidone is used in the presence of cardiovascular disease. Long-term use of risperidone may produce elevated glucose levels and increase patients' risk of diabetes.[32]

Olanzapine is an atypical antipsychotic that can produce extrapyramidal side effects and anticholinergic effects. It has been associated with orthostatic hypotension, especially upon initiation of the medication. Olanzapine can also cause weight gain and elevate lipid and glucose levels. Because of its dopamine blocking ability, olanzapine can increase prolactin levels and cause galactorrhea and menstrual irregularities in women.[32]

Quetiapine is an atypical antipsychotic medication frequently associated with orthostatic hypotension, especially during the first 3 to 5 days of its use. It is commonly associated with sedation and fatigue occurring as frequently as in 1 in 5 patients. Quetiapine can also cause seizures and hypothyroidism. Like other high-potency neuroleptics, quetiapine can produce extrapyramidal side effects, especially neuroleptic malignant syndrome and tardive dyskinesia. Quetiapine, like olanzapine, can elevate glucose and lipid levels and produce metabolic syndrome.[32]

There has been much debate in the literature regarding the cardiovascular mortality associated with atypical antipsychotics and their use in the acutely ill individual with cardiovascular disease. Some studies postulate that atypical antipsychotic medications can produce a one- to eightfold increase in the incidence of cardiovascular disease and death. It has long been known that atypical agents can contribute to metabolic syndrome, which is associated with higher morbidity and mortality from cardiovascular disorders. New studies show that atypical antipsychotics may independently increase the risk of stroke in elderly individuals with dementia.[33]

In a Public Health Advisory issued in April of 2005, the Food and Drug Administration (FDA) warned that the use of atypical antipsychotic medications may increase mortality among elderly patients with dementia.[34] This advisory was

issued on the basis of data from 4 randomized controlled trials that found that more risperidone-treated patients experienced strokes and transient ischemic attacks than did placebo-treated patients.[35] A "black box" warning was added to the labels of all such agents warning that they were not approved for use in the elderly patient with dementia. Since this warning was issued, however, several studies have been published that dispute this claim.

In a study published in 2001, Glassman and Bigger[36] found no association of olanzapine, quetiapine, or risperidone with cases of torsades de pointes and sudden death. In 2004, Herrmann et al[35] conducted a retrospective study of 11,400 antipsychotic-naïve subjects who began a regimen of typical antipsychotics, risperidone, or olanzapine. The study concluded that olanzapine and risperidone use was not associated with a statistically significant increased risk of stroke compared with typical antipsychotic use. Gill et al[37] published a similar retrospective study in the *British Medical Journal* in 2005 demonstrating that participants receiving atypical antipsychotics showed no significant increase in risk of ischemic stroke compared with typical antipsychotics. Similarly, Layton et al[38] found no statistical difference between risperidone and quetiapine in the relative rates of cerebral vascular accident/transient ischemic attack (CVA/TIA) after adjustment for age, sex, and indication.

Limitations of the Study

While most of the studies reviewed indicate that the atypical antipsychotics were just as effective and safe as the typical antipsychotics, these studies have several limitations. The first and greatest limitation is the general lack of randomized controlled trials in this area of research. Since confounding variables and biases cannot be adequately controlled in less rigorously conducted prospective studies, only limited conclusions can be drawn from the evidence available. The second limitation is the small number of patients studied in the open-label trials, which have insufficient statistical power. The relatively small number of patients limits the ability to generalize the results. The possibility of a type II error also cannot be excluded. The third limitation is the heterogeneity of the patient population studied. Most of the trials enrolled patients with wide age ranges and did not control for pharmacokinetic differences between races. This may have biased the results of the trials, since the pharmacokinetics of psychotropic agents have been shown to vary according to race. For example, the pharmacokinetics in the Asian and non-Asian populations has been well studied and differences are known to exist in drug metabolism.[8] Another limitation of the studies is the lack of quantification of drug side effects. Most of the trials conducted on delirious patients do not use a formal objective rating scale to quantify side effects. Patient self-reporting was most often the vehicle used to assess side effects, and self-reporting is a less effective measure in delirious patients than it may be in other patient populations.

Another problem with the studies is associated with measuring the effectiveness of antipsychotic medication. In practice, medical management is always instituted simultaneously with prescription antipsychotic drugs. This fact makes it very difficult for clinicians to isolate the relative effect of an antipsychotic drug on the resolution of delirium.[39] Most clinicians have the impression that antipsychotic drugs speed recovery in delirium, but this has never been definitely proven in controlled studies. To date there are no controlled studies that prove that antipsychotics affect the course of delirium. There are also no studies that show antipsychotics alter the length of hospitalization for delirium. A recent double-blind, placebo-controlled trial of outpatients with Alzheimer's disease found that the adverse effects of atypical antipsychotic drugs may offset the advantages for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease.[40] Two studies have looked at preventive measures and early intervention for elderly patients with delirium and found that these measures are effective in more rapidly improving cognition in elderly patients; both studies failed to demonstrate an effect on mortality, institutionalization, or length of hospital stay.[12,41]

A greater problem of these studies is the fundamental difficulty of investigating an entity such as delirium. Delirium, by its very nature, cannot be easily studied in a randomized, controlled trial. Assessing the efficacy of antipsychotics for the delirium can certainly be confounded by the simultaneous treatment of the underlying medical condition that is thought to underlie the delirium. It is difficult to eliminate this confounder, since it would be unethical to withhold treatment for the underlying medical condition while testing the efficacy of an antipsychotic medication.

CONCLUSION

This report has documented the results of several case studies, prospective studies and retrospective studies in the use of risperidone, olanzapine, and quetiapine for the treatment of delirium in the elderly individual. The evidence reviewed suggests that the atypical antipsychotics, with their similar rates of efficacy and lower rate of extrapyramidal side effects, may be a viable option to traditional high-potency neuroleptics. Because of the challenges in designing randomized controlled trials to study delirium in isolation, it is difficult to generate results not confounded by the simultaneous treatment of elderly patients' underlying medical conditions. Future randomized controlled trials on delirium need to be designed in a way that allows for comparison of atypical agents verses haloperidol but still adheres ethically to the standard of care (treating the underlying illness). Once the problem with confounding is acknowledged and dealt with accordingly, groups can be stratified and systematically compared. This review, based on studies to date, supports that atypical agents appear to be as effective as typical antipsychotics in the treatment of delirium in the elderly individual.

REFERENCES

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994, pp. 129–133.
2. Kaplan H, Sadock B. Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences, Clinical Psychiatry. MD: Philadelphia, PA: Lippincott Williams & Wilkins, 1998.

3. Katz PR, Grossberg GT, Potter JF, et al. Delirium. Geriatrics Syllabus for Specialists 2002; 26:2.
4. Nayeem K, O'Keeffe ST. CME elderly medicine. Clin Med 2003;3(5): 412–415.
5. Inouye SK. Delirium in older persons. N Engl J Med 2006;354(11):1157–1165.
6. Thorp L. The treatment of psychotic disorders in late life. Can J Psychiatry 1997;42(Suppl 1):19S–27S.
7. Mittal D, Jimerson NA, Neely EP, et al. Risperidone in the treatment of delirium: Results from a prospective open–label trial. J Clin Psychiatry 2004;65(5):662–667.
8. Han C, Kim Y. A double–blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics 2004;45(4):297–301.
9. Nassisi D, Korc B, Hahn S, et al. The evaluation and management of the acutely agitated elderly patient. Mt Sinai J Med 2006;73(7):976–984.
10. Targum SD. Treating psychotic symptoms in elderly patients. Primary Care Companion. J Clin Psychiatry 2001;3(4):156–163.
11. Jackson JC. Delirium and long–term cognitive impairment: An overview. Clinical Window Web Journal: Outcome after Intensive Care Delirium, #21, Vol. 6, January 2006. Available at: http://www.clinicalwindow.net. Accessed July 27, 2007.
12. Rathier MO, McElhaney J. Delirium in elderly patients: How you can help. Applied Neurology. August 2005.
13. Schwartz TL, Masand PS. The role of atypical antipsychotics in the treatment of delirium. Psychosomatics 2002;43(3):171–173.
14. Flaherty JH, Rudolph J, Shay K, et al. Delirium is a serious and under–recognized problem: Why assessment of mental status should be the sixth vital sign. J Am Med Dir Assoc 2007:273–275.
15. Shingo M, Yamamoto K, Hoshino S, et al. Comparison of the risk of adverse events between risperidone and haloperidol in delirium patients. Psychiatry Clin Neurosci 2007;61:275–282.
16. Lacasse H, Perreault MM, Williamson DR. Systematic review of antipsychotics for the treatment of hospital–associated delirium in medically or surgically ill patients. Ann Pharmacother 2006;40:1966–1973.
17. Sipahimalani A, Masand P. Use of risperidone in delirium: Case reports. Ann Clin Psychiatry 1997;9(2):105–107.
18. Bourgeois JA, Hilty DM. Prolonged delirium managed with risperidone. Psychosomatics 2005;46(1):90–91.
19. Ravona–Springer R, Dolberg OT, Hirschmann, S, et al. Delirium in elderly patients treated with risperidone: A report of three cases. J Clin Psychopharmacol 1998;18(2):171–172.
20. Horikawa N, Yamazaki T, Miyamoto K, et al. Treatment of delirium with risperidone: Results of a prospective open trial with 10 patients. Gen Hosp Psychiatry 2003;25(4):289–292.
21. Zarate CA, Baldessarini RJ, Siegel AJ, et al. Risperidone in the elderly: A pharmacoepidemiologic study. J Clin Psychiatry 1997;58(7):311–317.
22. Gupta N, Sharma P, Mattoo SK. Effectiveness of risperidone in delirium. Can J Psychiatry 2005;50:75.
23. Lim, CJ, Trevino C, Tampi RR. Can olanzapine cause delirium in the elderly? Ann Pharmacother 2006;40:135–138.
24. Skrobik Y, Bergeron N, Dumont M, et al. Olanzapine vs haloperidol: Treating delirium in a critical care setting. Intens Care Med 2004;30: 444–449.
25. Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics 2002;43(3):175–182.
26. Kim, K, Pae C, Chae J, et al. An open pilot trial of olanzapine for delirium in the Korean population. Psychiatry Clin Neurosci 2001;55: 515–519.
27. Sipahimalani A, Masand PS. Olanzapine in the treatment of delirium. Psychosomatics 1998;39:422–430.
28. Kim KY, Bader GM, Kotlyar V, et al. Treatment of delirium in older adults with quetiapine. J Geriatr Psychiatry Neurol 2003;16(1):29–32.
29. Sasaki Y, Matsuyama T, Inoue S, et al. A prospective, open–label, flexible–dose study of quetiapine in the treatment of delirium. J Clin Psychiatry 2003;64(11):1316–1321.
30. Neil W, Curran S, Wattis J. Antipsychotic prescribing in older people. Age Ageing 2003;32(5):475–483.
31. Zayas EM, Grossberg GT. The treatment of psychosis in later life. J Clin Psychiatry 1998;59(suppl 1):5–10
32. Mosby's Drug Consult. Mosby, Inc. 2006. Available at: http://www.mdconsult.com. Accessed February 16, 2006.
33. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: Meta–analysis of randomized placebo–controlled trials. JAMA 2005;294:1934–1943.
34. Wang, PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 2005;353(22):2335–2341.
35. Herrmann N, Mamdani M, Lanctot K. Atypical antipsychotics and risk of cerebrovascular accidents. Am J Psychiatry 2004;161(6):1113–1115.
36. Glassman AH, Bigger JT. Antipsychotic drugs: Prolonged QTc interval, Torsade de Pointes, and sudden death. Am J Psychiatry 2001;158: 1774–1782.
37. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: Population based retrospective cohort study. BMJ 2005;330:445–451.
38. Layton D, Harris S, Wilton L, et al. Comparison of incidence rates of cerebrovascular accidents and transient ischaemic attacks in observational cohort studies of patients prescribed risperidone, quetiapine or olanzapine in general practice in England including patients with dementia. J Psychopharmacol 2005;19(5):473–482.
39. Ryan CJ. Optimising management of delirium. BMJ 2001;322:1602.
40. Schneider, LS, Tariot, PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355(15):1525–1538.
41. Pitkala KH, Laurila JV, Strandberg TE, et al. Multicomponent geriatric intervention for elderly inpatients with delirium: A randomized, controlled trial. J Gerontol 2006;61(2):176–181.
42. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340(9):669–676.