Psychiatry and Clinical Neurosciences 2013; **67**: 323–331 doi:10.1111/pcn.12066

Review Article

Atypical antipsychotics in the treatment of delirium

Hee Ryung Wang, MD, Young Sup Woo, MD, PhD and Won-Myong Bahk, MD, PhD*

Department of Psychiatry, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

The aim of this study was to review the efficacy and safety of atypical antipsychotics, comparing within class, placebo, or compared to another active treatment for delirium. A literature search was conducted using PubMed, EMBASE, and the Cochrane database (1 January 1990–5 November 2012). Selection criteria for review were prospective, controlled studies (comparison studies), using validated delirium rating scales as outcome measures. A total of six prospective, randomized controlled studies were included in the review. It was found that atypical antipsychotics are effective and safe in treating delirium, even though there seemed to be no difference between each agent. In particular, comparison studies with haloperidol showed that the efficacy of atypical antipsychotics was similar to that of low-dose haloperidol. It was concluded that atypical antipsychotics appear to be effective and tolerable in the management of delirium, even though the evidence is limited.

Key words: atypical antipsychotic, delirium, efficacy, safety, treatment.

DELIRIUM IS AN acute, confusional state that is characterized by consciousness disturbance, changes in cognition and attention, and reduced awareness or perceptual disturbances that develop acutely and have a fluctuating course.[1] Delirium is a common neuropsychiatric condition observed in medically ill patients. Lipowski reported that, among patients hospitalized for medical and surgical reasons, the incidence of delirium ranged from 10% to 18% and that the development of delirium is associated with a high mortality and morbidity.[2] The elderly are known to be at high risk for developing delirium. According to Han and Kim, 10–40% of hospitalized elderly patients develop delirium during hospitalization.[3]

For non-pharmacological interventions for delirium, clinicians should correct and treat the underlying medical condition responsible for the delirium.[4,5] Conservative management such as preventing medical complications and providing patients with a supportive environment is also very important. In terms of pharmacological interventions, antipsychotic agents have been regarded as the treatment of choice, because various antipsychotic agents have been shown to ameliorate a range of delirium symptoms effectively in many previous studies.[6–8] Among antipsychotics, haloperidol has been the most widely used because of its higher dopamine receptor potency, lower anticholinergic effects, and the availability of various routes of use.[9] Side-effects, however, have been reported, especially extrapyramidal effects.[10] Due to the side-effects of typical antipsychotics, the use of atypical antipsychotics in the treatment of delirium has been increasing because of the lower incidence of extrapyramidal symptoms with atypical compared to typical antipsychotics.[11,12]

Despite the increasing usage of atypical antipsychotics for delirium in clinical practice, limited evidence is available on their efficacy and tolerability.[11,12] Accordingly, the primary aim of this paper was to review the existing published literature on the role of atypical antipsychotics in the management of delirium.

*Correspondence: Won-Myong Bahk, MD, PhD, Department of Psychiatry, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 62 Yeouido-Dong, Youngdeungpo-Gu, Seoul 150-713, Korea. Email: wmbahk@catholic.ac.kr
Received 18 January 2013; revised 5 April 2013; accepted 26 May 2013.

METHODS

Search methods and selection criteria

To review the efficacy and tolerability of atypical antipsychotics in treating delirium, we conducted a literature search using PubMed, EMBASE, and the Cochrane database (1 January 1990–5 November 2012) using the following search terms in various combinations: 'delirium', 'antipsychotic agent', 'neuroleptic agent', 'olanzapine', 'risperidone', 'aripiprazole', 'quetiapine', 'ziprasidone', 'amisulpride', 'zotepine', 'paliperidone'. Prospective, randomized controlled studies were selected for review. Specifically, studies were included that compared the efficacy and tolerability of atypical antipsychotics either with placebo or another active treatment such as haloperidol, or that compared two or more atypical antipsychotics to each other. The literature review was also limited to studies that used standardized diagnostic criteria for delirium and validated instruments to rate delirium (e.g. Memorial Delirium Assessment Scale [MDAS],[13] Delirium Rating Scale [DRS],[14] Delirium Index [DI],[15] or the revised version of DRS [DRS-R 98][16]). Studies such as case series, or case reports, studies using retrospective design, studies of substance-associated delirium, and single-agent studies without an adequate control group were excluded. Studies investigating the effectiveness of atypical antipsychotics in preventing delirium in high-risk patients were also excluded. Only studies written in English were reviewed.

RESULTS

Search results

We initially identified 789 articles from PubMed, 2627 from EMBASE, and 61 from the Cochrane database. Among them, 552 articles overlapped. After we reviewed the abstracts of the 2925 articles identified, we retrieved 85 and reviewed them thoroughly. Among these 85, six articles met the selection criteria and were chosen for review by the two reviewers (WMB and HRW). The characteristics of the six articles are listed in Table 1.

One study was a randomized, open prospective study that compared amisulpride and quetiapine in the treatment of delirium. Two studies were randomized controlled studies that investigated the efficacy and safety of olanzapine. One of these two was a comparative trial that compared olanzapine and haloperidol. The other investigated the effectiveness of olanzapine and risperidone compared to haloperidol. There was one randomized, placebo-controlled study that investigated the effectiveness of quetiapine. The remaining two articles were comparative trials of risperidone. Among these, one compared

Table 1. Studies of the clinical use of atypical antipsychotics in delirium

Study	Study setting	Sample size	Medication	Mean dose (mg/day)	Scale
Lee *et al.*, 2005[17]	Referred to the Psychiatric Consultation Service	40	Amisulpride Quetiapine	156.4 113.0	DRS-R-98
Skrobik *et al.*, 2004[18]	Medical-surgical intensive care unit	73	Olanzapine Haloperidol	4.54 6.50	DI
Grover *et al.*, 2011[19]	Referred to the consultation-liaison psychiatry	74	Olanzapine Risperidone Haloperidol	3.05 0.95 0.88	DRS-R-98
Tahir *et al.*, 2010[20]	Medical, surgical and orthopedic wards at a university hospital	42	Quetiapine (placebo controlled)	40.0	DRS-R-98
Han and Kim, 2004[3]	Medical wards, intensive care units, and oncology wards	28	Risperidone Haloperidol	1.02 1.71	MDAS
Kim *et al.*, 2010[21]	Referred to the Psychiatric Consultation	32	Olanzapine Risperidone	1.8 0.6	DRS-R-98

DI, Delirium Index; DRS-R-98, revised version of the Delirium Rating Scale; MDAS, Memorial Delirium Assessment Scale.

risperidone and haloperidol, and the other compared risperidone and olanzapine.

Atypical antipsychotics in delirium

Amisulpride

We reviewed two studies on the efficacy of amisulpride for the treatment of delirium.[17,22] One was an uncontrolled study,[22] so it was excluded from further review. One randomized, open prospective study investigating the effectiveness of amisulpride for delirium met the selection criteria for this review.[17]

Lee *et al*. compared the effectiveness and safety of amisulpride and quetiapine in patients with delirium.[17] They also compared the effect of each drug on sleep and recovery time. A total of 40 patients who were referred for psychiatric consultation at a university hospital were enrolled. The patients who had taken antipsychotic agents, who seemed to resolve spontaneously, and who had a prior history of psychiatric disorder were excluded. The subjects were randomized into either amisulpride or quetiapine groups. The dose was flexible depending on clinician decision. The instruments used for delirium ratings were the Clinical Global Impression-Severity (CGI-S) scale,[23] and the DRS-R 98. Sixteen subjects in the amisulpride group and 15 subjects in the quetiapine group completed the study. In the amisulpride group, subjects were prescribed a mean dose of 156.4 ± 97.5 mg/day (range, 50–800 mg/day). In the quetiapine group, subjects were prescribed a mean daily dose of 113 ± 85.5 mg/day (range, 50–300 mg/day). Treatment was terminated when CGI-S reached ≤2. Benzodiazepine or other antipsychotics were not allowed. In both groups, the DRS-R 98 score significantly decreased after treatment (from 10.5 ± 4.1 to 3.5 ± 1.4 for the amisulpride group, $P < 0.001$; from 10.1 ± 4.1 to 3.5 ± 2.6 for the quetiapine group, $P = 0.001$), but there was no significant group difference. The recovery time from delirium did not differ between the two groups (6.3 ± 4.4 days for the amisulpride group and 7.4 ± 4.1 days for the quetiapine group). The percentage of patients who had >50% symptom reduction after treatment was 81.3% ($n = 13$) in the amisulpride group and 80% ($n = 12$) in the quetiapine group. No serious adverse events were reported during the study period. That study thus demonstrated that both amisulpride and quetiapine were effective in treating delirium and both were well-tolerated.

Olanzapine

There have been a number of published studies examining the effectiveness of olanzapine.[18,19,21,24–29]

Three of those studies assessed the clinical efficacy and safety of olanzapine using a prospective, randomized controlled design.[18,19,21]

Skrobik *et al*. compared the use of olanzapine and haloperidol over 5 days in the treatment of delirium.[18] This study was a prospective, randomized controlled trial in a critical care unit setting. Subjects were patients admitted to the medical–surgical intensive care unit and diagnosed with delirium based on DSM-IV criteria.[30] The patients who had received any antipsychotic agent within 10 days prior to admission to hospital or intensive care unit, who had gastrointestinal dysfunction, impeding oral/enteral drug treatment, and who had neurological status that disturbed an adequate psychiatric evaluation were excluded. The subjects were randomly assigned to either olanzapine or haloperidol on an even/odd day basis. Dosing titration depended on clinician judgment. Benzodiazpine as adjuvant treatment and i.v. haloperidol as rescue medication were allowed. The severity of delirium was measured using the DI. A total of 73 patients were included in the analysis. The mean age of the study group was 63.26 ± 11.66 years for the haloperidol group and 67.50 ± 6.04 years for the olanzapine group, respectively. The mean daily doses were 6.5 mg (range, 1–28 mg) in the haloperidol group and 4.54 mg in the olanzapine group (range, 2.5–13.5 mg). In both group, DI scores were significantly reduced after 5 days of treatment with each medication, but DI scores did not differ between the two groups. Overall, DI scores in all patients went from 7.05 on day 1 to 5.05 on day 5. There were no adverse effects reported in the olanzapine group, whereas six subjects in the haloperidol group experienced extrapyramidal symptoms. That study indicated that olanzapine has clinical utility and is tolerable for the management of delirium in critically ill patients.[18]

Grover *et al*. examined the efficacy and tolerability of olanzapine and risperidone compared to haloperidol for delirium.[19] That study had a prospective, single-blinded, randomized controlled design. Subjects were patients who had been admitted to the medical and surgical ward and referred for psychiatric consultation for delirium. Delirium was diagnosed based on the DRS-R 98 and the Confusion Assessment Method Scale (CAM).[31] Those who had alcohol

or benzodiazepine withdrawal delirium, who had dementia, who were unresponsive to any physical or verbal stimulus, who suffered from a terminal illness, and who had psychotic or mood disorders were excluded from the study. Subjects who had profound hearing or visual difficulty, aphasia, Parkinson's disease, prior history of neuroleptic malignant syndrome, and prolonged QTc interval (defined as >500 ms) were also excluded. Delirium severity was assessed using the DRS-R 98. Seventy-four patients were randomly assigned to three medication groups: risperidone ($n = 22$), olanzapine ($n = 26$), or haloperidol ($n = 26$). Among these patients, 64 completed the study. The dosing schedule was based on clinical judgment. The mean daily dose of each drug was 0.88 ± 0.98 mg/day for haloperidol, 3.05 ± 1.44 mg/day for olanzapine, and 0.95 ± 0.28 mg/day for risperidone. All groups showed a significant reduction from baseline in DRS-R 98 scores on days 3 and 6, but there were no significant differences among the three groups in terms of the degree of reduction in DRS-R 98 scores. Four subjects in the haloperidol group, six in the risperidone group and two in the olanzapine group reported some side-effects, but there was no group difference. This study showed that the two second-generation antipsychotics (olanzapine and risperidone) were similarly effective and tolerable compared to haloperidol.

Kim *et al*. conducted a 7-day, randomized controlled trial to compare olanzapine and risperidone for delirium treatment.[21] Subjects were delirious patients in three university hospitals who were referred for psychiatric consultation. The diagnosis of delirium was based on DSM-IV criteria. Those who had dementia, and who had taken antipsychotics due to behavioral problems prior to referral were excluded. For efficacy, the DRS-R 98 was used to measure delirium severity. The Udvalg for Kliniske Undersogelser neurological side-effect scale[32] was used to assess neurological side-effects. The dosing schedule was based on clinical judgment depending on each patient's medical condition over the 7 days. Rescue medication such as a haloperidol or benzodiazepine injection was allowed. Among the 32 patients enrolled, 17 were randomized to risperidone and 15 were randomized to olanzapine. Among these, 12 subjects in the risperidone group and eight in the olanzapine group completed the trial. The mean initial doses were 0.6 ± 0.2 mg/day for risperidone and 1.8 ± 0.6 mg/day for olanzapine. The mean daily doses were 0.9 ± 0.6 mg/day for risperidone and 2.4 ± 1.7 mg/day for olanzapine. There was significant improvement in DRS-R 98 scores from baseline to day 7 in both groups, but the two groups did not differ from each other. There was also no statistically significant difference in response rates between the risperidone and olanzapine groups. Three patients in the olanzapine group and two in the risperidone group reported extrapyramidal symptoms, but all were mild to moderate. This study indicates that both representative atypical antipsychotics are similarly effective in the treatment of delirium.[21]

Quetiapine

Since Schwartz and Masand reported the clinical efficacy of quetiapine in the treatment of delirium in a retrospective chart review study,[33] many studies have investigated the efficacy of quetiapine for delirium.[17,34–39] Most of these studies have been uncontrolled, single-agent studies, but there have been three prospective, randomized controlled trials that investigated the efficacy and safety of quetiapine for delirium.[17,20,39] Among the three studies, the Devlin *et al*. study was excluded from review because the primary outcome measure was the time to first resolution of delirium, not the change of delirium severity measured on a validated delirium rating scale.[39] Among the remaining two randomized controlled studies, one was a comparison study that tested the effectiveness of amisulpride and quetiapine, which has been described in the amisulpride section.[17]

Tahir *et al*. assessed the clinical utility of quetiapine in the management of delirium.[20] This was a double-blind, randomized controlled trial. The sample consisted of patients who were admitted to medical, surgical, and orthopedic wards at a university hospital. Among these patients, those who met the DSM-IV criteria for delirium and whose DRS-R 98 total score was ≥ 15 were recruited. Those who had pre-existing cognitive disturbances, pre-existing psychosis, substance dependence, alcohol withdrawal, or who took medication interacting with quetiapine were excluded. Among the 372 patients screened, a total of 42 patients were recruited for this trial. The mean age of the subjects was 84.2 ± 8.3 years (range, 58–98 years). Twenty-nine patients completed the trial: 16 patients in the quetiapine group and 13 patients in the placebo group. The DRS-R 98, Brief Psychiatric Rating Scale (BPRS),[40] CGI, and Mini-Mental State Examination (MMSE)[41] were used. The Abnormal

Involuntary Movements Scale (AIMS)[42] and a clinical examination were used to assess side-effects of quetiapine. Subjects were evaluated on days 1, 2, 3, 4, 7 and 10 after randomization and followed up on day 30. Forty-two subjects were randomly assigned to either quetiapine or placebo with a flexible dose. The starting dose for quetiapine was 25 mg once daily. The dose was increased by 25 mg per day to a maximum dose of 175 mg if the DRS-R 98 score did not improve after treatment. If symptoms of delirium were resolved as based on the DRS-R 98, the dose was decreased. The highest mean daily dose of quetiapine was 40 mg on day 4 (25 mg/day on day 1, and 37.50 mg/day on day 10). The quetiapine group showed more rapid improvement in DRS-R 98 scores than the placebo group. Additionally, the quetiapine compared to the placebo group showed faster improvement on the non-cognitive subscale of the DRS-R 98 (items 1–8) but not on the cognitive subscale (items 9–13). There were no differences in the MMSE, BPRS, and CGI scores between the two groups. Seven subjects died within 30 days after entering the trial (four in the quetiapine group and three in the placebo group). One subject was withdrawn from quetiapine because of sedation. Abnormal involuntary movements were reported in both groups (4.8% of the quetiapine group and 14.3% of the placebo group). Even though the study was terminated early due to concerns of the Food and Drug Administration regarding the usage of an antipsychotic agent in the elderly, that study demonstrated the potential of quetiapine for a more rapid reduction in the severity of non-cognitive symptoms of delirium.[20]

Risperidone

A number of studies have tested the use of risperidone in the management of delirium.[14,31,43–48]

There have been three prospective trials on the use of risperidone in the treatment of delirium.[3,19,21] Among them, one study examined the efficacy and tolerability of olanzapine and risperidone compared to haloperidol.[19] Another was a 7-day, randomized controlled trial that compared olanzapine and risperidone.[21] Both studies are reviewed in the olanzapine section. We discuss the remaining study in this section.[3]

Han and Kim conducted a double-blind, randomized controlled trial to compare risperidone and haloperidol for the treatment of delirium.[3] The sample consisted of patients who were referred for psychiatric consultation at a university hospital and diagnosed with delirium based on the Structured Clinical Interview for DSM-III-R (SCID).[45] Those who had any type of dementia or other psychiatric disorders identified using the SCID were excluded. A total of 28 patients were randomized to receive risperidone or haloperidol with flexible doses. The starting dose was 1.5 mg for haloperidol and 1.0 mg for risperidone. The dose could be increased based on clinical judgment during the 7 days of the study period. Two subjects in the haloperidol group and two in the risperidone group dropped out. The mean daily doses were 1.71 ± 0.84 mg for haloperidol and 1.02 ± 0.41 mg for risperidone. The MDAS was used to measure delirium severity. The initial DRS score for all patients was 22.76 ± 4.30, with no significant difference between groups. Both groups had a significant decrease in MDAS scores from screening to day 7, but the two groups did not differ. There was also no significant difference between the groups in response rate, defined as MDAS <13 (risperidone group 42%; haloperidol group 75%). No side-effects were reported by subjects in either group. The results of that study indicate that risperidone has similar efficacy and tolerability to haloperidol.[3]

Ziprasidone

There have been no prospective, randomized, controlled studies of the effectiveness and tolerability of ziprasidone using validated instruments to assess delirium. There have been several case reports[49–51] and one randomized, placebo-controlled trial.[52] The only randomized controlled trial on the use of ziprasidone, performed by Girard *et al.*,[52] was excluded from the present review because validated instruments were not used for primary outcome measures.

Aripiprazole

Only case reports,[28,53] uncontrolled studies[54,55] and one non-randomized study[56] have reported regarding the use of aripiprazole for delirium. There have been no prospective, randomized controlled studies that have examined aripiprazole's effectiveness and tolerability using validated instruments to assess delirium.

Other atypical antipsychotics

There is a prospective open-label trial that examined the efficacy of paliperidone in the treatment of

delirium,[57] but there have been no randomized controlled studies on the efficacy of paliperidone for delirium.

To our knowledge, there have been no clinical studies to have tested the efficacy and tolerability of zotepine for the treatment of delirium.

DISCUSSION

In this review, we discussed studies that tested the efficacy and safety of atypical antipsychotics in the treatment of delirium. Since their introduction, atypical antipsychotics have replaced typical antipsychotics in various clinical uses because of their favorable side-effect profiles.[58] For the same reasons, the use of second-generation antipsychotics in the management of delirium has increased, which reflects a change in prescription patterns. Since one of the first studies of the use of atypical antipsychotics for delirium,[48] there have been numerous published reports regarding their clinical efficacy and tolerability; but when we consider that many etiologies are known to cause delirium and that delirium has a fluctuating nature, it is difficult to affirm that the significant improvement in delirium symptoms observed in many previous clinical trials after the use of atypical antipsychotics is purely due to the effect of atypical antipsychotics. Thus, we selected only well-controlled studies to separate the influence of atypical antipsychotics on delirium symptoms from other variables that could influence the treatment response and course of delirium.

We conducted a literature search and found a total of six randomized controlled, prospective clinical trials that tested the utility of atypical antipsychotics in delirium.

Among the six studies reviewed, only one was a placebo-controlled study.[20] The rest were comparison studies, some of which compared the efficacy of atypical antipsychotics to haloperidol,[3,18,19] and the others compared different atypical antipsychotics to each other.[17,19,21]

The only placebo-controlled study examined the efficacy of quetiapine among general hospital inpatients whose DRS-R 98 total scores were ≥ 15.[20] Although the quetiapine and placebo groups did not differ in their delirium severity at any time point, the quetiapine group had a more rapid improvement in symptoms. But because that study was prematurely discontinued, we are unable to draw any definitive conclusions.

Three studies were comparison studies that directly compared two antipsychotics to each other.[17,19,21] One study used haloperidol as an active comparator.[19] All three comparison studies showed improvements in delirium symptoms after use of atypical antipsychotics, and there were no between-group differences in efficacy and tolerability.

The other two studies were haloperidol-controlled studies that examined the effectiveness of olanzapine and risperidone.[3,18] Both studies reported similar efficacy of each atypical antipsychotic agent compared to haloperidol, suggesting the potential use of each atypical antipsychotic agent as a safe alternative to haloperidol.

Across the six studies, extrapyramidal symptoms were one of the most common adverse events reported, while the metabolic side-effects were much less frequently reported. That might be because the treatment duration for delirium in these studies was relatively shorter than the duration for other major psychiatric disorders, such as affective disorders or psychotic disorders.

While reviewing the extant literature, we identified several concerns and methodological limitations. First, most studies had small sample sizes. The sample sizes across the six studies were between 20 and 80, which is too small a sample to generalize the results. Second, there was significant heterogeneity across studies in terms of the characteristics of the study groups and the etiology of delirium. Participants across the six studies presented with delirium symptomatology at admission to medical or surgical wards or developed delirium while undergoing treatment in intensive care units. The underlying etiology of delirium for each participant also varied, and included etiologies such as malignant tumors, orthopedic problems, pneumonia, neurosurgical conditions, and other medical and surgical conditions. Third, no study reported controlling for these heterogeneous differences in their analyses or controlling for any treatment (including non-specific, non-pharmacological treatments) given to patients to manage an underlying medical/surgical condition. Because these can be confounding variables, future studies should describe and explain these variables in their assessment and analyses. Fourth, we found that there were few studies that investigated the tolerability systematically. There were no validated assessment tools for drug side-effects used in the six studies except the scales assessing the extrapyramidal symptoms.

There are some limitations to the present review. First, we included only randomized controlled, prospective studies that were written in English. We may have excluded important studies written in other languages or with uncontrolled, naturalistic, or retrospective designs, which can also provide valuable information about the utility of atypical antipsychotics. Second, we included only studies that used validated delirium rating scales as efficacy outcome measures. Thus, we excluded some trials that included critically ill patients with delirium with whom validated delirium rating scales could not be used.

Despite these limitations, overall we found that atypical antipsychotics are efficacious and relatively safe in treating delirium. Specifically, it appears that atypical antipsychotics are as equally efficacious as haloperidol, which is the most widely used medication for treating delirium. Furthermore, there seemed to be no significant difference in the efficacy and tolerability among atypical antipsychotics, although very few studies directly compared two atypical antipsychotics to each other.

Meanwhile there have been some reports of delirium caused or induced by atypical antipsychotics, during the treatment of major psychiatric disorders with atypical antipsychotics.[59–64] Thus, these reports could lead to medical concern for the potential of atypical antipsychotics in aggravating the delirium symptoms or complicating the treatment of delirium during the delirium management. In most studies reviewed here, however, the efficacy of atypical antipsychotics for delirium was shown at a lower dosage than the usual dosage used for the management of major psychiatric disorders or for controlling psychotic symptoms. But we think that it is important for clinicians to pay special attention to the elderly patients or medically vulnerable patients when using atypical antipsychotics for delirium and to monitor the course of delirium closely.

In summary, considering several methodological limitations and problems with previous studies mentioned here, future studies need to be well-controlled, have large sample sizes, use more systematic assessment tools for side-effects, and explore the effects of various factors (e.g. underlying medical disorder-related or medical treatment-related factors) on the resolution of delirium to further clarify the role of atypical antipsychotics in the treatment of delirium. In addition, future studies are also warranted to further investigate the differences in the effectiveness of atypical antipsychotics for the treatment of delirium according to the motor subtypes or various delirium etiologies.

ACKNOWLEDGMENT

The authors have no conflict of interest to declare.

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