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Review Article

Atypical antipsychotics in the treatment of delirium

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Delirium is common in all medical settings. Atypical antipsychotics are increasingly used for the management of delirium symptomatology but their effectiveness has not been systematically studied. The aim of the present study was therefore to provide an up-to-date review on the use of atypical antipsychotics in the treatment of delirium. A search was conducted of the databases of MEDLINE, PsycINFO and EMBASE from 1997 to 2008 for English-language articles using the key words 'delirium' and the names of all the atypical antipsychotics. A total of 23 studies were used for this review. Fifteen of the studies were single-agent trials. Four studies were comparison trials, including one double-blind trial, and four studies were retrospective, including three comparison studies. All studies reported improvement of delirium symptomatology after the administration of atypical antipsychotics. No study included a placebo group. Other limitations included sample heterogeneity, small sample size, different rating scales for delirium, and lack of adequate controls. The improvement in delirium was observed within a few days after treatment initiation and the doses given were relatively low. Atypical antipsychotics were well tolerated, but safety was not evaluated systematically. Atypical antipsychotics appear to be effective and safe in symptomatic treatment of delirium but the evidence is limited and inconclusive. There are no double-blind, placebo-controlled studies assessing the efficacy and safety of these agents in delirium. Further research is needed with well-designed studies.

Key words: atypical antipsychotics, delirium, olanzapine, quetiapine, risperidone.

DELIRIUM IS A complex neuropsychiatric syndrome that is common in all medical settings. It is characterized by altered level of consciousness and cognitive impairment, which affect orientation, attention and memory, and perceptual disturbance.[1,2] Certain patients are prone to develop delirium. Elderly patients and those with pre-existing dementia are high-risk groups.[3] Delirium is associated with increased morbidity, increased mortality, and increased health services utilization.[4] The management of delirium is challenging for clinicians and involves both etiological and symptomatic treatment. Although supportive and environmental measures are useful, the cornerstone of treatment is drug administration.[5] Antipsychotics are widely used for the management of some disturbing symptoms of delirium, such as agitation, but the evidence for their use is limited.[6] Haloperidol is the most studied agent and is commonly used by clinicians in all medical settings. It has the advantage of i.v. administration. Extrapyramidal side-effects are common with haloperidol and may be troublesome. Furthermore, the i.v. route of administration has been associated with the development of Torsades de Pointes, a dangerous and life-threatening condition.[7,8]

In recent years several new antipsychotic agents have been developed: the second-generation, or so-called atypical antipsychotics. These agents are now widely used for the treatment of schizophrenia and other psychoses. There is ongoing research in the

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usage of these drugs in delirium and they seem to be an effective and promising treatment for these patients, although the evidence is still preliminary and inconclusive.[9] Atypical antipsychotics are at least as effective as haloperidol and they are clearly better tolerated.[10] In the present study we intend to provide an up-to-date review on the use of atypical antipsychotics for the treatment of delirium and to examine the effectiveness and safety of these agents in delirious patients.

METHODS

We conducted a search of MEDLINE, PsycINFO and EMBASE databases (January 1997–December 2008) combining the key words 'delirium', 'acute confusional state', and the names of all the atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, amisulpride) with the exception of clozapine and sertindole. Clozapine was excluded from our search because it is unlikely to be given for delirium due to the severe limitations in its usage. Sertindole was also excluded because it has been withdrawn from the market for several years due to safety concerns. Perospirone was added to the search because we identified reports from Japan regarding the use of this drug in delirium. Case reports and case series were excluded. We also searched the references of the articles for additional reports that might have been initially overlooked. Only articles in English were considered.

RESULTS

The search initially retrieved 214 studies published between 1997, when the first study was published,[11] and 2008. Review of the references of these studies found an additional 25 reports. All these abstracts were reviewed and 36 articles were retrieved for detailed review. We finally included 23 studies in the review. Fifteen of the studies were single-agent trials. Treatment included olanzapine (four studies),[12–15] risperidone (nine studies),[11,16–23] quetiapine (seven studies),[24–30] aripiprazole (one study)[31] and finally perospirone (two studies).[32,33] Four studies were comparison trials, including one double-blind trial, and four studies were retrospective, including three comparison studies. A total of 538 individuals with delirium received atypical antipsychotics in these studies. With the exception of the first ever published study on the treatment of delirium with an atypical agent, in which the Clinical Global Impressions (CGI) scale was used,[11] all studies evaluated efficacy by comparing the scores achieved on a delirium severity scale at two time points: before and after treatment initiation. These severity scales specific to delirium are the Delirium Rating Scale (DRS), the Memorial Delirium Assessment Scale (MDAS), the Delirium Index (DI), and the Delirium Rating Scale Revised (DRS-R-98; Table 1).

Study characteristics

Open label studies

Risperidone trials

The first published study by Sipahimalani *et al.* examined the efficacy of risperidone in the treatment of delirium.[11] Eleven consecutive patients received risperidone at an average dose of 1.59 ± 0.8 mg/day. The authors did not use a rating scale for delirium and treatment outcome was measured on the CGI scale. Eight out of 11 patients showed some improvement, whereas in six out of eight responders marked improvement was observed. Regarding safety, only one patient developed extrapyramidal symptoms (EPS) and another experienced dizziness.

Horikawa *et al.* conducted a prospective open trial in 10 individuals with delirium (mean age 56.8 years).[16] Efficacy was assessed on the DRS. Mean DRS score at baseline was 20.0 ± 4.5, and this dropped to 10.3 ± 4.8 after treatment. Risperidone administered at the low dose of 1.7 mg/day was effective in 80% of patients. Sleepiness was observed in three patients and mild drug-induced parkinsonism (evaluated on the Drug-Induced Extrapyramidal Symptoms Scale) was observed in one.

Mittal *et al.* also conducted an open-label prospective trial in which they included the same number of patients with delirium (mean age 64.7 years).[17] Mean daily risperidone dose was even lower (0.75 mg). DRS scores improved from day 1 (25.2 ± 0.9) to the day maintenance dose was initiated, and remained improved at day 6 (11.3 ± 1.5). Patient condition was also evaluated on the Cognitive Test for Delirium. Functional status (Karnofsky Scale of Performance Status), and medical burden (Cumulative Illness Rating Scale) were assessed at baseline and at day 6. At day 6 all scores were improved at a statistically significant level from baseline. No statistically significant differences were detected at day 6 in terms of extrapyramidal side-effects (as measured with the

Table 1. Studies on the use of atypical antipsychotics in the treatment of delirium

Study	Medication	Mean dose (mg/day)	Design	*n*	Scale	Score before treatment	Score after treatment
Sipahimalani and Masand,[12] 1998	Olanzapine	8.4 ± 3.4	Retrospective	11	DRS	17.9 ± 4.4	10.3 ± 4.8
Kim *et al.*,[13] 2001	Olanzapine	5.9 ± 1.5	Open label	20	DRS	20.0 ± 3.6	9.3 ± 4.6
Breitbart *et al.*,[14] 2002	Olanzapine	6.3	Open label	79	MDAS	19.85 ± 3.79	10.78 ± 7.31
Skrobik *et al.*,[15] 2004	Olanzapine	4.54	Open, randomized	28	DI	6.6 ± 1.2	5.5 ± 1.1
Sipahimalani *et al.*,[11] 1997	Risperidone	1.59 ± 0.8	Open label	11	CGI	NA	NA
Horikawa *et al.*,[16] 2003	Risperidone	1.7	Open label	10	DRS	20.0 ± 5.0	10.6 ± 5.5
Mittal *et al.*,[17] 2004	Risperidone	0.75	Open label	10	DRS	25.2 ± 0.9	11.3 ± 1.5
Han and Kim,[18] 2004	Risperidone	1.02	Randomized, double-blind	12	MDAS	25	16.5
Parellada *et al.*, 2004[19]	Risperidone	2.6 ± 1.7	Open label	64	DRS	22.5 ± 4.6	6.8 ± 7.0
Kim *et al.*,[22] 2005	Risperidone	1.19 ± 1.14	Open label	18	DRS-R-98	21.61 ± 4.2	9.72 ± 4.87
Liu *et al.*,[20] 2004	Risperidone	1.17 ± 0.76	Retrospective	41	Ten-point visual analog scales	6.44 ± 0.84 for hyperactive symptoms 3.9 ± 2.4 for hypoactive symptoms	0.20 ± 1.26 for hyperactive symptoms 0.4 ± 0.96 for hypoactive symptoms
Toda *et al.*,[21] 2005	Risperidone	0.5	Open label	10	DRS	19.6 ± 3.2	11.3 ± 5.5
Ikezawa *et al.*,[23] 2008	Risperidone	1.5 ± 0.7	Open label	22	DRS	20.7 ± 3.0	6.2 ± 1.5
Schwartz and Masand,[24] 2000	Quetiapine	211.4	Retrospective	11	DRS	20.9 ± 2.3	2.7 ± 1.1
Kim *et al.*,[25] 2003	Quetiapine	93.75 ± 23.31	Open label	12	DRS	18.25 ± 6.05	0.63 ± 1.21
Sasaki *et al.*,[26] 2003	Quetiapine	44.9 ± 31	Open label	12	DRS-J	18.1 ± 4.2	9.3 ± 1.6
Omura and Amano,[27] 2003	Quetiapine	54.7	Open label	24	DRS	18.1 ± 3.7	8.9 ± 3.9
Pae *et al.*,[28] 2004	Quetiapine	127.1 ± 72.2	Open label	22	DRS-R-98	21.8 ± 3.2	9.3 ± 3.8
Lee *et al.*,[30] 2005	Quetiapine and amisulpride	113 and 156.4	Open, randomized	15 and 16	DRS-R-98	10.1 ± 4.1 and 10.5 ± 4.1	3.5 ± 2.6 and 3.5 ± 1.4
Maneeton *et al.*,[29] 2007	Quetiapine	45.7 ± 28.7	Open label	22	DRS	24.5 ± 3.2	9.6 ± 6.0
Straker *et al.*,[31] 2006	Aripiprazole	8.9	Open label	14	DRS-R-98	25.1 ± 5.2	9.4 ± 4.9
Takeuchi *et al.*,[32] 2007	Perospirone	10.0 ± 5.3	Open label	38	DRS-R-98	23.9 ± 7.6	7.0 ± 6.0
Ushijima *et al.*,[33] 2008	Perospirone and risperidone	7.1 ± 1.8 and 1.1 ± 0.2	Retrospective	16	DRS	22.8 ± 2.9 and 23.0 ± 2.8	16.3 ± 5.9 and 18.6 ± 4.4

CGI, Clinical Global Impressions; DI, Delirium Index; DRS, Delirium Rating Scale; DRS-J, Delirium Rating Scale, Japanese version; DRS-R-98, Delirium Rating Scale Revised; MDAS, Memorial Delirium Assessment Scale; NA, not available.

modified Extrapyramidal Symptom Rating Scale) and QTc changes in the electrocardiogram. Mild sedation occurred in two patients with deteriorated medical conditions and thus could not be clearly attributed to risperidone.

Parellada *et al.* conducted a prospective, multicenter, observational 7-day study on risperidone efficacy in delirium.[19] They recruited 64 individuals with delirium, (mean age 67.3 years) who were hospitalized due to a medical condition. Fifty-six patients received treatment for ≤7 days, while eight patients continued treatment for >7 days. Authors assessed efficacy on the DRS, the positive subscale of the Positive and Negative Syndrome Scale (PANSS-P), the Mini Mental State Examination (MMSE) and the CGI. They assessed safety on the UKU Side-Effect Rating Scale. Risperidone (mean dose 2.6 ± 1.7 mg/day at day 3) was administered at the time of diagnosis, and treatment maintained according to clinical response. Response to treatment was defined as a resolution in DRS score to <13 within the first 72 h. Authors reported efficacy in the vast majority (90.6%) of patients. Scores were statistically significantly improved from baseline to day 7 on all scales. Mean scores were as follows: DRS, 22.5 ± 4.6 at baseline to 6.8 ± 7.0 at day 7; PANSS-P, 21.5 ± 8.8 to 10.1 ± 7.3; MMSE, 13.1 ± 10.9 to 26.4 ± 8.9; and CGI, 4.5 ± 0.9 to 1.9 ± 1.2. Three patients (4.7%) experienced adverse events, namely drowsiness and nausea, but none developed EPS.

Toda *et al.* conducted a prospective, open-label, flexible-dose study of risperidone oral solution in order to examine the relationship between plasma concentration levels of the medication and clinical effects in the treatment of delirium.[21] They assessed 10 individuals with delirium, and the DRS and plasma levels were assessed 30 min after the first administration of a 0.5-mg dose. Seven patients whose plasma levels concentration were medium achieved remission with no adverse events. Mean DRS scores significantly reduced from 19.6 ± 3.2 before treatment to 11.3 ± 5.5 after treatment. Two patients with high plasma levels experienced excessive daytime somnolence, whereas one patient with the lowest plasma levels did not achieve remission.

More recently Ikezawa *et al.* conducted an open-label study, using the DRS, to assess the efficacy and tolerability of risperidone in elderly delirious patients (mean age 73.6 ± 7.8 years).[23] Twenty-two patients with the hyperactive variant of delirium received risperidone at a mean dose of 1.5 ± 0.7 mg/day. The mean DRS score at baseline was 20.7 ± 3.0, which dropped to 6.3 ± 1.5 at day 7 and 6.2 ± 1.5 at day 14 of treatment. Six patients (27.3%) presented mild side-effects, namely somnolence, fatigue, limb weakness and EPS, which did not require dose decrement or discontinuation of the drug.

Olanzapine trials

Kim *et al.* reported findings from an open label trial, in which 20 patients with delirium (mean age 45.8 years) due to multiple medicosurgical conditions were treated with olanzapine at a dose of 5.9 ± 1.5 mg/day.[13] Efficacy was evaluated on the DRS. The average duration of treatment was 6.6 ± 1.7 days and the day of maximal response was 3.8 ± 1.7 treated days. Mean DRS score at baseline (20.0 ± 3.6) and after treatment (9.3 ± 4.6) were significantly different ($P < 0.001$). Seventy percent of the patients showed significant improvement (>50% score reduction) on DRS score. No patient discontinued the drug due to side-effects; mild sedation and dry mouth appeared in two patients.

Breitbart *et al.* conducted an open prospective trial of olanzapine for the treatment of delirium in a sample of 79 hospitalized cancer patients (mean age 60.6 years).[14] They used the MDAS as a measure of delirium severity, phenomenology and resolution over the course of a 7-day treatment period. The mean dose of olanzapine at the end of the study was 6.3 mg (range 2.5–20 mg). MDAS scores improved significantly from baseline after treatment initiation. The mean baseline MDAS score (19.85 ± 3.79) was significantly lower (10.78 ± 7.31) at 4–7 days after treatment initiation. More than 75% of patients achieved complete resolution of their delirium by the end of the study. Side-effects were rated on a checklist according to investigators' clinical judgment. The most common adverse effect was sedation, which appeared in 30% of patients. In two patients olanzapine worsened the delirium and an additional 3.8% of patients experienced several mild side-effects, such as rash, nausea, dizziness, headache and so on. These side-effects were not rated as severe enough to interrupt treatment, with the exception of the two patients whose symptomatology worsened.

Quetiapine trials

Kim *et al.* investigated quetiapine efficacy in an open-label trial in which they recruited 12 elderly

individuals with delirium (mean age 74 years).[25] The authors used the DRS, MMSE and the Clock Drawing Test (CDT) to assess efficacy, the scores of all of which significantly decreased after treatment. The mean duration for stabilization was 5.91 ± 2.22 days, and the mean dose was 93.75 ± 23.31 mg/day. Scores on the DRS were significantly reduced, from 18.25 ± 6.05 at baseline to 0.63 ± 1.21 at the end of the observation period. None of the patients experienced EPS, while drowsiness was observed in two patients.

Sasaki *et al.* conducted a prospective, open-label, flexible-dose trial to assess the efficacy and safety of quetiapine in delirium.[26] They recruited 12 patients (mean age 67.3 years). The mean dose of quetiapine was 44.9 ± 31 mg/day. For efficacy assessments they used the DRS and the MMSE. For safety assessment they used the Drug-Induced Extrapyramidal Symptom Scale. All patients achieved remission several days (mean: 4.8 ± 3.5 days) after treatment initiation: mean DRS before treatment was 18.1 ± 4.2, and that after treatment was 9.3 ± 1.6. The authors did not detect any clinically relevant change in EPS, nor did they observe any anticholinergic effects or laboratory safety parameter changes.

Omura and Amano conducted a prospective open-label trial on quetiapine in the treatment of elderly individuals with delirium.[27] They included 24 patients in their study (mean age 76.5 years) and the mean quetiapine dose was 54.7 mg/day (range 25–125 mg/day). Efficacy was assessed on the DRS, which was significantly reduced after 7 days of treatment (18.1 ± 3.7 before treatment initiation to 8.9 ± 3.9 at day 7). In terms of safety, only somnolence was reported in three patients, which improved after 1–2 days without any dose decrement.

Pae *et al.* investigated quetiapine efficacy in a prospective, open-label, flexible-dose trial in 22 individuals with delirium (mean age 69.1 years).[28] They assessed efficacy on the DRS-R-98, and the CGI-Severity (CGI-S). Both scores were significantly reduced after treatment. Mean DRS-R-98 before treatment was 21.8 ± 3.2, compared to 9.3 ± 3.8 after treatment. None of the patients developed EPS, while one patient discontinued treatment due to sedation.

Maneeton *et al.* assessed efficacy and safety of quetiapine in 22 individuals with delirium (mean age 55.6 years) recruited in a prospective, open-label study.[29] Measurements of efficacy included the DRS and the CGI-S. Safety was assessed on the Modified (nine-item) Simpson-Angus Scale. Mean dose was 45.7 ± 28.7 mg/day and treatment duration was 6.5 ± 2.0 days. After treatment, the efficacy scores were statistically significantly reduced. Mean DRS before treatment was 24.5 ± 3.2, compared to 9.6 ± 6.0 after treatment. The authors reported several mild adverse effects, such as tremor (two cases), hypotension (two cases), dry mouth (two cases) and daytime sleepiness (13 patients).

Aripiprazole trial

Straker *et al.* evaluated aripiprazole efficacy in treating delirium in 14 individuals.[31] They used the DRS-R-98 and CGI as efficacy measurements. The mean DRS-R-98 scores were 25.1 ± 5.2 at baseline and 9.4 ± 4.9 at treatment end-point. Twelve patients had a >50% reduction in DRS-R-98 after treatment. No significant effect on metabolic and cardiovascular parameters was observed. The authors did not use a rating scale to measure extrapyramidal side-effects.

Perospirone trial

Takeuchi *et al.* reported on an open-label study in 28 individuals with delirium.[32] They used the DRS-R-98 to assess efficacy. Treatment was effective in 86.8% of patients. Scores on the DRS-R-98 before and after treatment were 23.9 ± 7.6 and 7.0 ± 6.0, respectively. Mean time to treatment effect was 5.1 ± 4.9 days. Initial dose was 6.5 ± 3.7 mg/day and maximum dose was 10.0 ± 5.3 mg/day. The authors did not report any serious adverse event, but fatigue (in 15.2% of the patients) and, less frequently, akathisia, sleepiness and decline of blood pressure were observed.

Comparison trials

Skrobik *et al.* in an open prospective randomized trial compared the efficacy and safety profile of olanzapine and haloperidol in the treatment of delirium in a critical care setting.[15] Twenty-eight out of the 73 recruited patients (age range 18–75 years) received olanzapine (mean 4.54 mg/day, dose range 2.5–13.5 mg/day) and the DI was measured at baseline and again 5 days after treatment to assess treatment effects of both. Clinical improvement was similar in both arms, whereas haloperidol was associated with extrapyramidal side-effects, because six out of 45 patients presented such symptoms, measured on the Ross Chouinard and Simpson-Angus scales. Patients

on olanzapine had no extrapyramidal manifestations. Mean DI score in the olanzapine-treated group dropped from 6.6 ± 1.2 at baseline to 5.5 ± 1.1 after treatment. The study was limited by the fact that it was not blinded, and this was noted by the authors.

Han and Kim compared the efficacy of haloperidol and risperidone in a randomized double-blind trial.[18] They recruited 28 individuals with delirium; 12 were in the risperidone arm (mean age 65.8 years). Both arms received a flexible-dose regimen over 7 days. They assessed delirium severity on the MDAS. Scores for each group decreased significantly over the study period, but the differences between groups were not statistically significant. They did not find any significant difference in the frequency of response to the drugs between groups. One patient in the haloperidol group experienced mild akathisia, but they did not record any other clinical significant side-effect.

The only study so far that compared two atypical agents in the treatment of delirium was that by Lee *et al.*[30] These authors conducted a prospective, randomized, open-label study to investigate efficacy and tolerability of quetiapine and amisulpride in the treatment of delirium. They also evaluated sleep quality and its relation to recovery time. Forty individuals with delirium were recruited in both arms, whereas the study was completed by 15 subjects in the amisulpride group and 16 subjects in the quetiapine group. Efficacy measurements were the DRS-R-98 and the CGI-S. Mean duration of stabilization was 6.3 ± 4.4 days for the amisulpride group and 7.4 ± 4.1 days for the quetiapine group. Total sleep time and quality were not different between the groups. Duration of stabilization was inversely correlated to the sleep quality and length. DRS-R-98 was statistically significantly reduced in both groups (from 10.5 ± 4.1 to 3.5 ± 1.4 and from 10.1 ± 4.1 to 3.5 ± 2.6, respectively) and there was no between-group difference. One patient from each group dropped out of the study due to oversedation. Extrapyramidal adverse events were observed in neither group.

Kim *et al.* investigated the optimal doses of haloperidol and risperidone and the association between treatment response and dopamine transporter gene polymorphisms in delirium patients in a prospective open-label study.[22] Forty-two participants (mean age 71.26 years) received either haloperidol or risperidone in a flexible-dosage regimen. The dosage was adjusted according to symptoms severity. A total of 18 participants received risperidone. Risperidone dose on the recovery day was 1.19 ± 1.14 mg/day. The mean response time for the risperidone-treated group was 4.81 ± 3.43 days. DRS-R-98 was used to assess efficacy. The relative scores were 21.61 ± 4.2 at baseline and 9.72 ± 4.87 at recovery day. By the seventh day 15 patients (77.8%) had responded to the risperidone treatment. No patient developed EPS during the study period. One patient in the haloperidol group experienced mild, transient drowsiness.

Retrospective studies

Sipahimalani and Masand, based on a retrospective chart review, compared olanzapine and haloperidol in the treatment of delirium.[12] Eleven elderly individuals with delirium had received olanzapine at a mean dose of 8.4 ± 3.4 mg and 11 individuals with delirium had received haloperidol at a mean dose of 5.1 ± 3.5 mg. Efficacy was assessed with the DRS, which had a mean of 17.9 ± 4.4 at baseline as compared to 10.3 ± 4.8 after treatment for the olanzapine group. Five of the 11 olanzapine-treated individuals showed significant improvement (>50% in score reduction), similar to that obtained in the haloperidol group (six out of 11 with improvement). None of the olanzapine-treated patients presented side-effects, whereas five individuals in the haloperidol group experienced EPS or excessive sedation.

Liu *et al.* retrospectively analyzed data for 41 individuals with delirium (mean age 67.88 years) who received risperidone, and for 36 patients who received haloperidol.[20] Two psychiatrists examined the medical records and determined the global severity of the syndrome for each patient, using 10-point visual analog scales for hyperactive and hypoactive syndromes of delirium. Patients treated with haloperidol had severely hyperactive symptoms, while risperidone-treated patients (mean dose: 1.17 ± 0.76 mg/day) were older and had moderate hyperactive symptoms. Hyperactive symptom scores significantly reduced from 6.44 ± 0.84 before treatment to 0.20 ± 1.26 after treatment. Hypoactive symptoms scores were also significantly reduced from 3.85 ± 2.35 before treatment, to 0.4 ± 0.96 after treatment with risperidone. Only three patients in the risperidone group received anticholinergic medication, compared to 25 patients in the haloperidol group.

Schwartz and Masand retrospectively reviewed the medical records of 11 individuals with delirium (mean age 57.6 years) who were receiving quetiapine

at a mean dose of 211.4 mg/day.[24] Mean duration of treatment was 13 days. DRS scores dropped from 20.9 ± 2.3 before treatment initiation to 2.1 ± 1.1 after treatment. The results were compared to those of a group of 11 haloperidol-treated delirious patients. The two compounds were equal in terms of efficacy, but two patients on haloperidol developed EPS and discontinued the drug. Two patients on quetiapine presented mild–moderate sedation.

More recently, Ushijima *et al.* retrospectively studied data involving 16 elderly patients (mean age 84.9 years; range 67–94 years) with delirium who were treated either with perospirone ($n = 9$) or risperidone ($n = 7$).[33] They found that total DRS scores were significantly decreased from baseline (from 22.8 ± 2.9 to 16.3 ± 5.9 and from 23.0 ± 2.8 to 18.6 ± 4.4, respectively) on the 10th day of treatment. Minor adverse events, namely dizziness and somnolence, were recorded in four patients on perospirone and three patients on risperidone, while one patient of the latter group experienced EPS.

There was also a recent prophylaxis study assessing the efficacy of risperidone for prevention of postoperative delirium in patients undergoing cardiac surgery.[34] In that randomized, double-blind, placebo-controlled study 126 patients were assigned to receive either a single dose of 1-mg risperidone or placebo. Postoperative delirium was assessed using the Confusion Assessment Method for intensive care unit. The incidence of postoperative delirium in the risperidone group was significantly lower than the placebo group (11.1% vs 31.7% respectively, $P = 0.009$).

DISCUSSION

We conducted the present study to examine existing evidence on the use of atypical antipsychotics in the treatment of delirium. We found that since 1997, when the first study was published,[11] until 2008, a total number of 23 trials have been conducted, and a large number of individuals with delirium have participated in these. All studies reported a significant reduction in delirium symptomatology after atypical antipsychotic administration (Table 1), but no study included a blinded placebo comparison group. Considering that delirium has a fluctuating course and that treatment of the underlying medical disorders may result in the resolution of the symptomatology, it is unclear whether the observed symptom reduction is accounted for by the administration of atypical agents.

The vast majority of trials are not well-controlled trials, because only one is double blind,[18] all but one[19] are single center, and four were retrospective medical records review.[12,20,24,33] Only three were randomized.[15,18,30] Each of them recruited a small number of patients resulting in a doubtful study power.

Despite these important limitations, all trials included in the present review assessed efficacy by measuring the performance of each person at least twice: before treatment initiation and at symptom resolution. Three studies also measured performance at different time-points from drug administration to the end of treatment[14,23,27]. Different scales in each trial were used to assess efficacy. Safety was assessed either using specific scales[29] or by investigator judgment,[14] and adverse events were reported by the patients themselves. Antipsychotic administration was discontinued when resolution in delirium symptoms was achieved; this duration was approximately 1 week for all medications used. In total, dosage of all medications was lower than that used to treat schizophrenia patients.

When a comparison with haloperidol was performed, this indicated the same efficacy between treatment options but atypical medications were better tolerated.[12,15,18] A recent Cochrane review on the use of antipsychotics for delirium, reported no significant differences in the overall effect on delirium of olanzapine or risperidone compared with haloperidol.[35] It further suggested that these atypical antipsychotics be considered as first-line drugs in patients who require high-dose haloperidol for the control of delirium or for those individuals who have an increased likelihood of developing extrapyramidal or cardiac manifestations of haloperidol toxicity.

Taken together, the present findings indicate that atypical antipsychotic medication could be a reliable alternative to haloperidol in the treatment of delirium. This is even more important for patients who may be vulnerable to the development of EPS, or who may have an underlying cardiologic disease.

The limitations of the studies include the sample heterogeneity, small sample sizes, use of different rating scales for delirium, and lack of adequately controlled trials. It is also possible that we have missed important studies published in a language different from English, because we restricted the search to only English-language publications.

Regarding implications for future research, we believe that future studies should be adequately controlled, well-designed and sufficiently powered to ensure validity of the results. Last, we would recommend that future research address safety evaluation in a more concise manner, focusing on short-term adverse effects of atypical antipsychotics. Some well-recognized long-term side-effects of atypical antipsychotics such as obesity and metabolic dysregulation[36] may not be considered as problematic in delirium patients because the treatment of delirium requires only short-term drug administration. The substantial difference in cost between atypical and conventional agents may also not be relevant due to the short treatment duration.

Regarding comparative efficacy of atypical antipsychotics in the treatment of delirium, there appear to be no differences between olanzapine, risperidone and quetiapine, the three most studied agents. The relatively small number of participants for each drug, however, does not allow any firm conclusions to be made. It has been demonstrated that some atypical agents are more efficacious than conventional antipsychotics in the treatment of schizophrenia.[37] These authors also indicated that there may be differences in efficacy among atypical antipsychotics. Such a question regarding comparative efficacy of atypical antipsychotics in delirium may be the subject of future research.

Finally, ongoing research on the pathophysiology of delirium may offer an opportunity for a better and deeper understanding of the development and progress of this syndrome, as well as for the role of atypical antipsychotics in the symptomatic treatment.

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