

Review Article

Efficacy and Tolerability of Atypical Antipsychotics in the Treatment of Delirium: A Systematic Review of the Literature

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Background: *Although haloperidol is the most widely used drug in the treatment of delirium, evidence on the relevance of atypical antipsychotics (AAPs) is growing.*
Objective: *To review the literature on the efficacy and tolerability of AAPs in the treatment of delirium.*
Methods: *A systematic search of the literature published before April 2018 was performed on PubMed using the following search strings: "Delirium" and "Atypical antipsychotics", "Novel antipsychotics", "New antipsychotics", "Quetiapine", "Olanzapine", "Aripiprazole", "Risperidone", "Paliperidone", "Clozapine", "Asenapine", "Iloperidone", "Amisulpiride", "Ziprasidone", "Zotepine", "Sertindole", "Lurasidone" or "Perospirone".*
Results: *Twelve randomized controlled trials (RCTs) and 22 open trials were considered. Despite an overall lack of large-scale RCTs, there is some evidence supporting the efficacy of olanzapine and quetiapine in placebo controlled trials. In a recent and large RCT in elderly patients, risperidone and/or haloperidol were associated with a significantly worse outcome than placebo. While preliminary, the current comparative studies suggest that haloperidol and the AAPs olanzapine, quetiapine and risperidone are similarly effective, although treatment with AAPs is associated with a reduced incidence of extrapyramidal symptoms. Ziprasidone was not shown to be effective. No RCTs are available for other AAPs.*
Conclusions: *Although the current evidence of the efficacy and tolerability of AAPs in the treatment of delirium is limited and the heterogeneity of the data precluded a meta-analysis, olanzapine and quetiapine seem to be adequate alternatives to haloperidol, especially in patients who are vulnerable for extrapyramidal symptoms, who require sedation or who have a history of haloperidol intolerance. Evidently, larger-scale RCTs are urgently required.*

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Key words: Delirium, Atypical antipsychotics, New antipsychotics, Novel antipsychotics.

INTRODUCTION

Delirium is a common, acute, and serious neuropsychiatric syndrome characterized by fluctuating levels of consciousness and impairment of cognitive functioning. Occurrence rates in the general hospital range from 10% to 31%, depending on patient and department characteristics and the assessment methods used. Particularly older and severely ill patients are at high risk of delirium. The condition is associated with increased length of hospital stay and higher rates of institutionalization and mortality while in hospital and 12 months after discharge.[1]

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To date, haloperidol has been the most widely used drug in the treatment of delirium, mainly because it is relatively safe in somatically ill and older patients, with minimal anticholinergic and sedative effects.[2] In their systematic review conducted in 2007, Seitz et al.[3] stated that up till then there were no published double-blind, randomized, placebo-controlled trials to establish the efficacy or safety of any antipsychotic medication in the management of delirium. Although haloperidol has long been the only antipsychotic recommended for the management of the syndrome, a meta-analysis also conducted in 2007 concludes that there was no systematic evidence that, taken in low dosages, the agent's efficacy was superior to that of olanzapine and risperidone or that adverse effects were more frequent than recorded for the latter drugs. The authors noted that high-dose haloperidol was associated with a higher incidence of side effects, mainly parkinsonism, than the atypical antipsychotics (AAPs). However, the authors base their conclusions on 3 studies of which only 2 explored treatment rather than prevention effects.[4]

In the most recent guidelines of the National Institute for Health and Care Excellence olanzapine is recommended as an alternative to haloperidol when (i) a person with delirium is distressed or (ii) is considered a risk to himself or others when verbal and nonverbal de-escalation techniques are ineffective or inappropriate.[5] Moreover, due to its extrapyramidal symptoms (EPS), the use of haloperidol is contraindicated in patients with Lewy body dementia and Parkinson's disease. In their 2013 review on the treatment of delirium with antipsychotics, Meagher et al.[6] found a clinical response in around 75% of the delirious patients having received short-term treatment with low-dose antipsychotics. They could not find any significant differences in the efficacy of haloperidol versus atypical agents but do report higher rates of EPS with haloperidol. They note that it is not known to what extent the therapeutic effects can be explained by the alleviation of specific symptoms (e.g., sleep or behavioral disturbances) or by a syndromal effect that encompasses both cognitive and noncognitive symptoms of delirium. Notably, the authors did not include the important 2006 study of Hu et al.[7] in their review.

With regard to more specific populations of patients, having conducted a broad review on delirium in older people, Inouye et al.[8] stated there was no convincing, reproducible evidence that any of the researched pharmacological treatments are effective either in the prevention or the treatment of the syndrome. They even observed that the outcome of olanzapine was worse than placebo in the prevention of delirium.[9] Furthermore, Barr et al.[10] published an update on the clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit (ICU). They concluded that there was no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients, while AAPs may do so.

Taking into account the reports of more recent trials and also including the study of Hu et al. 2006,[7] in the current study we provide a systematic review of the literature on the efficacy and tolerability of AAPs in the treatment of delirium while examining whether AAPs are indeed adequate alternatives for haloperidol.

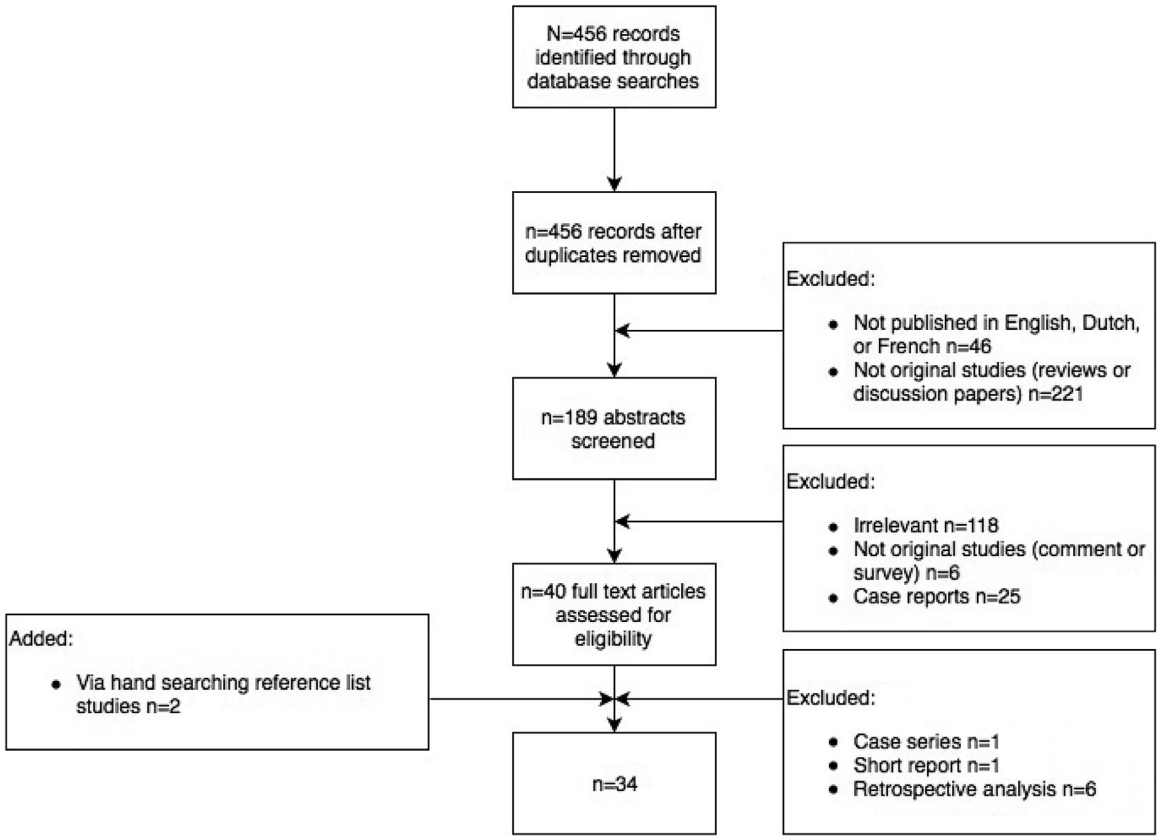
METHODS

Without imposing a preliminary restriction of language, we performed a systematic search of the literature published before April 2018 using PubMed. As alcohol-related and nonalcohol-related delirium are 2 separate disorders requiring a different approach, we opted to focus on the latter only.

We used the following search terms “delirium” or “acute confusional state” and “atypical antipsychotics”, “novel antipsychotics”, “new antipsychotics”, “quetiapine”, “olanzapine”, “aripiprazole”, “risperidone”, “paliperidone”, “clozapine”, “asenapine”, “iloperidone”, “amisulpiride”, “ziprasidone”, “zotepine”, “sertindole”, “lurasidone” or “perospirone”. An additional manual search was conducted using the reference lists of all relevant articles.

Eligible studies needed to report 4 outcome measures: (i) number of delirium days; (ii) severity of delirium; (iii) length of hospital stay; and (iv) mortality. From the resulting publications, we included randomized controlled trials (RCTs) in adult patients (18 years and older) written in English, Dutch, or French that compared delirium treatment with AAPs to placebo or an active comparison drug. Because of the relative scarcity of RCTs, we also included non-controlled clinical trials. Studies on the pharmacological prevention of delirium and studies on alcohol-related delirium were excluded. See Figure 1 for an overview of the search and selection process.

FIGURE 1. Search Strategy



RESULTS

Of the 902 citations screened for eligibility, 34 publications met our selection criteria, of which 12 were RCTs (see Table 1) and 22 noncontrolled clinical trials (see Table 2). We will discuss our findings for the RCTs and open trials separately.

Randomised Controlled Trials

Five double-blinded RCTs compared AAPs to placebo[7,11–14], another 6 (both single- and double-blinded RCTs) AAPs to haloperidol,[15–19] with 1 single-blinded RCT comparing 2 AAPs[20] (Table 1).

RCTs with Placebo Control

Comparing haloperidol and risperidone with placebo in patients receiving palliative care, Agar et al.[11] performed the largest RCT. The primary outcome was the mean of the last 2 delirium symptom scores as assessed with the Memorial Delirium Assessment Scale[21] (MDAS) while correcting for baseline scores. In the primary intention-to-treat analysis, the endpoint scores of the participants in the risperidone arm were significantly higher than those of the participants in the placebo arm, with scores for those taking haloperidol being higher than those receiving placebo. Compared with placebo, patients in both active arms had more EPS. Overall survival was higher in the placebo group than it was in the haloperidol group, but this was not significant for placebo vs risperidone, with patients receiving risperidone and haloperidol being more likely to die than those receiving placebo (29% and 73%, respectively). Symptom control in the patients taking placebo was best, without increased use of rescue midazolam and less dose titration for patients under the age of 65 years.

TABLE 1. Summary of Randomised Clinical Trials with Atypical Antipsychotics

Author	Year	Patients	Scale	Drug	Sample size	Age (years, mean (SD))	*Conclusion*
Agar et al.[11]	2017	Palliative care	MDAS	Risperidone Haloperidol Placebo	82 81 84	74.5 (10.6) 76.5 (8.2) 73.8 (10.7)	*In patients receiving palliative care, individualized management of delirium precipitants and supportive strategies result in lower scores and shorter duration of distressing delirium symptoms than when risperidone or haloperidol are administered.*
Tahir et al.[12]	2010	Hospitalized	DRS-R-98	Quetiapine Placebo	21 21	84.1 (9.45) 84.3 (7.16)	*Quetiapine has the potential to more quickly reduce the severity of noncognitive aspects of delirium than placebo.*
Devlin et al.[13]	2010	ICU	ICDSC	Quetiapine Placebo	18 18	62.4 (14.56) 63.6 (15.3)	*Quetiapine may resolve several intensive care unit (ICU) delirium symptoms faster than placebo.*
Girard et al.[14]	2010	ICU	CAM-ICU	Ziprasidone Haloperidol Placebo	54 35 14	54 (47-66) 51 (35-59) 56 (35-68)	*Compared to placebo, neither ziprasidone nor haloperidol increases the number of days alive without delirium or coma, nor do they cause more adverse outcomes.*
Hu et al.[7]	2006	Hospitalized	CGI-SI, CGI-GI	Olanzapine Haloperidol Placebo	74 72 29		*Olanzapine and haloperidol have similar effects when treating senile delirium. However, olanzapine is faster to take effect than haloperidol. Both olanzapine and haloperidol had a faster response and were more effective in ameliorating delirium symptoms than placebo.*
Maneeton et al.[15]	2013	Hospitalized	DRS-R-98	Quetiapine Haloperidol	24 28	56.6 (12.0) 57.0 (11.9)	*Low-dose quetiapine and haloperidol may be equally effective and safe in controlling delirium symptoms.*
Grover et al.[16]	2016	Hospitalized	DRS-R-98	Quetiapine Haloperidol	31 32	48.51 (19.75) 44.40 (16.76)	*Quetiapine is as effective as haloperidol in the management of delirium.*
Han and Kim[17]	2004	Hospitalized	DRS, MDAS	Risperidone Haloperidol	12 12	65.6 (8.3) 66.5 (15.9)	*No differences were found in the efficacy or response rates of haloperidol and risperidone in patients with delirium.*
Grover et al.[19]	2011	Hospitalized	DRS-R-98	Olanzapine Risperidone Haloperidol	23 21 20	45.39 (19.18) 46.50 (14.51) 44.09 (16.48)	*Risperidone and olanzapine are as efficacious as haloperidol in the treatment of delirium.*
Kim et al.[20]	2010	Hospitalized	DRS-R-98	Risperidone Olanzapine	12 8	Range: 36-82	*Risperidone and olanzapine were equally effective in reducing delirium symptoms. The response to risperidone was poorer in the older age group.*
Skrobik et al.[18]	2004	ICU	ICU-DSC	Olanzapine Haloperidol	25 45	67 (6.04) 63.26 (11.66)	*Olanzapine is a safe alternative to haloperidol in delirious critical-care patients and may be of particular interest for those in whom haloperidol is contraindicated.*
Jain et al.[23]	2017	Hospitalized	CAM, MDAS	Olanzapine Haloperidol	47 53		*Low-dose haloperidol and olanzapine were equally efficacious and well tolerated in delirium.*

CAM = Confusion Assessment Method; CAM-ICU = Confusion Assessment Method for the ICU; CGI-GI = Clinical Global Impression Scale-Global Improvement; CGI-SI = Clinical Global Impression Scale-Severity of Illness; DRS = Delirium Rating Scale; DRS-R-98 = Delirium Rating Scale-Revised-98; ICDSC = Intensive Care Delirium Screening Checklist; ICU = Intensive Care Unit; MDAS = Memorial Delirium Assessment Scale.

TABLE 2. Summary of Open Trials with Atypical Antipsychotics

Author	Year	Population	Rating scale	Study drug/Control	Sample size, n	Age, years (mean (SD))
Maneeton et al.[24]	2007	Hospitalized	DRS	Quetiapine	17	55.6 (18.6)
Sasaki et al.[25]	2003	Hospitalized	DRS-J	Quetiapine	12	67.3 (14.8)
Omura and Amano[26]	2003	Hospitalized	DRS	Quetiapine	24	76.5
Kim et al.[27]	2003	Hospitalized	DRS	Quetiapine	12	74 (7)
Tanimukai et al.[28]	2014	Hospitalized	MDAS	Risperidone	6	72.17 (10.53)
				Olanzapine	3	70.33 (6.23)
				Quetiapine	11	73.09 (5.89)
				Haloperidol	7	70.43 (21.63)
Yoon et al.[29]	2013	Hospitalized	DRS-K	Risperidone	21	70.1 (9.5)
				Olanzapine	18	69.5 (15.9)
				Quetiapine	18	73.3 (10.7)
				Haloperidol	23	74.0 (9.9)
Lee et al.[30]	2005	Hospitalized	DRS-R-98	Amisulpride	16	60.8 (18.4)
				Quetiapine	15	63.1 (14.5)
Pintor et al.[43]	2009	Hospitalized	DRS	Amisulpride	40	73 (15.7)
Kim et al.[31]	2005	Hospitalized	DRS-R-98	Risperidone	18	71.26 (7.22)
				Haloperidol	24	
Horikawa et al.[32]	2003	Hospitalized	DRS	Risperidone	10	56.8 (22.7)
Parellada et al.[33]	2009	Hospitalized	DRS	Risperidone	64	67.3 (11.4)
Kishi et al.[34]	2012	Cancer patients	DRS-R-98	Risperidone	29	68.9 (12.5)
Mittal et al.[35]	2004	Hospitalized	DRS	Risperidone	10	64.7 (4.8)
Ikezawa et al.[36]	2008	Hospitalized	DRS	Risperidone	22	73.6 (7.8)
Boettger et al.[37]	2015	Cancer patients	MDAS	Risperidone	21	67.2 (11.7)
				Olanzapine	21	35.6 (13.4)
				Aripiprazole	21	69.6 (11.9)
				Haloperidol	21	64.0 (11.7)
Sipahimalani and Masand[38]	1998	Hospitalized	DRS	Olanzapine	11	63.5 (23.2)
				Haloperidol	11	64 (18.3)
Breitbart et al.[39]	2002	Cancer patients	MDAS	Olanzapine	79	69.6 (11.9)
Kim et al.[40]	2001	Hospitalized	DRS	Olanzapine	20	45.8 (18.3)
Boettger et al.[41]	2011	Hospitalized	MDAS	Aripiprazole	21	69.6 (11.9)
				Haloperidol	21	64.0 (11.7)
Boettger and Breitbart[42]	2011	Cancer patients	MDAS	Aripiprazole	21	69.6 (11.9)
Yoon et al.[44]	2011	Hospitalized	MDAS	Paliperidone	15	66.09 (20.69)
Takeuchi et al.[45]	2007	Hospitalized	DRS-R-98	Perospirone	38	69.4 (10.1)

DRS = Delirium Rating Scale; DRS-J = Japanese version of the DRS; DRS-K = Korean version of the DRS; DRS-R-98 = Delirium Rating Scale-Revised-98; MDAS = Memorial Delirium Assessment Scale.

The second largest RCT contrasted the effects of olanzapine and haloperidol with placebo on senile delirium.[7] The post-treatment scores of the Intensive Care Delirium Screening Checklist[22] (CGI-SI) were clinically significantly decreased in all 3 groups, with reductions of 82.4% for olanzapine, 87.5% for haloperidol, and 31.0% for placebo being noted. Both olanzapine and haloperidol already began to take effect at low dosages, with the effects of olanzapine manifesting the fastest, followed by haloperidol, while the effects of placebo were the slowest to occur. The patients treated with olanzapine reported more drowsiness, while there was dry mouth and EPS in the patients receiving haloperidol.

Girard et al.[14] found that, compared with placebo, neither haloperidol nor ziprasidone significantly increased the number of days patients survived without delirium or coma in an ICU setting. The authors also found no differences in the duration of delirium and coma for the 2 active agents.

Two small studies comparing quetiapine to placebo both suggested a more rapid decrease of delirium and its noncognitive symptoms following quetiapine.[12,13]

RCTs with an Active Comparator (No Placebo)

Two studies compared quetiapine to haloperidol, with neither finding any significant differences in their

efficacy.[15,16] The agents' improvement and tolerability rates were also similar.[15] Hypersomnia was common in the quetiapine group but not significantly higher than it was in the haloperidol group. Grover et al.[16] reported the effectiveness of both medications to be similar in their adult and elderly (≥60 years) patients.

We found 4 studies evaluating haloperidol, risperidone, and/or olanzapine.[17,19,20,23] Overall, neither risperidone and haloperidol nor risperidone and olanzapine showed any differences in efficacy or the development of side effects. One study found that, compared to olanzapine, the response to risperidone was significantly poorer in patients ≥70 years than it was in those <70 years.[20]

Skrobik et al.[14] compared the safety and response profiles of olanzapine and haloperidol in delirious patients in a critical care setting and found a comparable reduction in the delirium index over 5 days in both groups without differences in benzodiazepine doses. No side effects were noted for the olanzapine group, whereas the use of haloperidol was associated with EPS.

Open Trials with and Without an Active Comparison Group

The non-controlled trials are listed in Table 2. In seven, quetiapine was found to be effective and safe in the treatment of delirium,[24–30] which was also the case in eight of the nine trials investigating the effects of risperidone.[29,31–37]

Four open trials concluded that olanzapine was a potential alternative to haloperidol in the treatment of delirium as the AAP was found to be as effective.[28,29,37,38] It was proposed that haloperidol may cause more EPS whereas olanzapine may be more sedating.[37] Two single-drug trials investigating olanzapine found the agent to be safe and effective[39,40], which was also the conclusion of 3 studies assessing aripiprazol[37,41,42] and 2 studies reporting on amisulpride.[31,43] In one study, a low dose of paliperidone was well tolerated and effective in reducing delirium symptoms,[44] while, finally, another single-drug study suggested perospirone to be effective and safe.[45]

DISCUSSION

We conducted a systematic review of the literature to examine the evidence on the efficacy and tolerability of AAPs in the treatment of delirium. Although olanzapine was found to be as effective and as safe as haloperidol in several controlled trials, with uncontrolled studies also reporting beneficial effects and hence deeming olanzapine a safe alternative to haloperidol, the data are not sufficiently robust to support the agent's efficacy.[7,12–14,19–20,23,29–32] Of the other AAPs reported on, only quetiapine, risperidone, and ziprasidone had also been studied in RCT designs. Small-scale RCTs suggest quetiapine to be an effective and safe alternative to haloperidol, as do the trials on risperidone barring one, the largest RCT, which reported poorer outcomes compared to placebo, with the chance of survival being lower after haloperidol and risperidone.[11] The various open trials investigating these 3 and other AAPs (amisulpride, aripiprazole, paliperidone, and perospirone) we reviewed also concluded the agents to be effective and safe in treating delirium.

A meta-analysis published in 2016 investigated both the prevention and treatment of delirium. Of the 19 studies included, 12 treatment trials examined both typical and AAPs, with 5 of these comparing antipsychotics to placebo or no treatment. Three of these studies concerned AAPs: 2 investigating quetiapine (n = 78) and 1 ziprasidone (n = 101). The other 7 studies compared the effectiveness of different antipsychotics. Pointing to the high heterogeneity of the studies reviewed, the authors' overall conclusion was that, in contrast to the findings described above, the use of antipsychotics was not associated with a change in delirium duration or severity, length of hospital or ICU stay, or mortality. However, as the primary aim of this meta-analysis was not the investigation of AAPs but antipsychotics in general, this led to a very broad scope of agents being described in limited numbers of studies. This raises questions about the validity of the authors' conclusions. Also, it might be interesting to look at different populations, such as ICU patients, given that some of the studies we evaluated point to the drugs' efficacy and safety in this population.[13,18] Furthermore, Neufeld et al.[46] did not differentiate the severity of delirium, agitation or psychosis, which may be highly relevant in the choice of treatment where, for example, sedation is desired in patients in a very agitated state.

As the side-effect profiles for antipsychotics differ (in terms of weight gain, EPS, prolactin increase, QTc prolongation, and sedation), it is desirable to make the

choice of antipsychotic and its dose contingent on patient characteristics. However, this is complicated by the fact that most AAPs are only available in (melt) tablet form, whereas haloperidol is available in tablets, drops, and (intramuscular or intravenous) injection solutions. Notably, this approach was adopted in only one of the studies we reviewed. Although Kim et al.[20] observed that the side-effect profiles of the 2 AAPs they investigated were similar, they found risperidone to be less effective in older patients (70+) than olanzapine. In this perspective, it is noteworthy that Agar et al.[11], who found a lower survival rate with risperidone compared to nonpharmacological treatment, also investigated an older population (patients had a mean age of 74.5 years), as did Tahir et al.,[12] who reported a positive effect of quetiapine on delirium. If the side effects of AAPs in patients with delirium were to be better delineated, clinicians could base their decision on the patient's clinical profile and the type of delirium. They could then opt for an antipsychotic with a sedative profile to treat hyperactive delirium and another for hypoactive delirium, for instance. At this point, there is insufficient evidence to make any recommendations, underscoring the need for research into AAP safety profiles in relation to patient and delirium profiles.

Although it is known to be one of the less potent antipsychotics, with dosages varying widely across trials, some small studies suggest a positive influence on delirium symptoms for quetiapine.[47] But what may then be its mechanism of action? Is it its sedative power that dampens the delirium symptoms? It is furthermore noteworthy that for the more sedative AAPs like quetiapine and olanzapine, all studies used small dosages. Looking at the RCTs, the mean daily dosages for quetiapine were 67.6 ± 9.7[15], 110 (88−191)[13] and 31.83 ± 4.10[16] mg/day and for olanzapine 2.4 ± 1.7[20] and 3.05 ± 1.44[19] mg/day. Comparing haloperidol and quetiapine, one study used a mean dose of 40 mg, which relatively high dose may explain the low level of side effects for the AAP.[12] This again raises the mechanism-of-action question. Is delirium resolved more rapidly due to the antipsychotic potential of these drugs or do they provide relief for the behavioral symptoms that occur with delirium, such as agitation, shouting, and wandering? Causing sedation, AAPs may then relieve a patient's suffering while buying the clinician time to resolve the cause and facilitating factors of the delirium. Morandi et al.[48] conducted a survey among European delirium specialists looking for their thoughts and actions in treating the syndrome. They report that for the management of hyperactive delirium the first-line choice (61%) was a combination of nonpharmacological and pharmacological approaches, while in 67% of cases of hypoactive delirium a nonpharmacological regimen was opted for. In the pharmacological management schemes the most frequently prescribed drug was haloperidol (62% for hyperactive and 46% for hypoactive delirium).

Quetiapine and olanzapine are also known for their anticholinergic side effects, particularly a dry mouth, constipation, urine retention, mydriasis, and sinus tachycardia. In older persons, some of these adverse events may easily cause confusion and delirium.[49] Evaluating the longitudinal association between the use of anticholinergic medications and the severity of delirium symptoms, Han et al.[50] found that exposure to anticholinergic agents coincided with an increase in delirium symptom severity in elderly medical inpatients. Once more, we can ask ourselves whether these drugs treat delirium or merely cause sedation. The studies we reviewed do not provide any answers as to their mechanisms of action in relation to these side effects or their use in specific patient groups.

Some limitations should be considered when interpreting the results of our review. First, we found only 12 RCTs, with treatment groups ranging from 8 to 84 patients. Six of the 12 trials had treatment groups of 21 patients or less. Most other studies were open trials, again with small sample sizes varying from 3 to 79 patients. Another problem was the methodological heterogeneity of the studies, with effectiveness and side-effect measures and study-group characteristics differing widely. Most studies used a scale to evaluate delirium, most frequently the Delirium Rating Scale-Revised-98 (DRS-R-98) or the DRS[51,52], followed by the Memorial Delirium Assessment Scale[21] and last the Confusion Assessment Method for the ICU (CAM-ICU)[53]. Third, most studies did not use a validated rating scale to assess the side effects of the pharmacotherapy and those that did used different scales. Featuring in 2 RCTs and 6 open trials, the Udvalg for Kliniske Undersogelser side-effect rating scale[54] was used the most. Overall, outcomes reported appear to show a trend toward more EPS with haloperidol and risperidone and more sedation with olanzapine. Finally, the patients that were diagnosed with delirium were either hospitalized, being treated at medical or surgical wards,

or had been admitted to an ICU, with the etiologies of delirium being either medical or surgical.

While taking these limitations into account, we can summarize that some RCTs and open studies support the efficacy of olanzapine and quetiapine in the treatment of delirium. In a recent and large RCT in elderly patients in a palliative care unit, risperidone, and/or haloperidol were associated with a significantly worse outcome than placebo. Ziprasidone was not shown to be effective. The data on other AAPs are scarce, preventing any conclusions as to their effectiveness. Based on the current findings we can tentatively conclude that, although haloperidol is the most widely used drug to treat delirium and the treatment of choice in most delirium guidelines, there is yet no evidence that AAPs are less efficacious than haloperidol. Considering the high burden of delirium, we feel additional larger-scale RCTs that evaluate the efficacy, tolerability, and side-effect profiles of AAPs in various patient groups compared to haloperidol and placebo are urgently required. Such studies may then hopefully result in guidelines that will help clinicians target antipsychotics to patient groups and different types of delirium. Unfortunately, we could not find any new placebo-controlled studies in this field on ClinicalTrials.gov.[55]

References

1. Siddiqi N, House AO, Holmes JD: Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing 2006; 35(4):350–364
2. 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(11):1966–1973
3. Seitz DP, Gill SS, van Zyl LT: Antipsychotics in the treatment of delirium: a systematic review. J Clin Psychiatry 2007; 68(1):11–21
4. Lonergan E, Britton AM, Luxenberg J, Wyller T: Antipsychotics for delirium. Cochrane Database Syst Rev 2007; (2):CD005594
5. National clinical guideline center: DELIRIUM. Diagn Prev Manag 2010
6. Meagher DJ, McLoughlin L, Leonard M, Hannon N, Dunne C: O'Regan N: what do we really know about the treatment of delirium with antipsychotics? Ten key issues for delirium pharmacotherapy. Am J Geriatr Psychiatry 2013; 21(12):1223–1238
7. Hu H, Deng W, Yang H, Liu Y: Olanzapine and haloperidol for senile delirium: a randomized controlled observation. Chin J Clin Rehabil 2006; 10(42):188–190
8. Inouye SK, Westendorp RGJ, Saczynski JS: Delirium in elderly people. Lancet 2014; 383(9920):911–922
9. Larsen KA, Kelly SE, Stern TA, et al: Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. Psychosomatics 2010; 51(5):409–418
10. Barr J, Fraser GL, Puntillo K, et al: Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013; 41(1):263–306
11. Agar MR, Lawlor PG, Quinn S, et al: Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. JAMA Intern Med 2017; 177(1):34–42
12. Tahir T, E Eeles, Karapareddy V, et al: A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. J Psychosom Res 2010; 69(5):485–490
13. Devlin JW, Roberts RJ, Fong JJ, et al: Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2010; 38(2):419–427
14. Girard TD, Pandharipande PP, Carson SS, et al: Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med 2010; 38(2):428–437
15. Maneeton B, Maneeton N, Srisurapanont M, Chittawatanarat K: Quetiapine versus haloperidol in the treatment of delirium: a double-blind, randomized, controlled trial. Drug Des Dev Ther 2013; 7:657–667
16. Grover S, Mahajan S, Chakrabarti S, Avasthi A: Comparative effectiveness of quetiapine and haloperidol in delirium: a single blind randomized controlled study. World J Psychiatry 2016; 6(3):365–371
17. Han C-S, Kim Y-K: A double-blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics 2004; 45(4):297–301
18. Skrobik YK, Bergeron N, Dumont M, Gottfried SB: Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004; 30(3):444–449
19. Grover S, Kumar V, Chakrabarti S: Comparative efficacy study of haloperidol, olanzapine and risperidone in delirium. J Psychosom Res 2011; 71(4):277–281
20. Kim S-W, Yoo J-A, Lee S-Y, et al: Risperidone versus olanzapine for the treatment of delirium. Hum Psychopharmacol 2010; 25(4):298–302
21. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S: The memorial delirium assessment scale. J Pain Symptom Manag 1997; 13(3):128–137
22. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y: Intensive care delirium screening checklist: evaluation of a new screening tool. Intensive Care Med 2001; 27(5):859–864
23. Jain R, Arun P, Sidana A, Sachdev A: Comparison of efficacy of haloperidol and olanzapine in the treatment of delirium. Indian J Psychiatry 2017; 59(4):451–456

24. Maneeton B, Maneeton N, Srisurapanont M: An open-label study of quetiapine for delirium. J Med Assoc Thai 2007; 90 (10):2158–2163
25. 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
26. Omura K AN: Clinical experience of quetiapine in 24 elderly patients with delirium. Psychogeriatrics 2003; 3:69–72
27. Kim KY, Bader GM, Kotlyar V, Gropper D: Treatment of delirium in older adults with quetiapine. J Geriatr Psychiatry Neurol 2003; 16(1):29–31
28. Tanimukai H, Tsujimoto H, Matsuda Y, et al: Novel therapeutic strategies for delirium in patients with cancer: a preliminary study. Am J Hosp Palliat Care 2016; 33(5):456–462
29. Yoon H-J, Park K-M, Choi W-J, et al: Efficacy and safety of haloperidol versus atypical antipsychotic medications in the treatment of delirium. BMC Psychiatry 2013; 13(1):240
30. Lee K-U, Won W-Y, Lee H-K, et al: Amisulpride versus quetiapine for the treatment of delirium: a randomized, open prospective study. Int Clin Psychopharmacol 2005; 20(6): 311–314
31. Kim J-Y, Jung I-K, Han C, et al: Antipsychotics and dopamine transporter gene polymorphisms in delirium patients. Psychiatry Clin Neurosci 2005; 59(2):183–188
32. Horikawa N, Yamazaki T, Miyamoto K, et al: Treatment for delirium with risperidone: results of a prospective open trial with 10 patients. Gen Hosp Psychiatry 2003; 25(4):289–292
33. Parellada E, Baeza I, de Pablo J, Martínez G: Risperidone in the treatment of patients with delirium. J Clin Psychiatry 2004; 65(3):348–353
34. Kishi Y, Kato M, Okuyama T, Thurber S: Treatment of delirium with risperidone in cancer patients. Psychiatry Clin Neurosci 2012; 66(5):411–417
35. Mittal D, a JimersonN, 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
36. Ikezawa K, Canuet L, Ishii R, Iwase M, Teshima Y TM: Efficacy of risperidone in the treatment of delirium in elderly patients. Psychogeriatrics 2008; 8:62–65
37. Boettger S, Jenewein J, Breitbart W: Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: a comparison of efficacy, safety, and side effects. Palliat Support Care 2015; 13(4):1079–1085
38. Sipahimalani A, Masand PS: Olanzapine in the treatment of delirium. Psychosomatics 1998; 39(5):422–430
39. 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
40. Kim KS, Pae CU, Chae JH, Bahk WM, Jun T: An open pilot trial of olanzapine for delirium in the Korean population. Psychiatry Clin Neurosci 2001; 55(5):515–519
41. Boettger S, Friedlander M, Breitbart W, Passik S: Aripiprazole and haloperidol in the treatment of delirium. Aust N Z J Psychiatry 2011; 45(6):477–482
42. Boettger S, Breitbart W: An open trial of aripiprazole for the treatment of delirium in hospitalized cancer patients. Palliat Support Care 2011; 9(4):351–357
43. Pintor L, Fuente E, Bailles E, Matrai S: Study on the efficacy and tolerability of amisulpride in medical/surgical inpatients with delirium admitted to a general hospital. Eur Psychiatry 2009; 24(7):450–455
44. Yoon H-K, Kim Y-K, Han C, et al: Paliperidone in the treatment of delirium: results of a prospective open-label pilot trial. Acta Neuropsychiatr 2011; 23(4):179–183
45. Takeuchi T, Furuta K, Hirasawa T, et al: Perospirone in the treatment of patients with delirium. Psychiatry Clin Neurosci 2007; 61(1):67–70
46. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM: Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. J Am Geriatr Soc 2016; 64(4):705–714
47. Leucht S, Cipriani A, Spineli L, et al: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013; 382(9896):951–962
48. Morandi A, Davis D, Taylor JK, et al: Consensus and variations in opinions on delirium care: a survey of European delirium specialists. Int Psychogeriatr 2013; 25(12):2067–2075
49. Dierick M, Claes S, De Nayer A, Cosyns P, Constant E, Souery D: Handboek psychofarmacotherapie. Gent: Academia Press; 2012
50. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M: Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001; 161(8):1099–1105
51. Adamis D, Slor CJ, Leonard M, et al: Reliability of Delirium Rating Scale (DRS) and Delirium Rating Scale-Revised-98 (DRS-R98) using variance-based multivariate modelling. J Psychiatr Res 2013; 47(7):966–971
52. Trzepacz PT, Mittal D, Torres R, et al: Validation of the Delirium Rating Scale-Revised-98: comparison with the Delirium Rating Scale and the cognitive test for delirium. J Neuropsychiatry Clin Neurosci 2001; 13(2):229–242
53. Gusmao-Flores D, Salluh JIF, Chalhub RA, Quarantini LC: The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. Crit Care 2012; 16(4):R115
54. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K: The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987; 334:1–100
55. U.S. National Library of Medicine: ClinicalTrials.gov