Efficacy and tolerability of atypical antipsychotics in the treatment of delirium : a systematic review of the literature

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Efficacy and tolerability of atypical antipsychotics in the treatment of delirium: a systematic review of the literature

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Abstract

Background: Delirium is an acute neurocognitive disorder characterised by fluctuating levels of consciousness and impairment of cognitive functioning. Although haloperidol is the most widely used drug in the treatment of the condition, evidence on the relevance of atypical antipsychotics is growing.

Objective: To review the literature on the efficacy and tolerability of atypical antipsychotics (AAPs) in the treatment of delirium.

Methods: A systematic search of the literature up to January 2017 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: Eleven randomised 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. The efficacy of risperidone is poorer and the agent is even associated with delirium exacerbation, while ziprasidone was not shown to be effective. Few data are available for other AAPs. While preliminary, the current data suggest that haloperidol and some AAPs are similarly effective and well-tolerated.

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 that require sedation or have a history of haloperidol intolerance. Risperidone is deemed less suitable for the treatment of delirium. Evidently, larger-scale RCTs are urgently required.

Keywords: delirium, atypical antipsychotics, new antipsychotics, novel antipsychotics

Introduction

Delirium is a common, acute and serious neuropsychiatric syndrome characterised by fluctuating levels of consciousness and impairment of cognitive functioning. Occurrence rates in the general hospital range from 10-31%, 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 (LOS) and higher rates of institutionalisation and mortality while in hospital and 12 months after discharge.[1]

To date, haloperidol is 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] Although haloperidol has long been the only antipsychotic recommended for the management of the syndrome, a meta-analysis 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 three studies of which only two explored treatment rather than prevention effects.[3]

Considering the growing number of studies exploring their use for delirium and their pharmacological profiles and side effects, we wished to know whether AAPs are indeed adequate alternatives for haloperidol. In the current study we report on our systematic review of the literature on their efficacy and tolerability in the treatment of delirium.

Methods

Without imposing a preliminary restriction of language, we performed a systematic search of the literature published before January 2017 using PubMed. As alcohol-related and non-alcohol-related delirium are two separate disorders requiring a different approach, we opted to focus on the latter only.

We used the following search terms “delirium” 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 four 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 randomised controlled trials (RCTs) in adult patients (18 years and older) written in English, Dutch and 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.

Insert Figure 1 about here

Results

Of the 902 citations screened for eligibility, 33 publications met our selection criteria, of which 11 were RCTs (see Table 1) and 22 non-controlled 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 AAP to placebo[4–8], another five (both single- and double-blinded RCTs) AAP to haloperidol[9–12,14], with one single-blinded RCT comparing two AAPs[13] (Table 1).

RCTs with placebo control

Comparing haloperidol and risperidone with placebo in patients receiving palliative care, Agar et al[4] performed the largest RCT. The primary outcome was the mean of the last two delirium symptom scores as assessed with the Memorial Delirium Assessment Scale (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 extrapyramidal effects. Overall survival was higher in the placebo group than it was in the haloperidol group, but this was not significant for placebo versus 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.

The second largest RCT contrasted the effects of olanzapine and haloperidol with placebo on senile delirium.[8] The post-treatment scores of the intensive care delirium screening checklist (CGI-SI) were clinically significantly decreased in all three 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 this was dry mouth and extrapyramidal side effects (EPS) in the patients receiving haloperidol.

Girard et al.[7] 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 two active agents.

Two small studies comparing quetiapine to placebo both suggested a more rapid decrease of delirium and its noncognitive symptoms following quetiapine.[5,6]

RCTs with an active comparator (no placebo)

Two studies compared quetiapine to haloperidol, with neither finding any significant differences in their efficacy.[9,10]. The agents' improvement and tolerability rates were also similar.[9] Hypersomnia was common in the quetiapine group but not significantly higher than it was in the haloperidol group. Grover et al[10] reported the effectiveness of both medications to be similar in their adult and elderly (≥60 years) patients.

We found three studies evaluating haloperidol, risperidone and/or olanzapine.[11–13] 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.[13]

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 five 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,[15–21] which was also the case in eight of the nine trials investigating the effects of risperidone.[20,23–29]

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.[19,20,29,30] It was proposed that haloperidol may cause

more EPS whereas olanzapine may be more sedating.[29] Two single-drug trials investigating olanzapine found the agent to be safe and effective[31,32] , which was also the conclusion of three studies assessing aripiprazol[29,33,34] and two studies reporting on amisulpride.[22,23] In one study, a low dose of paliperidone was well tolerated and effective in reducing delirium symptoms,[35] while, finally, another single-drug study suggested perospirone to be effective and safe.[36]

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.[8,12-14,19-20,29-32] 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.[4] The various open trials investigating these three and other AAPs (amisulpride, aripiprazole, paliperidone and perospirone) we reviewed also concluded the agents to be effective and safe in treating delirium.

In the most recent guidelines of the National Institute for Health and Care Excellence (NICE) 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 non-verbal de-escalation techniques are ineffective or inappropriate.[37] Moreover, due to its EPS, the use of haloperidol is contraindicated in patients with Lewy body dementia and Parkinson's disease. However, in 2016, a meta-analysis was published that investigated both the prevention and treatment of delirium.[38] Of the 19 studies included, 12 treatment trials investigated both typical and atypical antipsychotics, with five of these comparing antipsychotics to placebo or no treatment. Three of these studies concerned AAPs: two investigating quetiapine (n=78) and one ziprasidone (n=101). The other seven studies compared the effectiveness of different antipsychotics. Pointing to the high heterogeneity of the studies reviewed, the authors' overall conclusion was that the use of antipsychotics was not associated with a change in delirium duration or severity, length of hospital or ICU stay, or mortality. Furthermore, having conducted a broad review on delirium in older people, Inouye et al[39] 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.[40]

As the side-effect profiles for antipsychotics differ (i.e. 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[13] observe that the side-effect profiles of the two AAPs they investigated are similar, they found risperidone to be less effective in older patients (70+) than olanzapine. If the side effects of AAPs in patients with delirium are better delineated, clinicians can base their decision on the patient's clinical profile and the type of delirium. They may 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[41]. 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[9], 110 (88-191)[6] and 31.83 ± 4.10[10] mg/day and for olanzapine 2.4 ± 1.7[13] and 3.05 ± 1.44[12] 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.[5] 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 behavioural 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. 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.[42] 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 the current systematic review. Firtsly, we found only nine RCTs, with treatment groups ranging from 8 to 84 patients. Six of the nine trials had treatment groups of 21 patients or less. Most other studies were open trials, again with small sample sizes varying from three 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, followed by the MDAS and lastly the confusion assessment method for the ICU (CAM-ICU). Thirdly, 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 two RCTs and six open trials, the Udvalg for Kliniske Undersogelser (UKU) side-effect rating scale was used the most. Overall, outcomes reported appear to show a trend towards more EPS with haloperidol and risperidone and more sedation with olanzapine. Finally, the patients that were diagnosed with delirium were either hospitalised, being treated at medical or surgical wards, or had been admitted to an ICU, with the aetiologies of delirium being either internal or surgical.

While taking these limitations into account, we can summarise that some RCTs and open studies support the efficacy of olanzapine and quetiapine in the treatment of delirium. Risperidone is found to be less effective and is even associated with a worsening of delirium symptoms, while for ziprasidone no effects were recorded. 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 as yet no evidence that AAPs are less efficacious than haloperidol. In conclusion, there is as yet no strong evidence to suggest that atypical antipsychotics in general help resolve delirium more so than haloperidol or placebo. Taking the high burden of delirium into account, 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.

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Figure 1: Search strategy

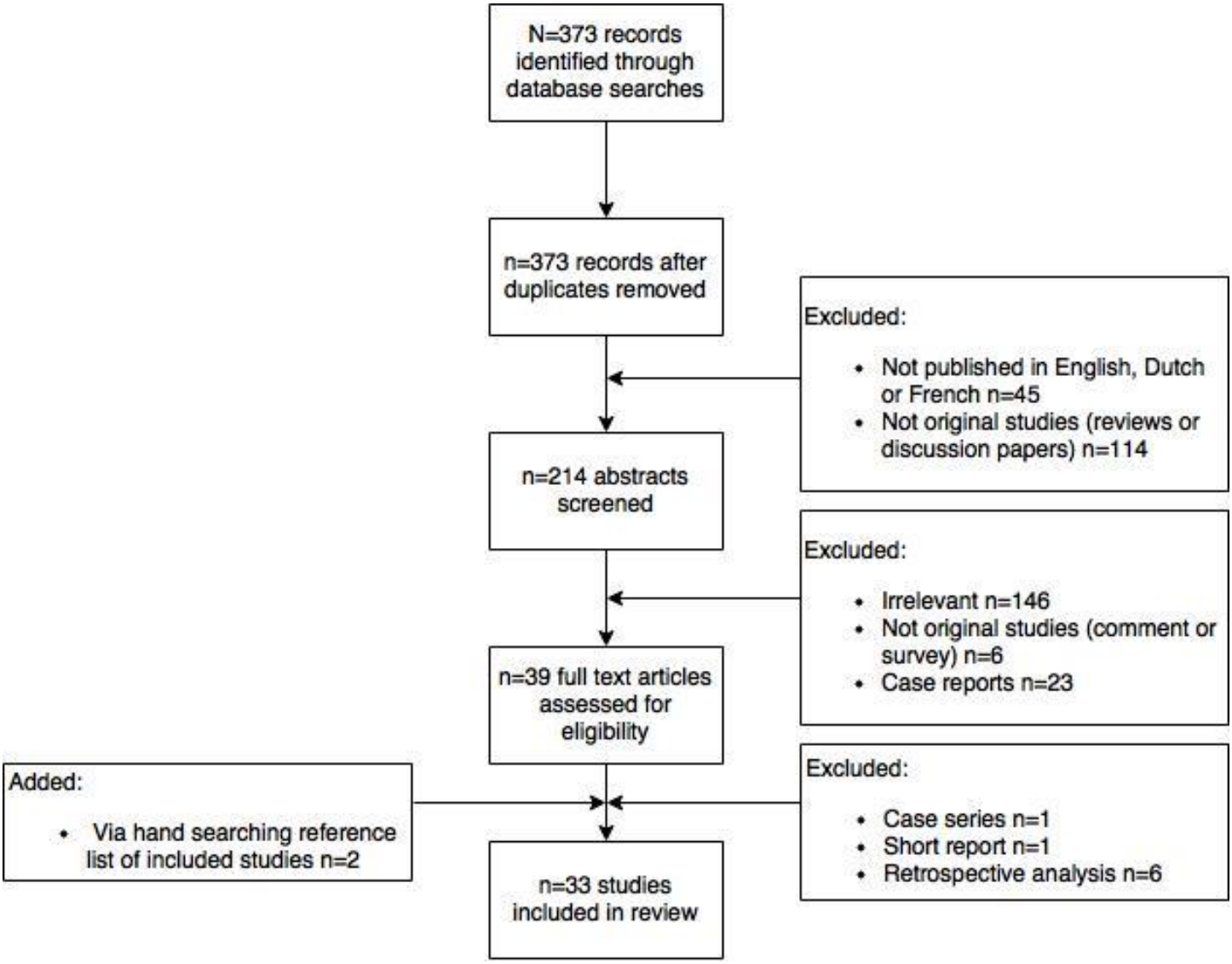

TABLE 1.

Author	Year	Patients	Scale	Drug	Sample size	*Conclusion*
Agar et al.[4]	2017	Palliative care	MDAS	Risperidone	82	*In patients receiving palliative care, individualised 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.*
				Haloperidol	81	
				Placebo	84	
Tahir et a.l[5]	2010	Hospitalised	DRS-R-98	Quetiapine	21	*Quetiapine has the potential to more quickly reduce the severity of noncognitive aspects of delirium than placebo.*
				Placebo	21	
Devlin et al.[6]	2010	ICU	ICDSC	Quetiapine	18	*Quetiapine may resolve several intensive care unit (ICU) delirium symptoms faster than placebo.*
				Placebo	18	
Girard et al.[7]	2010	ICU	CAM-ICU	Ziprasidone	54	*Compared to placebo, neither ziprasidone nor haloperidol increase the number of days alive without delirium or coma, nor do they cause more adverse outcomes.*
				Haloperidol	35	
				Placebo	14	
Hu et al[8]	2006	Hospitalised	CGI-SI, CGI-GI	Olanzapine	74	*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.*
				Haloperidol	72	
				Placebo	29	
Maneeton et al.[9]	2013	Hospitalised	DRS-R-98	Quetiapine	24	*Low-dose quetiapine and haloperidol may be equally effective and safe in controlling delirium symptoms.*
				Haloperidol	28	
Grover et al[10].	2016	Hospitalised	DRS-R-98	Quetiapine	31	*Quetiapine is as effective as haloperidol in the management of delirium.*
				Haloperidol	32	
Han and Kim[11]	2004	Hospitalised	DRS, MDAS	Risperidone	12	*No differences were found in the efficacy or response rates of haloperidol and risperidone in patients with delirium.*
				Haloperidol	12	
Grover et al[12].	2011	Hospitalised	DRS-R-98	Olanzapine	23	*Risperidone and olanzapine are as efficacious as haloperidol in the treatment of delirium.*
				Risperidone	21	
				Haloperidol	20	
Kim et al.[13]	2010	Hospitalised	DRS-R-98	Risperidone	12	*Risperidone and olanzapine were equally effective in reducing delirium symptoms. The response to risperidone was poorer in the older age group.*
				Olanzapine	8	
Skrobik et al[14].	2004	ICU	ICU-DSC	Olanzapine	25	*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.*
				Haloperidol	45	

ICU: intensive care unit, MDAS: memorial delirium assessment scale, DRS-R-98: delirium rating scale-revised-98, ICDSC: intensive care delirium screening checklist, CAM-ICU: confusion assessment method for the ICU, CGI-SI: clinical global impression scale-severity of illness, CGI-GI: clinical global impression scale-global improvement, DRS delirium rating scale.

TABLE 2. Open trials

Author	Year	Population	Rating scale	Study drug / Control	Sample size, n
Maneeton et al.[15]	2007	Hospitalised	DRS	Quetiapine	17
Sasaki et al.[16]	2003	Hospitalized	DRS-J	Quetiapine	12
Omura and Amano[17]	2003	Hospitalised	DRS	Quetiapine	24
Kim et al.[18]	2003	Hospitalised	DRS	Quetiapine	12
Tanimukai et al.[19]	2014	Hospitalised	MDAS	Risperidone	6
				Olanzapine	3
				Quetiapine	11
				Haloperidol	7
Yoon et al.[20]	2013	Hospitalised	DRS-K	Risperidone	21
				Olanzapine	18
				Quetiapine	18
				Haloperidol	23
Lee et al.[21]	2005	Hospitalised	DRS-R-98	Amisulpride	16
				Quetiapine	15
Pintor et al.[22]	2009	Hospitalised	DRS	Amisulpride	40
Kim et al.[23]	2005	Hospitalised	DRS-R-98	Risperidone	18
				Haloperidol	24
Horikawa et al.[24]	2003	Hospitalised	DRS	Risperidone	10
Parellada et al.[25]	2009	Hospitalised	DRS	Risperidone	64
Kishi et al.[26]	2012	Cancer patients	DRS-R-98	Risperidone	29
Mittal et al.[27]	2004	Hospitalised	DRS	Risperidone	10
Ikezawa et al.[28]	2008	Hospitalised	DRS	Risperidone	22
Boettger et al.[29]	2015	Cancer patients	MDAS	Risperidone	21
				Olanzapine	21
				Aripiprazole	21
				Haloperidol	21
Sipahimalani and Masand[30]	1998	Hospitalised	DRS	Olanzapine	11
				Haloperidol	11
Breitbart et al.[31]	2002	Cancer patients	MDAS	Olanzapine	79
Kim et al.[32]	2001	Hospitalised	DRS	Olanzapine	20
Boettger et al.[33]	2011	Hospitalised	MDAS	Aripiprazole	21
				Haloperidol	21
Boettger and Breitbart[34]	2011	Cancer patients	MDAS	Aripiprazole	21
Yoon et al.[35]	2011	Hospitalised	MDAS	Paliperidone	15

Takeuchi et al.[36]	2007	Hospitalised	DRS-R-98	Perospirone	38

DRS: delirium rating scale; DRS-J: Japanese version of the DRS; MDAS: memorial delirium assessment scale; DRS-R-98: delirium rating scale-revised-98; DRS-K: Korean version of the DRS.