

Antipsychotics in the Treatment of Delirium: A Systematic Review

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Objective: Antipsychotics are frequently used in the management of delirium, although there is limited information regarding the safety and efficacy of antipsychotics in treating delirium. The purpose of this study was to systematically evaluate the evidence for the efficacy and safety of antipsychotics in treating delirium.

Sources: MEDLINE (July 1980 to July 2005) and Cochrane databases were searched for English language articles using keywords.

Study Selection: Prospective studies with standardized criteria for diagnosing delirium and evaluating its severity.

Data Synthesis: In total, 14 studies (9 single agent studies and 5 comparison trials) met inclusion criteria. Study medications included haloperidol, chlorpromazine, olanzapine, risperidone, and quetiapine. Improvements in delirium severity were reported with all of these antipsychotic medications. No study included a placebo comparison to account for spontaneous improvements in delirium. Other methodological limitations included inadequate blinding, randomization, and handling of participant withdrawals. The improvements in delirium tended to occur soon after initiation of treatment, and most of the studies examined used relatively low doses of antipsychotic medication. Serious adverse events attributable to antipsychotic medication were uncommon in studies, although side effects were not evaluated systematically in most studies.

Conclusion: To date, there are no published double-blind, randomized, placebo-controlled trials to establish the efficacy or safety of any antipsychotic medication in the management of delirium. There is limited evidence from uncontrolled studies that supports the use of low-dose, short-term treatment of delirium with some antipsychotics. Further study with well-designed clinical trials is required in this area.

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Delirium is a common disorder among older adults admitted to hospital and is associated with a number of serious adverse outcomes.¹ Studies conducted in a variety of medical and surgical inpatient settings have demonstrated that 15% to 70% of subjects experience delirium at some point during their hospital stay.^{2–6} Delirium is independently associated with several major adverse outcomes including prolonged hospital stays,^{5–7} increased likelihood of discharge to a nursing home,^{5,8,9} and increased risk of mortality.^{5–7,9–13} Delirium is also experienced as distressing by patients, their caregivers, and nursing staff.¹⁴

Psychoactive medications are used in managing the majority of delirium cases as confirmed by surveys of psychiatrists¹⁵ and intensive care physicians.¹⁶ The medications most frequently utilized are the typical antipsychotic haloperidol, various benzodiazepines, and, increasingly, the atypical antipsychotics.^{15,16} The American Psychiatric Association guidelines for treating delirium also recommend the use of psychoactive medications as adjuncts in delirium management.¹⁷ Nonetheless, several studies have found that exposure to psychoactive medications, including antipsychotics, poses a risk for the subsequent development of delirium^{18–22}; however, many of these studies do not establish the temporal relationship between delirium onset and use of antipsychotics. Furthermore, antipsychotics are associated with a variety of adverse events, depending on the agent, including sedation, extrapyramidal symptoms, cardiac arrhythmias,^{23,24} and premature death²⁵ in patients with dementia. Inappropriate medication selection and dosing strategies in the delirious elderly have also been identified.²⁶

Two recent studies have raised concerns about the use of antipsychotics in the elderly. Schneider et al.²⁵ conducted a meta-analysis that demonstrated an elevated risk of mortality in older adults with dementia who were treated with atypical antipsychotics. This study raises concerns about the widespread use of these medications in delirium in the elderly because older patients with delirium may have underlying dementia.²⁷ A second study by Wang et al.²⁸ examined a retrospective cohort of elderly people prescribed antipsychotics for a variety of conditions including dementia and delirium. When mortality rates were compared, the investigators found that typical antipsychotics were associated with higher rates of mortality as compared to the atypical antipsychotics. Evidence suggests that many cases of delirium can be managed successfully without medications by using environmental interventions,²⁹ although these strategies are often underutilized.³⁰

Previous reviews have examined pharmacologic and nonpharmacologic treatment strategies in delirium.^{31–34} Our purpose was to systematically review the existing published literature that met certain study design criteria and that studied antipsychotic drugs to treat the symptoms of delirium.

METHOD

Search Strategy

A search of MEDLINE (January 1980 to July 2005) and the Cochrane databases was undertaken to identify relevant English language articles using the following terms: *delirium, confusion, acute confusional state, organic brain syndrome, therapy, drug therapy, treatment, and pharmacotherapy*. Our search was limited to articles published after 1980 to coincide with the publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (DSM-III),³⁵ which includes the first set of criteria to distinguish delirium from other “organic” conditions such as dementia. References of articles were searched for studies that may have been overlooked in the initial search. To include studies of the highest quality, we limited our review to studies that used: (1) a prospective study design, (2) a standardized method of diagnosing delirium, and (3) a standardized method of measuring delirium severity. Articles were excluded if the delirium was associated with a specific intoxication or withdrawal state (e.g., delirium tremens). All articles were reviewed by 2 of the study authors, and the decision to include articles was reached by consensus. Efforts were made to contact the authors of primary studies to clarify information when necessary.

Delirium Diagnostic Instruments

Although a number of delirium diagnostic instruments and severity scales exist, we limited our review to studies

that included both validated diagnostic instruments and severity scales. Delirium diagnostic instruments with established validity include: (1) DSM-III³⁵; (2) DSM-III, revised (DSM-III-R)³⁶; (3) DSM-IV³⁷; (4) DSM-IV, text revision (DSM-IV-TR)³⁸; and (5) the Confusion Assessment Method (CAM).³⁹ The DSM-III had a sensitivity of 83% and specificity of 100% for detecting delirium in a study of 48 elderly patients with delirium when compared to a geriatrician’s clinical diagnosis.⁴⁰ In the same study, the DSM-III-R displayed a sensitivity of 100% and a specificity of 98%.⁴⁰ The CAM was developed by operationalizing 4 of the delirium criteria from the DSM-III-R and has a sensitivity of 92% to 100% and a specificity of 46% to 95%.^{39,40} The DSM-IV has a reported sensitivity of 73% and a specificity of 93%.⁴¹ The DSM-IV-TR⁴⁰ criteria are identical to those of DSM-IV.

Delirium Severity Scales

Valid delirium severity scales include: (1) the Delirium Rating Scale (DRS),⁴² (2) the 1998 revision of the DRS (DRS-R-98),⁴³ (3) the Memorial Delirium Assessment Scale (MDAS),⁴⁴ and (4) the Delirium Index (DI).⁴⁵ The DRS is an observer-rated scale designed for use by psychiatrists. Ten items are contained in the scale and are scored from 0 to 4 points, with a maximum score of 32 indicating the greatest degree of delirium severity.^{42,46,47} A cut-off score of 12 points on the DRS has been suggested as the threshold for delirium.⁴⁷ The DRS-R-98 is a 16-item scale, 3 items of which aid in diagnosing delirium but not used in evaluating its severity.⁴³ The maximum severity score is 39 points. A suggested cut-off score on the DRS-R-98 is 15 points, which is associated with a sensitivity of 92% and a specificity of 93%.⁴³ The MDAS is a 10-item, 4-point clinician-rated scale, with a maximum score of 30 indicating greater delirium severity. Suggested cut-off scores of 10 and 13 have been proposed for the MDAS.⁴⁴ The DI contains 7 items rated on a 0 to 3 scale, with a maximum total score of 21.⁴⁵ Although cut-off scores for the DI have not been established, we selected a score of 5 based on the results of previous reports.⁴⁵ Several detailed reviews of delirium diagnostic instruments and severity rating scales are available.^{47–49}

Assessment of Study Quality

We rated the quality of articles meeting our inclusion criteria using general guidelines for examining study quality^{50,51} as well as factors specific to delirium outcomes.²⁷ Studies were examined for the following characteristics: the inclusion of a control group, use and adequate description of randomization and blinding procedures, adequate description of the balance in baseline patient characteristics in comparison trials, and completeness of follow-up including intention-to-treat analysis in randomized trials. Other criteria were: inclusion of patients with dementia, recording of subtypes of delirium

(hyperactive, hypoactive, or mixed delirium), the identification of pharmacologic co-interventions (e.g., breakthrough benzodiazepines or antipsychotics), systematic evaluation of medication side effects using established assessment instruments, duration of follow-up, and the frequency of assessment for primary outcomes in trials (using delirium severity scale scores).

A positive score ("Yes") indicating a higher study quality on each of these general variables was assigned if: (1) a control group consisting of a placebo was included in the trial; (2) groups enrolled in comparison or controlled trials had comparable demographic and clinical characteristics at the time of randomization; (3) randomization was carried out and described in sufficient detail; (4) trials ensured adequate blinding to minimize bias; and (5) follow-up was complete or dropouts or subjects who withdrew were accounted for, and, in randomized trials, intention-to-treat analysis was used.

Positive scores on characteristics specific to delirium trials were assigned based on the following definitions: (1) dementia patients were permitted in the trial and the proportion of individuals with dementia was reported; (2) the proportion of individuals with hyperactive, hypoactive, or mixed delirium presentations was described in the study; (3) pharmacologic co-interventions for delirium symptoms were either not permitted or, when allowed, were adequately accounted for in the final analysis; (4) assessment for side effects was undertaken with validated scales for both extrapyramidal symptoms (EPS) and general side effects; (5) the trial was of adequate duration (7 days or longer); and (6) assessment of delirium severity with delirium severity rating scales was described and occurred at least once every 24 hours during the trial. The decision to use 7 days to define adequate study duration was based on reports of the average duration of delirium from several studies.⁵²⁻⁵⁷ The decision to define the minimally adequate assessment interval as 24 hours was based on the reported symptom course of delirium.⁵¹

Clinical Outcomes

Group improvement was defined as the percent reduction in delirium severity score from baseline to last time interval, unless otherwise noted. An individual was considered to have responded in any given trial if there was a 50% reduction in their delirium severity score. Remission was defined as follows: DRS score \leq 12, DRS-R-98 score \leq 15, MDAS score \leq 13, or DI score \leq 5. Time to effect was defined as time until maximum improvement, unless otherwise noted. Treatment-emergent adverse events were classified as serious or minor. Serious adverse events were any adverse events requiring discontinuation of medication or withdrawal from the trial or adverse events resulting in death. Minor or nonserious treatment-emergent adverse events included (but were not limited to) EPS, including mild parkinsonism or aka-

thisia, and sedation. Medication dosage was the average dose of medication administered during a trial, unless otherwise noted, and was expressed as in milligrams (mg) and chlorpromazine equivalents.⁵⁸

RESULTS

Search Results

A total of 631 citations were retrieved from MEDLINE and 8 from the Cochrane library. Review of secondary references identified an additional 93 papers. After reviewing the abstracts of these papers, 180 articles were retrieved and reviewed in detail. After detailed review of these 180 articles, 14 studies⁵⁹⁻⁷² met the inclusion criteria and are discussed below.

Description of Included Studies

Nine of the 14 studies were single agent trials,⁵⁹⁻⁶⁷ and 5 were comparison trials⁶⁸⁻⁷² (Table 1). Drugs used in single agent trials included haloperidol,⁵⁹ olanzapine,^{60,61} risperidone,⁶²⁻⁶⁴ and quetiapine.⁶⁵⁻⁶⁷ Comparison trials included 1 with haloperidol, chlorpromazine and lorazepam⁶⁹; 1 with haloperidol and olanzapine⁷¹; 1 with haloperidol and mianserin⁶⁸; and 2 with haloperidol and risperidone.^{70,72}

Patients were selected to participate in trials from a variety of populations. Most subjects were enrolled in trials through referrals to psychiatry initiated by the patient's attending medical or surgical staff. Two studies screened inpatient populations for delirium and recruited patients for study who screened positive for delirium. Subjects enrolled varied considerably in age, both within studies and between studies. The age range of study participants varied and was between 19 and 92 years. The number of participants enrolled in studies was small, with a total of 448 individuals included in this review. The median number of participants per study arm was 12 (range, 10-79 participants). There was no evidence of an a priori estimation of the required sample size in any of these studies based on power analysis. Delirium severity, as measured on delirium severity scales, improved significantly over time during treatment with all agents except lorazepam. In comparison trials, there were no significant differences between agents compared in any given trial except for haloperidol and chlorpromazine, which were superior to lorazepam in the study comparing these medications.⁶⁹

Assessment of Study Quality

None of the identified studies included a placebo control group (Table 2). Furthermore, 12 of 14 studies were not double-blinded, 4 of 14 studies failed to account for the withdrawal of participants during the trial, and 4 of 5 comparison studies were not adequately randomized. Few trials included patients with dementia or described the proportion of individuals with the different subtypes of delirium. Only 2 of 14 studies systematically evaluated for

Table 1. Summary of Antipsychotic Treatment of Delirium Trials That Met Inclusion Criteria

Study	Medication	Diagnostic Instrument	Severity Scale	N	Age, Mean \pm SD, y	Population	Enrollment in Study	Improved ^a
Single agent studies								
Akechi et al, 1996 ⁵⁹	Haloperidol	DSM-III-R	DRS	10	63 \pm 13	Ca	Referred to psychiatry	Yes
Kim et al, 2001 ⁶⁰	Olanzapine	DSM-IV	DRS	20	45.8 \pm 18.3	Med/Sx/Ca	Referred to psychiatry	Yes
Breitbart et al, 2002 ⁶¹	Olanzapine	DSM-IV	MDAS	79	60.6 \pm 17.3	Ca	Referred to psychiatry	Yes
Horikawa et al, 2003 ⁶²	Risperidone	DSM-IV	DRS	10	56.8 \pm 22.7	Med/Sx/Ca	Referred to psychiatry	Yes
Mittal et al, 2004 ⁶³	Risperidone	DSM-IV, CAM	DRS	10	64.7 \pm 4.8	Med/Sx	Population screened	Yes
Parellada et al, 2004 ⁶⁴	Risperidone	DSM-IV	DRS	64	67.3 \pm 11.4	Med/Sx/Ca	Not specified	Yes
Kim et al, 2003 ⁶⁵	Quetiapine	DSM-IV	DRS	12	74 \pm 7	Med/Sx	Referred to psychiatry	Yes
Sasaki et al, 2003 ⁶⁶	Quetiapine	DSM-IV	DRS-J	12	67.3 \pm 14.8	Med/Sx/Ca	Not specified	Yes
Pae et al, 2004 ⁶⁷	Quetiapine	DSM-IV	DRS-R-98	22	69.1 \pm 9.8	Med/Sx/Ca	Referred to psychiatry	Yes
Comparison studies								
Nakamura et al, 1995 ⁶⁸	Haloperidol	DSM-III-R	DRS	46	63.0 \pm 12.4	Med/Sx/Ca	Referred to psychiatry	Yes
	Mianserin			17	67.7 \pm 15.0			Yes
Breitbart et al, 1996 ⁶⁹	Haloperidol	DSM-III-R	DRS	11	39.2 \pm 8.8	AIDS	Population screened	Yes
	Chlorpromazine			13				Yes
	Lorazepam			6				No
Han and Kim, 2004 ⁷⁰	Haloperidol	DSM-III-R, CAM	MDAS	12	66.5 \pm 15.9	Med/Sx/Ca	Referred to psychiatry	Yes
	Risperidone			12	65.6 \pm 8.3			Yes
Skrobik et al, 2004 ⁷¹	Haloperidol	DSM-IV	DI	45	63.26 \pm 11.66	ICU	Population screened	Yes
	Olanzapine			28	67.5 \pm 6.04			Yes
Kim et al, 2005 ⁷²	Haloperidol	DSM-IV, CAM	DRS-R-98	24	71.26 \pm 7.22	Med/Sx	Referred to psychiatry	Yes
	Risperidone			18				Yes

^aSignificant group improvement in delirium outcome scores over time.

Abbreviations: AIDS = acquired immunodeficiency syndrome, Ca = cancer population, CAM = Confusion Assessment Method, DI = Delirium Index, DRS = Delirium Rating Scale, DRS-J = Delirium Rating Scale–Japanese Version, DRS-R-98 = Delirium Rating Scale–Revised–1998, ICU = intensive care unit, MDAS = Memorial Delirium Assessment Scale, Med = medical population, Sx = surgical population.

possible drug side effects with assessment instruments for acute EPS and general side effects. Pharmacologic co-interventions were uncommon in the studies. Five studies did not have a total follow-up duration of at least 1 week, and 7 studies did not evaluate delirium severity at least once per day.

Clinical Outcomes

Clinical outcomes reported were the degree of group improvement in delirium severity scores, individual rates of response and remission, the time course of improvement in delirium, rates of adverse events, and medication dosage (Table 3). Delirium severity as measured on the various delirium scales was reduced by 43% to 70% in the 12 studies reporting this outcome, although baseline degree of delirium severity varied between trials. Six studies provided information regarding individual response rates and 6 provided information on remission rates. Response rates (i.e., the percent of cases in each study whose delirium severity decreased by $\geq 50\%$) were between 50% and 100%; remission rates were between 42% and 100%. The weighted mean remission rate by day 3 was 60.82% in the 5 studies reporting this outcome.^{61,64,66,70,72} Five studies^{61,63,66,70,72} reported remission rates by day 7 with a weighted mean remission rate of 69.46%. The maximum remission rate obtained by calculating the weighted mean remission rates from 6 studies^{61,63,64,66,70,72} was 76.62%. The duration of time until either any improvement or maximum improvement in delirium severity varied between 3.8 and 7.1 days. Serious adverse events were relatively uncommon in these studies, although the likelihood of any treatment-emergent adverse event occurring during trials varied between 0% and 40%. Serious adverse events varied between 0% to 5.9% in studies. Overall, the weighted mean rate of adverse events attributed to study medications was 12.6% for any minor adverse event and 1.48% for any serious adverse event. Three comparison studies found higher rates of minor adverse events with haloperidol when compared to olanzapine⁷¹ and risperidone.^{70,72} In these studies, the increased rate of adverse events with haloperidol was due to mild EPS when compared to the atypical antipsychotics. There were no deaths that were directly attributed to study medications in these studies. Daily mean dosage of medications varied between 36 mg and 325 mg of chlorpromazine equivalents.

DISCUSSION

Table 2. Assessment of Study Quality for Antipsychotic Treatment of Delirium Trials

Study	Placebo-Controlled	Similar At Baseline ^a	Randomized	Double-Blinded	Dropouts/Withdrawals ^b	Dementia Included ^c	Delirium Subtypes ^d	Co-Interventions ^e	Side Effect Evaluation ^f	Follow-Up Duration ≥ 7 days	Assessment Interval Daily ^g
Single agent trials											
Akechi et al, 1996 ⁵⁹	No	No	Yes	No	No	Yes	No	Yes	No
Kim et al, 2001 ⁶⁰	No	No	Yes	Yes	No	Yes	No	No	No
Breitbart et al, 2002 ⁶¹	No	No	Yes	Yes	Yes	Yes	No	No	No
Horikawa et al, 2003 ⁶²	No	No	Yes	No	No	No	No	Yes	No
Mittal et al, 2004 ⁶³	No	No	Yes	No	No	Yes	No	No	Yes
Parellada et al, 2004 ⁶⁴	No	No	Yes	No	No	Yes	Yes	Yes	Yes
Kim et al, 2003 ⁶⁵	No	No	No	Yes	No	Yes	No	Yes	No
Sasaki et al, 2003 ⁶⁶	No	No	Yes	No	No	No	No	Yes	Yes
Pae et al, 2004 ⁶⁷	No	No	Yes	Yes	No	Yes	No	No	No
Comparison trials											
Nakamura et al, 1995 ⁶⁸	No	Yes	No	No	No	No	No	Yes	No	Yes	Yes
Breitbart et al, 1996 ⁶⁹	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	No
Han and Kim, 2004 ⁷⁰	No	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes
Skrobik et al, 2004 ⁷¹	No	No	No	No	No	No	No	Yes	No	No	Yes
Kim et al, 2005 ⁷²	No	No	No	No	Yes	No	No	Yes	No	Yes	Yes

^aGroups enrolled in comparison or controlled trials had comparable demographic and clinical characteristics at the time of randomization.

^bDropouts and/or withdrawals were accounted for.

^cPatients with dementia were included.

^dDifferent subtypes of delirium were described.

^ePharmacologic co-interventions were not allowed or were adjusted for in the final analysis.

^fPossible drug side effects were evaluated with assessment instruments for acute extrapyramidal symptoms and general side effects.

^gDelirium severity evaluated at least once per day.

Most subjects with delirium in the studies we reviewed had improvements in delirium severity following treatment with antipsychotic medications, but no study had a blinded placebo comparison group. Comparison trials did not identify any particular antipsychotic medication as superior to another in terms of efficacy. The observed improvements in delirium severity tended to occur within the first week of treatment using conservative dosing strategies. Although severe medication-related side effects were infrequently noted, few studies systematically assessed for medication safety. In the absence of any controlled trials, it is difficult to determine whether the observed improvements in delirium severity are due to study medications, the natural history of the disorder, or treatment of underlying medical conditions.

We identified major methodological limitations in the studies evaluating antipsychotic treatments for delirium. Most importantly, we were unable to identify any published placebo-controlled trial in this area. Delirium is often a transient disorder,⁵² and many individuals with this condition would be expected to have improvements in their symptoms with specific treatment of the underlying medical conditions that likely precipitated their episode of delirium. For example, treatment of infections, metabolic disturbances, or discontinuing offending medications may lead to resolution of delirium symptoms without the need to initiate treatment with antipsychotic medications. Several studies have observed substantial improvements in delirium without reliance on antipsychotic medications. Cole et al.⁷³ conducted a randomized trial of systematic detection and nonpharmacologic intervention of delirium in older medical inpatients. The authors found that there were significant rates of improvement both in the intervention group and the usual care group (48% and 45%, respectively), although the proportion of individuals who may have received antipsychotics was not specified. A delirium intervention study by Lundstrom et al.,⁷⁴ focusing on nonpharmacologic aspects of delirium care, also found considerable rates of delirium improvement, with 69.8% of the intervention group and 40.3% of controls no longer having delirium 7 days after symptom onset.

The need for placebo-controlled studies is further supported by negative results obtained in 2 recently published randomized placebo-controlled trials for delirium prevention with haloperidol⁷⁵ and donepezil.⁷⁶ Although 1 of these trials found no significant difference in the incidence of postoperative delirium with the use of prophylactic haloperidol treatment, the authors noted a dramatic decline in the overall rate

Table 3. Clinical Outcomes of Trials for Antipsychotic Treatment of Delirium

Study	Initial Delirium Severity Score, Mean \pm SD ^a	Mean Reduction in Delirium Score, % ^b	Response Rate, %	Remission, %	Time to Improvement, Mean \pm SD, d	Treatment Emergent AEs, Minor AE/ Serious AE, %		Medication Dosage		Daily Dose, Mean \pm SD (CPZ equivalents) ^e
						Initial Daily Dose, Mean \pm SD	Daily Dose			
Single agent studies										
Akechi et al, 1996 ⁵⁹	20.4 \pm 3.9	54	100	...	6 ^c	0/0	0.75 mg	5.4 \pm 3.4 mg	270 \pm 170	
Kim et al, 2001 ⁶⁰	20.0 \pm 3.6	54	70	...	3.8 \pm 1.7	10/0	4.6 \pm 0.9 mg	5.9 \pm 1.5 mg	111 \pm 30	
Breitbart et al, 2002 ⁶¹	19.85 \pm 3.79	46	...	76	...	33.8/2.5	3.0 \pm 0.14 mg	6.3 \pm 0.52 mg ^f	126 \pm 10.4 ^f	
Horikawa et al, 2003 ⁶²	20.0 \pm 5.0	47	50	...	7.1 \pm 2.7	40/0	0.5 mg	1.7 \pm 0.8 mg ^g	85 \pm 40 ^g	
Mittal et al, 2004 ⁶³	25.2 \pm 0.9	55	60	...	3.89 \pm 0.31	20/0	0.5 mg bid	0.75 \pm 0.11 mg ^h	37.5 \pm 5.5 ^h	
Parellada et al, 2004 ⁶⁴	22.5 \pm 4.6	70	...	90.6	...	17/0	0.63–1.25 mg bid	2.6 \pm 1.3 mg ^h	130 \pm 85 ^h	
Kim et al, 2003 ⁶⁵	18.25 \pm 6.05	56	5.91 \pm 2.22 ^d	25/0	2.5 mg bid	93.75 \pm 23.31 mg ^h	125 \pm 31 ^h	
Sasaki et al, 2003 ⁶⁶	18.1 \pm 4.2	49	...	100	4.8 \pm 3.5	0/0	25–50 mg	44.9 \pm 31.0 mg	60 \pm 41	
Pae et al, 2004 ⁶⁷	21.8 \pm 3.2	57	86.3	...	7.1 \pm 3.9	0/9	37.5 \pm 12.8 mg	127.1 \pm 72.2 mg	169 \pm 96	
Comparison studies										
Nakamura et al, 1995 ⁶⁸										
Haloperidol	22.1 \pm 3.8	65	70.6	0/5.9	
Mianserin	21.3 \pm 4.1	55	67.4	0/0	NA	NA	NA	
Breitbart et al, 1996 ⁶⁹										
Haloperidol	20.45 \pm 3.45	43	0/0	0.25 mg	1.4 \pm 1.2 mg ^h	70 \pm 60 ^h	
Chlorpromazine	20.62 \pm 3.88	43	0/0	10 mg	36 \pm 18.4 mg ^h	36 \pm 18.4 ^h	
Lorazepam	18.33 \pm 2.58	7	0/100	NA	NA	NA	
Han and Kim, 2004 ⁷⁰										
Haloperidol	21.83 \pm 4.43	75	4.22 \pm 2.48	8.33/0	0.75 mg bid	1.7 \pm 0.84 mg	...	
Risperidone	23.5 \pm 4.19	42	4.17 \pm 2.14	0/0	0.5 mg bid	1.02 \pm 0.41 mg	...	
Skrobik et al, 2004 ⁷¹										
Haloperidol	7.3	13.3/0	5.0 mg	4.54 mg	325	
Olanzapine	6.6	0/0	2.5–5.0 mg	6.5 mg	90.8	
Kim et al, 2005 ⁷²										
Haloperidol	22.04 \pm 3.74	63	...	58.3	6.67 \pm 5.47	4.1/0	2.67 \pm 2.71 mg	1.67 \pm 1.32 mg ^f	83.5 \pm 66 ^f	
Risperidone	21.61 \pm 4.2	55	...	77.8	4.81 \pm 3.43	0/0	0.97 \pm 0.67 mg	1.19 \pm 1.14 mg ^f	59.5 \pm 57 ^f	

^aInitial score on delirium symptom rating scale (DRS, DRS-R-98, MDAS, DI).

^bPercent reduction of delirium severity rating scale.

^cMedian time until improvement.

^dTime until stabilization follow-up.

^eExpressed as mean daily dose \pm SD in chlorpromazine (CPZ) equivalents.⁵⁸

^fDose at end of study period.

^gAverage maximum daily dose.

^hMean maintenance dose during study period.

Abbreviations: AE = adverse event, DI = Delirium Index, DRS = Delirium Rating Scale, DRS-R-98 = Delirium Rating Scale-Revised-1998, MDAS = Memorial Delirium Assessment Scale, NA = not applicable.

Symbol: ... = data not available.

of postoperative delirium at their hospital, from 40% in the pretrial period to 16.5% in the trial's placebo group.⁷⁵ These findings support the effectiveness of systematic identification and nonpharmacologic care for patients at high risk of delirium and further the argument in favor of placebo-controlled trials to determine the balance of benefit and risk associated with use of antipsychotic medications to manage delirium.

Reducing delirium duration is another important outcome in assessing the effectiveness of any delirium intervention. Observational studies have shown that delirium is often a transient disorder with prompt treatment of precipitating medical illness. Several studies have found that delirium in postoperative populations lasts between 1 and 4 days in most cases.^{20,53–57,76} Delirium in medical patients tends to have a similar time course as that noted in surgical patients.^{3,52,77} Other studies have found a more protracted course of delirium, especially in cancer populations⁷⁸ and the elderly.^{40,79} Again, the absence of placebo-controlled trials makes it difficult to determine if the duration of delirium is influenced by treatment with antipsychotic medications.

Many of the antipsychotic treatment trials we reviewed had other important limitations. With potentially high rates of baseline improvement in delirium, adequate sample sizes are essential to detect potentially important benefits or harm resulting from interventions. Most trials had small sample sizes (median 12 participants) and are therefore likely underpowered to detect clinically important outcomes related to treatment with antipsychotics. Most studies also did not include a justification for their sample size based on primary study outcome.⁸⁰ Indeed, only 448 individuals were included in the studies we reviewed—less than 10% of the total number of individuals included in a meta-analysis of randomized controlled trials for antipsychotic treatment of behavioral disturbance in dementia.²⁵ Studies in this review tended to be of short duration (< 7 days in many cases), which may not have allowed for an adequate assessment of recovery from delirium or important adverse events. Delirium, by definition, has a fluctuating course of symptoms.³⁸ In studies that assessed patients infrequently, some individuals may appear to have recovered from delirium when in fact what was observed was a temporary fluctuation in symptoms.

Beyond the issues of internal validity discussed above, these studies of antipsychotic treatment of delirium may also have limited external validity or generalizability. In particular, many of the studies in our analysis either excluded patients with dementia^{63,70,72} or enrolled few patients with comorbid dementia.^{60,62,66,67} Dementia is a risk factor for delirium,^{77,81} and delirium superimposed on dementia tends to have less response to interventions than delirium in nondemented individuals.⁸² Of the studies included in our review, only one by Breitbart et al.⁶¹ reported data on dementia patients with delirium. The au-

thors found significant differences in delirium remission rates between individuals that had underlying dementia and those individuals without dementia (48% vs. 75.5%, $p < .05$) in univariate analysis, although this difference in delirium resolution was not statistically significant in subsequent logistic regression analysis. A substantial number of delirious individuals in clinical practice are likely to have comorbid dementia, which may predict a poorer response to antipsychotics than that reported by most of the trials included in our study.

The majority of studies in our review did not specify the proportion of individuals with either hyperactive or hypoactive delirium, although it has been shown that hyperactive delirium may be associated with a better prognosis than hypoactive delirium.^{7,79,83} Individuals with hyperactive delirium are also more likely to receive psychotropic medications.³⁰ Hyperactive delirium may place patients at greater risk for adverse events due to disruptive behaviors such as combativeness, wandering, and other behaviors that interfere with medical care such as pulling at intravenous lines. Francis et al.⁵ found that 28% of delirious elderly patients displayed such disruptive behaviors, although only 18% of individuals with delirium were prescribed antipsychotics, suggesting that some of these cases were successfully managed without antipsychotics.

In studies included in our review, only 1 by Breitbart et al.⁶¹ compared individuals with different subtypes of delirium and found significant differences in delirium remission with treatment, when individuals with hypoactive delirium were compared to those with a hyperactive subtype (48% vs. 83%, $p < .006$). One small study of delirious patients with acquired immunodeficiency syndrome (AIDS) that was not included in our review found chlorpromazine and haloperidol to be effective in reducing symptoms of delirium regardless of delirium subtype and that delirium severity was reduced prior to improvements in the severity of underlying medical illness.⁸⁴ Future studies of delirium interventions will need to control for delirium subtypes to determine if certain populations or presentations of delirium are more likely to benefit from antipsychotic treatment.

We were unable to identify any prospective studies comparing antipsychotic treatment to a control group of nonmedicated individuals, although some studies have attempted to assess the impact of antipsychotics on delirium outcomes using other methodologies. In a retrospective study of delirium in cancer patients, Olofsson et al.⁷⁸ found that patients who received haloperidol had a shorter duration of delirium compared with individuals that did not. In contrast, a prospective study by Manos and Wu⁸⁵ found that the duration of delirium was significantly longer in individuals referred for psychiatric consultation when they were treated with haloperidol as compared with those who did not receive the medication. In a retrospective study of intensive care unit patients, Milbrandt

et al.⁸⁶ reported that patients who received haloperidol had significantly reduced mortality over those who had not, although this may not have been an exclusively delirious patient population.

The recently published randomized, double-blind, placebo-controlled trial evaluating low dose preoperative and postoperative haloperidol treatment to prevent delirium in elderly hip surgery patients by Kalisvaart et al.⁷⁵ found no significant difference in the incidence of postoperative delirium with this intervention. However, this study did identify some promising results on secondary outcomes, and highlights several ways in which antipsychotic medications can be prescribed safely. Important safeguards against medication toxicity were implemented in this study, including a low-dosage of haloperidol (0.5 mg, 3 times daily), a maximum total duration of treatment of 6 days, and exclusion of patients at high-risk for cardiac arrhythmias by obtaining baseline electrocardiograms prior to administering any medication. Further studies are needed to confirm the safety and efficacy of this intervention.

Most of the studies utilizing haloperidol in our review primarily used orally administered medications^{68–70,72} and conservative dosing strategies.^{59,68–72} However, haloperidol is frequently administered parenterally to treat delirium, and considerable literature exists on its application in this setting.^{87–89} Again, however, there are no placebo-controlled trials of parenteral haloperidol to treat delirium. Suggested benefits of intravenous haloperidol include decreased rates of EPS, permitting increased doses of medication that would otherwise not be tolerated by the oral or intramuscular routes. Reduced rates of EPS with intravenous haloperidol alone⁹⁰ or in combination with lorazepam⁹¹ have been noted when compared with other routes of administration, although EPS is still possible with the intravenous route.⁹² Unfortunately, cardiac arrhythmias^{93–95} have been associated with intravenous haloperidol, limiting its usefulness and necessitating advanced cardiac monitoring when used. Guidelines for the use of intravenous haloperidol have been proposed and are available.⁹⁶ It should be recognized that currently no drug carries an official indication for treating delirium, and all use of parenteral haloperidol is off-label. Other reports have found that oral haloperidol has been successfully combined with lorazepam in a number of cases.⁹⁷ Uncontrolled studies that did not meet our inclusion criteria evaluated droperidol,^{98,99} pimozide,¹⁰⁰ loxapine,¹⁰¹ and ziprasidone¹⁰² and suggested that these antipsychotics might have some effect on the symptoms of delirium.

What does this mean for clinicians? To provide a context for our findings to clinicians who care for patients with delirium, we emphasize the following points. Delirium is often the only manifestation of serious but occult underlying disease. Furthermore, multiple conditions often conspire together to produce delirium in an individual.

Thus, clinicians should make a systematic effort to search for and correct all evident causes of delirium. Nonpharmacologic approaches to managing the symptoms of delirium should be instituted whenever possible. The American Psychiatric Association guidelines on delirium management¹⁷ suggest a number of environmental interventions for patients with delirium, including identifying underlying etiologies, coordinating care, preventing sensory deprivation and disorientation, monitoring safety, and educating the patient and family about the disorder. A comprehensive multifaceted approach to delirium management based on environmental strategies, combined with pharmacologic interventions in certain cases, is likely to have the greatest impact on patient care.^{103–106}

At times, distress or agitation secondary to delirium will threaten patient safety and care, necessitating pharmacologic interventions. Prior to initiating any treatment with antipsychotics, the following safety issues should be considered. First, clinicians should attempt to use low doses, particularly when treating elderly patients. Second, frequent reassessments are valuable to help limit the duration of antipsychotic use and encourage drug discontinuation as soon as it is feasible. Third, a baseline electrocardiogram should be carried out on all patients prior to antipsychotic treatment, both to rule out cardiac ischemia and possible susceptibility to antipsychotic-induced arrhythmia as indicated by prolongation of the QT interval.^{17,75,107} With these important safeguards to limit potential medication toxicity, the following recommendations for using antipsychotics may be useful. Currently, the American Psychiatric Association guidelines for delirium management recommend low-dose haloperidol (i.e., 1–2 mg p.o. q. 4 h as needed or 0.25–0.5 mg p.o. q. 4 h for the elderly) as the treatment of choice in cases where medications are necessary.¹⁷ No trial to date has demonstrated the superiority of any antipsychotic to haloperidol, although there are some limited data to suggest that the atypical antipsychotics risperidone^{70,72} and olanzapine⁷¹ may be associated with lower rates of medication-related adverse events. Risperidone, initiated at doses of 0.5–1.0 mg daily, or olanzapine, initiated at doses of 2.5–5.0 mg daily, in single or divided doses, titrated carefully to effect, may be reasonable alternatives to haloperidol, as these medications appear to have efficacy comparable to haloperidol in a limited number of head-to-head and open-label trials available in the literature. Initial doses of approximately one half the suggested doses may be necessary in frail older adults. As there is limited evidence to suggest the superiority of one antipsychotic over another for delirium, the decision of which antipsychotic to use may be based on several other factors. Important considerations in starting treatment with any antipsychotic for delirium may include: the patient's susceptibility to EPS and the propensity of the

medication to cause this side effect, the variable propensity and desirability for the medication to produce sedation, the patient's susceptibility to potential anticholinergic side effects, the risk of medication precipitating cardiac arrhythmia the availability of various routes for administering the medication, and potential drug-drug interactions.

There are some limitations to our study. We did not search the "grey literature" (i.e., data that have not been published in the peer-reviewed medical literature), although hand-searching for references increased the likelihood of finding relevant articles. It is possible that controlled trials for antipsychotics in the treatment of delirium exist, although we were unable to identify any in our search. The most likely effect of missing articles in the grey literature would be an overestimation of the efficacy of antipsychotics in treating delirium.¹⁰⁸ Our definitions of response and remission were selected to allow some comparison of clinical outcomes between studies, although our measures may not reflect clinically significant changes in delirium severity. Further investigation into clinically significant changes on delirium rating scales is required. We did not complete a meta-analysis or statistical comparison of trials because we felt the study design was too heterogeneous to allow this with any degree of validity.

CONCLUSIONS

We were unable to identify any published, placebo-controlled, randomized trials to support the safety or efficacy of antipsychotics in the treatment of delirium. At present there is limited evidence from uncontrolled trials to support the use of some antipsychotics using low doses on a short-term basis in the treatment of delirium. There is limited information regarding the safety of antipsychotics in treating delirium, although serious adverse events related to antipsychotic treatment were infrequently reported in these studies. Future placebo-controlled trials of antipsychotics are required to determine what impact these medications have on severity and duration of delirium as well as other important outcomes such as cognitive status, functional status, and mortality. Delirium is an important condition associated with a number of significant outcomes, and as such deserves its own focused treatment in addition to management of underlying medical conditions. Currently, it is unclear which treatments for delirium, whether medication-based or otherwise, are safe and effective or which patient populations or etiologies of delirium are most likely to respond to these interventions. Efforts should continue to be placed on improving access to effective multicomponent strategies to prevent delirium.^{73,105} Further studies are required to determine what role antipsychotic medications have in the routine management of delirium.

Drug names: chlorpromazine (Sonazine, Thorazine, and others), donepezil (Aricept), droperidol (Inapsine and others), haloperidol (haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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