A Meta-Analysis of the Risk of Acute Extrapyramidal Symptoms With Intramuscular Antipsychotics for the Treatment of Agitation

Theodore D. Satterthwaite, M.D.; Daniel H. Wolf, M.D., Ph.D.; Robert A. Rosenheck, M.D.; Raquel E. Gur, M.D., Ph.D.; and Stanley N. Caroff, M.D.

Objective: We examined the evidence for a decreased risk of extrapyramidal symptoms (EPS) with intramuscular second-generation antipsychotics (SGAs) versus intramuscular haloperidol alone or in combination with an anticholinergic agent.

Data Sources: We searched MEDLINE (1950 to the present), and EMBASE and the Cochrane Database through January 16, 2008, for studies published in English of intramuscular SGAs and intramuscular haloperidol alone or in combination with an anticholinergic agent using the following drug names: *ziprasidone*, *Geodon*, *olanzapine*, *Zyprexa*, *aripiprazole*, *Abilify*, *haloperidol*, and *Haldol*. We then searched this pool of studies for trials with the terms *intramuscular*, *IM*, or *injectable*. Initially, we included only randomized controlled trials (RCTs). To obtain more data comparing SGAs to the combination of haloperidol and an anticholinergic, we conducted a second analysis including studies of any methodology.

Study Selection: Seven RCTs that compared intramuscular SGAs to intramuscular haloperidol alone were identified. However, we found only one RCT of haloperidol plus an anticholinergic. In the second analysis, we identified 18 studies, including 4 using haloperidol combined with promethazine (an antihistamine with anticholinergic properties).

Data Extraction: The primary outcome measure was acute dystonia; secondary outcome measures included akathisia, parkinsonism, or the need for additional anticholinergic medication. For RCTs, risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for each outcome. When all studies were included in the second analysis, we calculated the risk of acute dystonia.

Data Synthesis: Among RCTs (N = 2032), SGAs were associated with a significantly lower risk of acute dystonia (RR = 0.19, 95% CI = 0.10 to 0.39), akathisia (RR = 0.25, 95% CI = 0.14 to 0.44), and anticholinergic use (RR = 0.19, 95% CI = 0.09 to 0.43) compared with haloperidol alone. When all trials were considered (N = 3425), rates of acute dystonia were higher for haloperidol alone (4.7%) than for SGAs (0.6%) or for haloperidol plus promethazine (0.0%).

Conclusions: Intramuscular SGAs have a significantly lower risk of acute EPS compared to haloperidol alone. However, intramuscular haloperidol plus promethazine has a risk of acute dystonia comparable to intramuscular SGAs. The decision to use SGAs should consider other factors in addition to the reduction of EPS, which can be prevented by the use of an anticholinergic agent.

(J Clin Psychiatry 2008;69:1869–1879)

Received Feb. 22, 2008; accepted May 19, 2008. *From the Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia (Drs. Satterthwaite, Wolf, Gur, and Caroff); the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn. (Dr. Rosenheck); Connecticut Veterans Affairs Health Care System, West Haven (Dr. Rosenheck); Philadelphia Veterans Affairs Medical Center, Philadelphia, Pa. (Drs. Gur and Caroff).*

Dr. Satterthwaite was awarded the Neuroleptic Malignant Syndrome Information Service 4th Annual Promising New Investigators Travel Scholarship for an earlier version of this article, but the award did not support this research directly.

Dr. Rosenheck has received grant/research support from Eli Lilly, Janssen, AstraZeneca, and Wyeth and is a consultant for GlaxoSmithKline, Bristol-Myers Squibb, Organon, and Janssen. Dr. Gur has received grant/research support from AstraZeneca. Dr. Caroff has received grant/research support from Pfizer and Bristol-Myers Squibb. Drs. Satterthwaite and Wolf have no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.

Corresponding author and reprints: Theodore D. Satterthwaite, M.D., Department of Psychiatry, University of Pennsylvania School of Medicine, 3535 Market St., 2nd Floor, Philadelphia, PA 19104 (e-mail: Ted.Satterthwaite@uphs.upenn.edu).

Agitation is a complex behavioral phenomenon with many etiologies.[1] Guidelines suggest initial verbal de-escalation and environmental interventions, but in practice, pharmacologic treatment via an intramuscular route often becomes necessary.[2] Antipsychotic drugs are an important part of pharmacotherapy for agitation.[3] Until recently, first-generation antipsychotics (FGAs) were the only intramuscular antipsychotics available. Early FGAs, such as chlorpromazine, were effective but often caused hypotension, and have been largely replaced in practice by the high-potency FGA haloperidol.[4] However, haloperidol poses a high risk for acute extrapyramidal symptoms (EPS) such as dystonia.[5] Such symptoms can be distressing, painful, or even life-threatening, and may erode patient trust and compliance.[6]

FOR CLINICAL USE

- Acute extrapyramidal symptoms (EPS) such as dystonia must be considered when selecting intramuscular pharmacotherapy to treat acute agitation.
- Intramuscular second-generation antipsychotics (aripiprazole, olanzapine, and ziprasidone) are less likely to cause acute EPS compared with intramuscular haloperidol alone.
- However, when intramuscular haloperidol is given in combination with an anticholinergic agent, the risk of dystonia is comparable to that of intramuscular second-generation antipsychotics.

Oral preparations of second-generation antipsychotics (SGAs) have a lower EPS burden compared to oral haloperidol.[6–8] In the past several years, intramuscular preparations of 3 SGAs (ziprasidone, olanzapine, and aripiprazole) have become available for the acute treatment of agitation or psychosis. Although some trials have provided limited evidence for a superior speed of onset[9] or degree of response,[10,11] other studies have not consistently demonstrated the superior efficacy of SGAs compared to haloperidol alone.[12–17] Therefore, in review articles[18–22] and industry marketing materials, most arguments for the preferential use of intramuscular SGAs highlight a reduced risk of EPS. However, it is important to note that industry-funded trials compared intramuscular SGAs to intramuscular haloperidol alone, without the use of an adjunctive anticholinergic.[9–11,13,14,17] This comparison may have diminished the relative tolerability of haloperidol, as agents with anticholinergic properties are often administered concomitantly to prevent acute EPS in routine clinical practice.[23–25]

Past reviews have confirmed a decreased risk of EPS for each of the intramuscular SGAs relative to haloperidol alone.[26–28] However, these reviews have not compared intramuscular SGAs to haloperidol plus anticholinergic agents, which would provide a more realistic evaluation of their relative tolerability in typical clinical settings. Given that most prior reviews have been qualitative in nature and that there is disagreement among consensus statements regarding the management of agitation,[2,29–38] we believe that there is a need for a more quantitative integration of data in order to guide clinical practice in this area. In addition, as both intramuscular and subsequent oral formulations of SGAs may cost 10 times as much as haloperidol,[39] the relative benefits of SGAs merit a careful assessment.

The objective of this study was to use a meta-analysis to systematically evaluate the evidence for a decreased risk of acute dystonia and other EPS for intramuscular SGAs versus intramuscular haloperidol with or without an anticholinergic agent. First, we evaluated randomized controlled trials (RCTs) that directly compared these agents. However, we found only one RCT that directly compared an intramuscular SGA to haloperidol plus an anticholinergic agent.[40] We therefore conducted a second analysis in order to include a wider range of studies, pooling data from all available trials of intramuscular SGAs or haloperidol plus an anticholinergic.

METHOD

Search Strategy

We searched MEDLINE (1950 to the present), EMBASE, and the Cochrane Registry of Controlled Trials (last search January 16, 2008) for studies published in English using the following drug names: *ziprasidone*, *Geodon*, *olanzapine*, *Zyprexa*, *aripiprazole*, *Abilify*, *haloperidol*, and *Haldol*. We then searched this pool of studies for trials with the terms *intramuscular*, *IM*, or *injectable*. References for each of these studies were in turn manually searched to look for studies that were not initially identified. Finally, other relevant primary studies, review papers, and major textbooks were checked. When data for the primary outcome measure were not reported by studies identified, we contacted the corresponding author or drug manufacturer to request unpublished data. Studies identified by the search previously described were rechecked to ensure that they met the inclusion criteria. One reviewer (T.D.S.) assessed methodological quality of the included studies according to the randomization procedure, blinding, intervention details, and outcome measures (described in Risk of Acute EPS: Randomized Controlled Trials, Outcome Measures).

Risk of Acute EPS: Randomized Controlled Trials

Studies included. We included RCTs that compared short-acting intramuscular SGAs (ziprasidone, olanzapine, or aripiprazole) to haloperidol with or without an anticholinergic agent. We did not include studies of long-acting intramuscular antipsychotics used for maintenance treatment (e.g., risperidone or haloperidol decanoate). Intramuscular FGAs other than haloperidol (fluphenazine, chlorpromazine, etc.) were not included, as they are used much less commonly than haloperidol[2,36] and they have not been used as comparison drugs in studies of intramuscular

SGAs. Included studies lasted at least 24 hours and included a minimum of 20 subjects. If a study had multiple treatment arms with variable doses, we included all subjects who received a therapeutic dose of an antipsychotic, but excluded subjects receiving subtherapeutic doses. Patient populations were not restricted to any particular diagnosis; any study in which the patient was agitated or acutely psychotic and in need of intramuscular medications was included.

Outcome measures. Due to its frequency during acute treatment, its serious consequences, and the ease with which it is objectively identified, we chose acute dystonia as the primary outcome measure. Dichotomous secondary outcome measures included akathisia, parkinsonism, or the need for anticholinergic medication. Continuous secondary outcome measures included changes on the Simpson-Angus Scale[41] or the Barnes Akathisia Scale.[42] We did not include "total EPS" as an outcome, given the lack of a precise definition and apparently inconsistent application across studies.[9,10,17]

Data analysis. Data analysis techniques were closely modeled on the rigorous methods developed by the Cochrane Collaboration.[43] Data were entered twice into Revman 4.2,[44] a program developed by the Cochrane Collaboration for meta-analyses. For a given outcome measure, we proceeded with the analysis described here only if it was reported by at least 2 studies. We found only 1 study that compared intramuscular SGAs to haloperidol plus an anticholinergic.[40] Therefore, this comparison was not considered in this analysis, but was instead addressed in a second analysis of all trials as discussed in Risk of Acute Dystonia: All Trials. In the case of studies in which patients were exposed to intramuscular antipsychotics for greater than 24 hours, corresponding authors were contacted to determine the number of events in the first 24 hours of the study. If this information could not be obtained, the daily risk of each outcome measure was calculated by dividing the total number of reported events by the median number of days of antipsychotic exposure, rounded to the nearest integer. This method provides a conservative estimate of acute EPS and avoids the confound of longer trials carrying a disproportionate weight. Furthermore, studies requiring this correction were excluded in a sensitivity analysis as described at the end of the next paragraph.

For all outcomes, a risk ratio with 95% confidence intervals was calculated using a fixed-effects model. Heterogeneity was assessed using a Mantel-Haenszel χ^2 test with an associated I-squared value. A significance level of less than 0.10 or an I-squared value of greater than 50% was interpreted as possible heterogeneity, in which case a random-effects model was employed. Furthermore, in order to provide increased utility to clinical practice, an NNTH (number needed to treat to produce an additional harmful outcome) with an associated 95% confidence interval is reported for each outcome. The NNTH is the inverse of the risk difference for each outcome; the risk difference was calculated independently of the risk ratio that served as our primary measure of statistical significance. Finally, 2 sensitivity analyses were conducted. First, RCTs were excluded if they were not double-blind, if there were other methodological concerns, or if there was ambiguity in the reporting of the outcomes. Another sensitivity analysis excluded trials with greater than 24 hours of antipsychotic exposure in which event frequencies were corrected by the method described previously. If either sensitivity analysis significantly influenced the result of any primary or secondary outcome measure, both results are reported.

Risk of Acute Dystonia: All Trials

Studies included and outcome measures. As noted previously, our search returned only one RCT comparing an intramuscular SGA (olanzapine) to haloperidol plus an antihistamine with anticholinergic properties (promethazine).[40] In order to identify more studies of patients treated with such a combination, we conducted a second analysis in which we broadened our search to include all published clinical trials of intramuscular SGAs or haloperidol plus an anticholinergic, regardless of trial methodology. Thus, here we included nonrandomized, naturalistic studies as well as the RCTs initially identified.

Whereas the RCTs all directly compared intramuscular SGAs to haloperidol, in this analysis we included any study that treated patients with an intramuscular SGA or with intramuscular haloperidol plus an anticholinergic agent, regardless of comparison drug. For example, studies that compared intramuscular SGAs to a benzodiazepine[45,46] were not included in the analysis of RCTs, but in this second analysis we included patients in the SGA arms of these studies. However, as the specific purpose of this second analysis was to identify studies that used a combination of haloperidol and an anticholinergic, older studies that evaluated only intramuscular haloperidol alone were not included. As in Correll et al.,[7] the risk of dystonia for intramuscular haloperidol alone was calculated from studies that used haloperidol as a comparison drug versus either SGAs or the combination of haloperidol plus an anticholinergic, including the RCTs from the first analysis. As described in Results, there was a more than adequate sample derived by this method.

Search strategy and inclusion criteria were otherwise the same as for the RCT analysis as described previously, including a minimum duration of 24 hours and a minimum sample size of 20 patients. For this second analysis, however, we only considered the primary outcome of acute dystonia.

Data analysis. Data were pooled across studies with a weighted mean in order to calculate the absolute risk of occurrence of acute dystonia for each of the 3 treatment

Table 1. Characteristics of Randomized Controlled Trials Comparing Intramuscular SGAs and Intramuscular Haloperidol

Study	Drug	Dose, mg	N	Male, %	Mean Age, y	Blinding	Symptoms Required	Outcomes Reported
Andrezina et al, 2006[17]	Aripiprazole	9.75	175	63	41.9	Double-blind	PANSS-EC scores 15–32; 2 items > 4	Dystonia
	Haloperidol	6.5	185	59	41.8			
Breier et al, 2002[13]	Olanzapine	5, 7.5, or 10	137	58	35.9	Double-blind	PANSS-EC score > 14, one item > 4	Dystonia, akathisia, anticholinergics
	Haloperidol	7.5	40	55	37.4			
Brook et al, 2000[10]	Ziprasidone	10, then 5–20	90	92	34.5	Open-label	Not specified	Dystonia, akathisia, anticholinergics
	Haloperidol	2.5–10	42	95	32.8			
Brook et al, 2005[11]	Ziprasidone	10 or 20	429	67	34.0	Single-blind	BPRS > 40	Dystonia, akathisia, anticholinergics
	Haloperidol	2.5 or 5	138	66	34.6			
Daniel et al, 2004[16]	Ziprasidone	5, 10, or 20	206	89	39.2	Open-label	Not specified	Dystonia, akathisia, anticholinergics
	Haloperidol	Up to 10	100	87	39.1			
Tran-Johnson et al, 2007[14]	Aripiprazole	5.25, 9.75, 15	176	60	41.6	Double-blind	PANSS-EC scores 15–32; 2 items > 4	Dystonia, akathisia
	Haloperidol	7.5	57	65	40.0			
Wright et al, 2001[9]	Olanzapine	10	131	NR[a]	38.2[a]	Double-blind	PANSS-EC score > 14, one item > 4	Dystonia, anticholinergics
	Haloperidol	7.5	126	NR[a]	38.2[a]			

[a]Wright et al.[9] did not report the proportion of male and female subjects or the mean age of each treatment arm.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, NR = not reported, PANSS-EC = Positive and Negative Syndrome Scale-excited component, SGA = second-generation antipsychotic.

groups: intramuscular SGAs, haloperidol plus an anticholinergic, or haloperidol alone. Studies with antipsychotic exposure lasting greater than 24 hours were corrected using the method described previously. This analysis provides estimated rates of acute dystonia in each group and permits descriptive comparisons between treatments. However, direct statistical comparisons between groups cannot be made using data pooled in this manner.[7]

RESULTS

Risk of Acute EPS in Randomized Controlled Trials

Study characteristics. Seven randomized controlled trials that compared an intramuscular SGA to haloperidol alone were included.[9–11,13,14,16,17] However, as noted previously, our search identified Raveendran et al.[40] as the only study to compare an intramuscular SGA to haloperidol plus an anticholinergic agent. We therefore did not consider this comparison in this analysis, but returned to it with an expanded pool of studies in the second analysis. The characteristics of the RCTs included are displayed in Table 1. Two studies using olanzapine and haloperidol were not included as they did not report EPS.[47,48] In total, 2032 patients from 7 studies were included; all of the intramuscular SGAs were represented in the analysis, including ziprasidone (3 studies, N = 725), olanzapine (2 studies, N = 268), and aripiprazole (2 studies, N = 351). Notably, all trials were double-blind except for the 3 ziprasidone trials. Two of these trials[10,16] were open label, while in one, Brook et al.,[11] patients were not blinded but all assessments were blinded to treatment assignment. Two trials included treatment arms with subtherapeutic doses of the SGA: subjects receiving 2.5 mg olanzapine[13] or 1 mg aripiprazole[14] were not included. All trials were 24 hours long, with the exception of the 3 ziprasidone trials,[10,11,16] which included a transition to oral treatment. For these ziprasidone trials, event rates were corrected for the duration of intramuscular antipsychotic exposure. Based on these factors, a sensitivity analysis excluded the ziprasidone trials. The patient population of trials included in the analysis was uniform: all patients were diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder, and patients with significant physical illness or comorbid active substance abuse were excluded. Participants were more likely to be male (range, 55%–95%), with a mean age range of 32.8–41.9 years.

Outcomes included. Included RCTs reported the specified outcome measures to a varying degree. Six of the 7 studies provided data on the primary outcome measure of acute dystonia; Andrezina et al.[17] did not specifically report dystonia, but these data were obtained from the authors (R. C. Josiassen, Ph.D., personal communication, Jan. 3, 2008). Five studies reported the occurrence of akathisia[10,11,13,14,16]; 5 also discussed anticholinergic use.[9–11,13,16] However, the ziprasidone studies[10,11,16] did not report sufficient details on anticholinergic use to be included. Parkinsonism was reported by only one study,[13] so this outcome measure was not included in the analysis. Similarly, the Simpson-Angus Scale and Barnes Akathisia Scale outcome measures were not included as only one study[10] reported baseline and endpoint standard deviations.

Primary outcome: acute dystonia. Seven trials with a total of 2032 randomly assigned patients reported on acute dystonia, with 1344 in the SGA group and 688 in the haloperidol group. Of this sample, there were only 12 dystonic reactions in the SGA group, while there were 30 in the haloperidol group. There was a nonsignificant amount of heterogeneity among studies (χ^2 p = .72, I-squared = 0%), so a fixed-effects model was employed.

Figure 1. Fixed-Effects Model of Risk of Acute Dystonia in Randomized Controlled Trials of Second-Generation Antipsychotics Versus Haloperidol

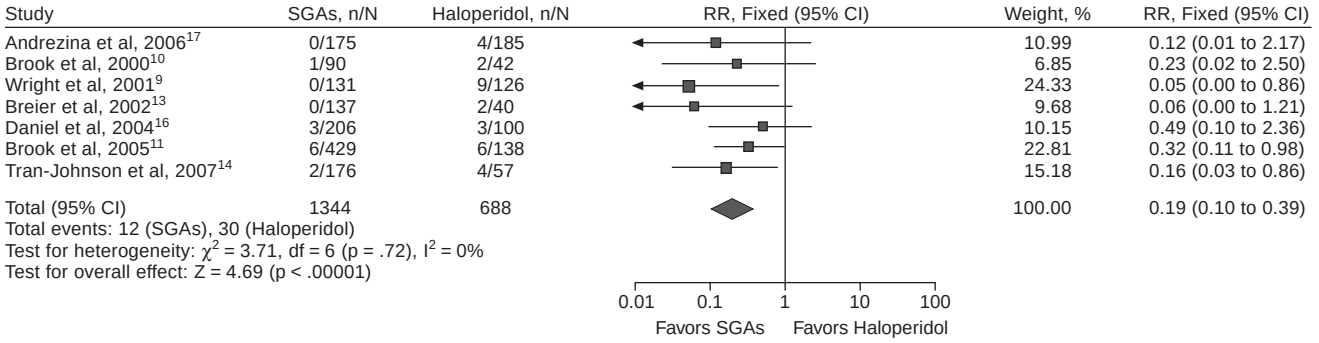


Figure 2. Fixed-Effect Model of Risk of Akathisia in Randomized Controlled Trials of Second-Generation Antipsychotics Versus Haloperidol

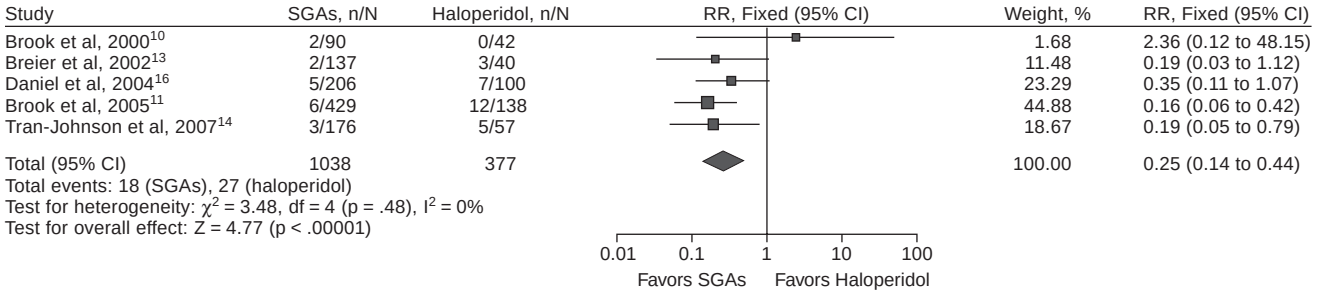
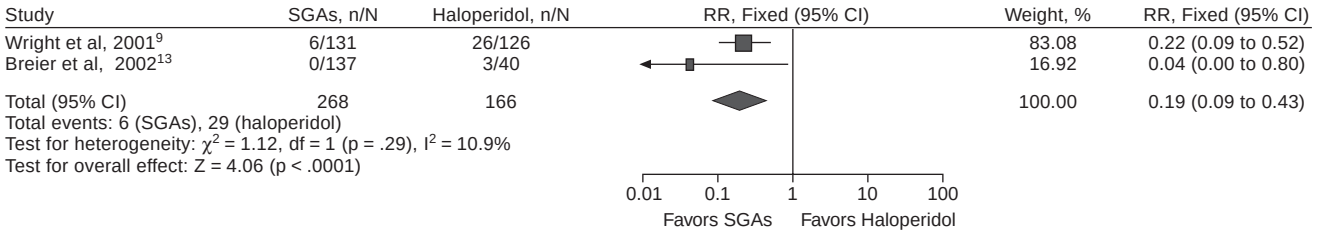


Figure 3. Fixed-Effect Model of Risk of Anticholinergic Use in Randomized Controlled Trials of Second-Generation Antipsychotics Versus Haloperidol



Using this model, patients treated with SGAs were significantly less likely to develop a dystonic reaction: risk ratio (RR) = 0.19, 95% confidence interval (CI) = 0.10 to 0.39 (Figure 1); NNTH = 25.0, 95% CI = 20.0 to 50.0. When the 3 ziprasidone trials[10,11,16] were excluded in a sensitivity analysis, the results did not change significantly.

Akathisia. Five trials with a total of 1415 patients reported on akathisia.[10,11,13,14,16] Of patients who received intramuscular SGAs, 18 of 1038 developed akathisia, while 27 of 377 patients who received haloperidol experienced this adverse event. There was a nonsignificant amount of heterogeneity among studies (χ^2 p = .48, I-squared = 0%), and a fixed-effects model was employed (Figure 2). There was a significantly lower risk of akathisia among SGAs than haloperidol (RR = 0.25, 95% CI = 0.14 to 0.44; NNTH = 20.0, 95% CI = 12.5 to 33.3). In the sensitivity analysis that excluded the 3 ziprasidone trials,[10,11,16] the results did not change significantly.

Anticholinergic use. Anticholinergic use was reported in 5 studies.[9–11,13,16] However, all ziprasidone studies were excluded: the precise number events were not reported for Daniel et al.[16] and it was not possible to distinguish between anticholinergics given during the intramuscular

Table 2. Characteristics of Additional Studies Included in Analysis of All Trials

Study	Drug	Dose, mg	N	Male, %	Mean Age, y	Study Design	Diagnosis	Severity
Alexander et al, 2004[45]	Haloperidol + Promethazine	5 or 10 + 25 or 50	100	55	30.9	Single-blind, RCT	Agitation	Requiring IM medications for agitation
Barak et al, 2006[50]	Ziprasidone	10 or 20	21	29	71.4	Naturalistic, open label	Age > 60, schizophrenia or schizoaffective	Requiring IM medications for agitation
Centorrino et al, 2007[56]	Olanzapine	10 (mean)	74	57	34.2	Naturalistic, open label	Bipolar or psychotic disorder	Requiring IM medications for agitation
Daniel et al, 2001[51]	Ziprasidone	20	41	78	39.9	Double-blind, RCT	Any psychotic disorder	PANSS > 3 on 3 agitation items
Huf et al, 2007[52]	Haloperidol + Promethazine	5 or 10 + 25 or 50	160	59	40.2	Single-blind, RCT	Agitation	Requiring IM medications for agitation
	Haloperidol	5 or 10	156	48	39.3			
Lesem et al, 2001[53]	Ziprasidone	10	63	66	32.9	Double-blind, RCT	Any psychotic disorder	PANSS > 3 on 3 agitation items
Meehan et al, 2001[54]	Olanzapine	10 × 2, then 5	99	58	40.2	Double-blind, RCT	Bipolar I, manic or mixed state	PANSS-EC > 14, one item > 4
Meehan et al, 2002[46]	Olanzapine	2.5 or 5	137	39	77.6	Double-blind, RCT	Age > 55 and probable dementia with agitation	PANSS-EC > 14, one item > 4
Raveendran et al, 2007[40]	Olanzapine	5 or 10	150	65	30.4	Single-blind, RCT	Agitation	Requiring IM medications for agitation
	Haloperidol + Promethazine	5 + 25 or 10 + 50	150	61	30.6			
San et al, 2006[55]	Olanzapine	10	92	48	36.5	Naturalistic, open label	Agitation	Requiring IM medications for agitation
TREC Collaborative, 2003[49]	Haloperidol + Promethazine	5 or 10 + 25 or 50	150	49	38.0	Single-blind, RCT	Agitation	Requiring IM medications for agitation

Abbreviations: IM = intramuscular, PANSS = Positive and Negative Syndrome Scale, PANSS-EC = Positive and Negative Syndrome Scale-excited component, RCT = randomized controlled trial.

versus oral phase of Brook et al.[10] and Brook et al.[11] Thus, the analysis included 434 patients from the 2 remaining studies. Among the 268 patients in the SGA group, 6 received anticholinergic treatment, compared with 29 of the 166 patients in the haloperidol group. There was little heterogeneity (χ^2 p = .29, I-squared = 10.9%) between studies, and the fixed-effects model employed found a significant advantage for intramuscular SGAs (RR = 0.19, 95% CI = 0.09 to 0.43; NNTH = 7.7, 95% CI = 5.3 to 14.3; Figure 3).

Risk of Acute Dystonia in All Trials

Study characteristics. Beyond the RCTs directly comparing SGAs and haloperidol identified previously (and also included here), 11 additional studies were identified when trials of any methodology were considered (see Table 2 for details).[40,45,46,49–56] Of the additional studies included, 8 had intramuscular SGA treatment arms, while 4 of the additional studies examined haloperidol plus promethazine (an antihistamine with anticholinergic properties). Among these studies, one study had a treatment arm using intramuscular haloperidol alone.[52]

Overall, the second analysis included 18 studies with 3425 patients: 2021 were treated with intramuscular SGAs, 844 were treated with intramuscular haloperidol alone, and 560 were treated with intramuscular haloperidol plus promethazine. The vast majority of the studies included in this second analysis were either double-blind randomized trials (N = 1367) or single-blind randomized trials (N = 1433); 2 studies were randomized open-label (N = 438)[10,16] and 3 were nonrandomized open-label (N = 187).[50,55,56] Notably, all 4 trials of haloperidol in combination with promethazine were randomized but were not double-blinded.[40,45,49,52] Subjects receiving 2 mg ziprasidone were not included.[51,53] Most patients carried a diagnosis of a primary psychotic disorder (60%), while a sizable minority of patients (30%) were from studies that did not require a diagnosis for study entry beyond symptomatic agitation.[40,45,49,52,55]

Despite the liberal inclusion criteria of this analysis, several studies were excluded. One study was excluded because it did not report the presence or absence of dystonic events[57]; 4 studies were excluded because they did not last at least 24 hours[58–61]; 5 studies were excluded because they included insufficient numbers of subjects[62–66]; and 4 were excluded because the patients were under 18 years old.[67–70]

Acute dystonia. There was a marked difference in the risk of acute dystonia between the 3 groups. Among 2021 patients treated with intramuscular SGAs, only 12 experienced a dystonic reaction (0.6%)—much less than the 40 of 844 patients (4.7%) treated with haloperidol alone. Critically, there were zero reported cases of acute dystonia among 560 patients treated with haloperidol plus

promethazine. Overall, with a sample of 3425 patients, these results suggest that haloperidol in combination with promethazine may have as low a risk of acute dystonia as intramuscular SGAs.

DISCUSSION

We examined RCTs comparing intramuscular SGAs to haloperidol alone and found evidence for a decreased risk of acute dystonia, akathisia, and the need for additional anticholinergic drugs. However, a second analysis pooling all studies of intramuscular SGAs or a combination of intramuscular haloperidol plus an anticholinergic suggests that the combination of haloperidol plus promethazine has an equally low risk of precipitating dystonia as SGAs.

SGAs Have a Reduced EPS Burden Compared to Haloperidol Alone

In 7 RCTs, we found that there was a significantly lower risk of acute dystonia (NNTH 25.0), akathisia (NNTH 20.0), and anticholinergic use (NNTH 7.7) with intramuscular SGAs. By quantitatively examining all available intramuscular SGAs as a group, these results extend the findings of previous reviews that considered each agent individually.[26–28] The intramuscular SGAs currently available are somewhat heterogeneous, with variable D2 receptor affinity. The current analysis was not designed to detect differential rates of EPS among these 3 drugs; rigorous evaluation of such risks would ideally require large head-to-head trials. Nonetheless, these results establish that as a group, the currently available intramuscular SGAs have a decreased risk of EPS compared to haloperidol alone.

Haloperidol Plus Promethazine May Avoid Dystonia to a Similar Degree as SGAs

Our search revealed only one RCT that directly compared an SGA (olanzapine) to haloperidol plus an anticholinergic agent (promethazine).[40] This study reported zero dystonic reactions among the 150 patients receiving each treatment. To avoid relying on a single study for this important comparison, we conducted a second analysis including all trials of intramuscular SGAs or haloperidol in combination with an anticholinergic, even if they were not randomized and did not directly compare the treatments. The results are striking: approximately 4.7% (40/844) of patients given intramuscular haloperidol alone experienced a dystonic reaction, in contrast to only 0.6% (12/2021) of patients given SGAs and 0% (0/560) of patients given haloperidol plus promethazine. Although rigorous statistical comparisons are not possible for data pooled in this manner, the differences in rates of dystonia strongly suggest that intramuscular haloperidol pluspromethazine is no more likely to precipitate dystonia than SGAs.

This finding is important for 2 reasons. First, the transition to using intramuscular SGAs as first-line agents for the management of agitation has been rationalized in large part by the decreased risk of EPS (especially acute dystonia). If the addition of a drug with anticholinergic properties can reduce the risk of acute dystonia to a similar degree, then this rationale for the use of SGAs is diminished. Second, given that intramuscular preparations of SGAs cost greater than 10 times more than haloperidol plus an antihistamine with anticholinergic properties (ziprasidone 20 mg, $11.76; aripiprazole 10 mg, $13.61; olanzapine 10 mg, $26.16; haloperidol 5 mg, $0.87; promethazine 25 mg, $0.63; diphenhydramine 25 mg, $0.59),[39] this decision may have financial implications. However, it is important to note that not all anticholinergic agents are inexpensive; a 2 mg benztropine injection may cost as much as $62.50 (list price).[39] Furthermore, it should be noted that acute treatment of agitation with intramuscular agents represents a relatively small part of overall costs when compared to the costs of emergency department visits, inpatient hospitalization, or maintenance pharmacotherapy. However, if an SGA is continued for maintenance therapy, the costs can be considerable.[71]

Limitations

There are several important limitations of this meta-analysis that reflect the complexities of conducting trials in acute care settings. Several merit special consideration: patient diagnosis, patient demographics, requirements for consent, study methodology, drug dosing, benzodiazepines, and search limits. First, all patients from the RCTs were diagnosed with a primary psychotic disorder (schizophrenia, schizoaffective disorder, or schizophreniform disorder); as such, very few were antipsychotic-naive. The second analysis including all trials had a wider range of patient diagnoses, but nonetheless, primary psychotic disorders were heavily represented in this sample as well. Patients with psychotic disorders who have received antipsychotics in the past may be less susceptible to acute EPS than first-episode patients,[72] as patients are typically at the greatest risk of dystonia at a young age when beginning treatment.[6] Conversely, such patients may also have been maintained on long-term treatment with anticholinergic medication at baseline. Abrupt withdrawal of such treatment can itself cause EPS,[73] which might bias reported rates of events. These factors may limit the ability to generalize our findings to antipsychotic-naive patients experiencing a first episode of psychosis.

Second, most studies included in this review enrolled nonelderly adults, with men more heavily represented than women. Dystonia is more common in men[6,74,75]; the higher proportion of men in this analysis could lead to an overestimation of the risk of dystonia. More importantly,

with the exception of 2 studies that explicitly considered the agitated elderly,[46,50] all other studies mainly enrolled nonelderly patients. As acute dystonia is far more common in young people,[74,75] this may limit the ability to apply these results to an elderly population. We chose acute dystonia as the primary outcome measure for this meta-analysis as it is a particularly unpleasant and sometimes dangerous adverse effect that occurs more commonly in the first 24 hours of treatment; in contrast, akathisia or parkinsonism typically have a more subacute onset.[6,76,77] Parkinsonism is a more common and important concern in elderly patients,[8] but this outcome was not evaluated in this review as we found only one RCT that explicitly reported its occurrence.[13] Furthermore, the addition of an anticholinergic agent may not be recommended in the elderly, as it can precipitate delirium and worsen cognitive deficits.[78]

Third, it is important to note that some patients may have been excluded from the RCTs because of the necessity of providing informed consent. Each study maintained inclusion criteria describing a minimum level of acceptable agitation. Most studies required that patients be able to provide consent themselves,[9,11,13,16] while others allowed consent of a surrogate.[10,14,17] Thus, some patients that were too agitated to provide consent may have been excluded. In addition, patients who had EPS secondary to haloperidol in the past may have been reluctant to consent to being randomized to receive it again, thus excluding patients who may be more susceptible to haloperidol-induced EPS. These factors suggest that industry-sponsored registration trials may not provide a complete picture of the EPS risk of intramuscular antipsychotics, and may limit the generalizability of these findings to very agitated patients. We addressed this issue to some degree in the second analysis by including many studies that did not require prospective informed consent.[40,45,49,52,55,56]

Fourth, our analysis has certain methodological limitations. In the RCT analysis, it should be noted that the NNTH reported is based on a risk difference calculation for each study; risk differences may be somewhat less stable outcomes than risk ratios in meta-analytic models.[43] Therefore, while the NNTH may provide a more clinically useful measure of absolute risk, it may be somewhat less statistically accurate than the risk ratio also reported. In the all-trials analysis, we pooled data for this analysis using a similar approach to that described by Correll et al.[7] However, some of the criticisms of Correll et al.[7] could be applied to our second analysis. Most saliently, Saraf and Chandra[79] noted that it is not ideal to pool data from a heterogeneous sample of studies. However, it is critical to note that the second analysis was only pursued once it was clear that there was just one RCT that directly compared an intramuscular SGA to haloperidol plus an anticholinergic agent.[40] Thus, this analysis was necessarily exploratory, and underscores the need for more trials that directly compare intramuscular SGAs to haloperidol plus agents with anticholinergic properties. Furthermore, it is important to note that our analysis of all trials considered only the primary outcome measure of acute dystonia, limiting the ability to generalize these data to other extrapyramidal syndromes.

Fifth, the haloperidol doses used for studies included in the review (6.5 mg–10 mg) were higher than the 5 mg dose typically used in clinical practice.[3] Given that higher doses of haloperidol could lead to more frequent dystonic reactions,[6,80,81] these doses might exaggerate the difference between haloperidol and comparison drugs.[82] The rates of dystonia with haloperidol reported here are well within previously reported ranges,[6] suggesting that a dose-related effect was small if it was present. Future studies should use the typical 5 mg dose of haloperidol to obviate such concerns and enhance the clinical relevance of results.

Sixth, this review did not consider benzodiazepines alone or in combination with haloperidol. Along with antipsychotics, benzodiazepines such as lorazepam are a mainstay of the pharmacologic treatment of agitation.[2,3] One well-designed trial by Battaglia et al.[83] and a recent review on the topic[84] found that the addition of a benzodiazepine reduces the risk of EPS compared to haloperidol alone. In our search, we did not encounter any studies that compared intramuscular SGAs to haloperidol plus a benzodiazepine. Beyond the Battaglia et al.[82] trial, there is a paucity of data currently available; given the prevalent use of this combination, future studies could ideally include this combination as an active comparison group.

Finally, the studies included in our search were limited to articles published in English. While we employed several databases in order to produce a comprehensive review, not considering articles published in other languages may have excluded certain studies.

Clinical Implications

While acute EPS are a very important consideration in the choice of antipsychotic for the treatment of agitation, the selection of pharmacotherapy requires evaluation of many factors on an individual level. Beyond EPS, some authors have postulated that intramuscular SGAs have other benefits. Notably, certain studies have found that intramuscular SGAs have an advantage in speed of onset or degree of response,[9–11] but not all studies have demonstrated such superiority.[12–16] Additionally, multiple studies have emphasized the ability of intramuscular SGAs to aid in the transition to oral use of the same SGA as a maintenance agent.[10–12,16,85–87] This may be an important advantage given that the availability of intramuscular preparations has been demonstrated to influence the choice of a maintenance agent,[88] and maintenance treatment with oral SGAs may be superior to haloperidol at reducing aggression.[89] However, the advantage for SGAs in preventing aggression may be primarily carried by clozapine,[89,90]

which is not available intramuscularly. Furthermore, it is important to note that maintenance treatment with FGAs such as haloperidol is associated with an increased risk of tardive dyskinesia (TD) compared to SGAs[7] and that treatment with anticholinergic agents also has been associated with increased risk of TD in some studies.[91] Finally, some authors have claimed that intramuscular SGAs produce a specific calming effect rather than nonspecific sedation,[92,93] although this has not been fully supported by a non–industry-funded trial.[40]

Promethazine was the only intramuscular anticholinergic agent that we found used in trials in combination with haloperidol. While these 4 trials[40,45,49,52] have been noted to be of very high methodological quality,[94] they were randomized but were not double-blind. The combination of promethazine and haloperidol is frequently used internationally,[52] but it is not commonly used in the United States. Although there are no contemporary studies available, commonly used agents with similar properties such as diphenhydramine or benztropine may reduce acute dystonia to a similar degree as promethazine.[95] Promethazine is a sedating antihistamine with anticholinergic properties; it is also a phenothiazine with a low D2 affinity.[96] While this study considers only adverse effects, the addition of promethazine may also provide some benefits in terms of efficacy as well as reduction of EPS.[52] To our knowledge, no study has evaluated promethazine or other antihistamines as monotherapy for agitation. Similarly, we are unaware of any studies confirming antipsychotic efficacy of this drug. Like other agents with strong antihistaminergic activity, promethazine is sedating and has been linked to respiratory depression in children.[97] However, this is a less common event in adults, with none of the patients in the trials included in this analysis experiencing respiratory depression or other serious adverse effects associated with phenothiazines, or other antihistaminergic or anticholinergic drugs.

Except in special situations, it may be best to avoid the use of haloperidol alone for the treatment of agitation, which places the patient at an unnecessarily high risk of acute dystonia. As noted by Huf et al., "Sole use of intramuscular haloperidol is not an acceptable way of managing acute aggression as it . . . carries with it the avoidable risk of acute dystonia."[52(p875)] Instead, future studies should consider using intramuscular haloperidol in combination with an agent to prevent EPS. This has been previously discussed regarding studies of oral maintenance treatment,[71] but the current results are the first to quantitatively demonstrate the importance of this issue with regard to intramuscular treatment.

CONCLUSIONS

Much of the rationale for the increasingly wide use of intramuscular SGAs emphasizes the avoidance of EPS. The results presented here confirm that the currently available intramuscular SGAs have a significantly lower risk of acute EPS compared to haloperidol alone. However, in an analysis of all published clinical trials with a large sample of patients, we found that intramuscular haloperidol and promethazine in combination are no more likely to cause acute dystonia than SGAs. These results suggest that the reduced risk of EPS associated with intramuscular SGAs should not be the only or most important factor in selecting an intramuscular antipsychotic for agitation, and that the choice of an intramuscular antipsychotic in acute care settings should be individualized and informed by multiple factors. Future trials should compare intramuscular SGAs to haloperidol plus an agent with anticholinergic properties instead of haloperidol alone.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), diphenhydramine (Benadryl and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), promethazine (Promethegan, Promethacon, and others), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, promethazine is not approved by the U.S. Food and Drug Administration for the treatment of extrapyramidal effects.

REFERENCES

1. Lindenmayer JP. The pathophysiology of agitation. J Clin Psychiatry 2000;61(suppl 14):5–10
2. Marder SR. A review of agitation in mental illness: treatment guidelines and current therapies. J Clin Psychiatry 2006;67(suppl 10):13–21
3. Rund DA, Ewing JD, Mitzel K, et al. The use of intramuscular benzodiazepines and antipsychotic agents in the treatment of acute agitation or violence in the emergency department. J Emerg Med 2006;31(3):317–324
4. Altamura AC, Sassella F, Santini A, et al. Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. Drugs 2003;63(5):493–512
5. Rosenbaum JF, Arana GW, Hyman SE, et al. Handbook of Psychiatric Drug Therapy. Philadelphia, Pa: Lipincott, Williams, and Wilkins; 2005
6. van Harten PN, Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. Br Med J 1999 Sep;319(7210):623–626
7. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004;161(3):414–425
8. Van Gerpen JA. Drug-induced parkinsonism. Neurologist 2002;8(6):363–370
9. Wright P, Birkett M, David SR, et al. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. Am J Psychiatry 2001;158(7):1149–1151
10. Brook S, Lucey JV, Gunn KP, for the Ziprasidone IM Study Group. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. J Clin Psychiatry 2000;61(12):933–941
11. Brook S, Walden J, Benattia I, et al. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. Psychopharmacology (Berl) 2005;178(4):514–523
12. Andrezina R, Marcus RN, Oren DA, et al. Intramuscular aripiprazole or haloperidol and transition to oral therapy in patients with agitation associated with schizophrenia: sub-analysis of a double-blind study. Curr Med Res Opin 2006;22(11):2209–2219
13. Breier A, Meehan K, Birkett M, et al. A double-blind, placebo-controlled

dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. Arch Gen Psychiatry 2002;59(5):441–448
14. Tran-Johnson TK, Sack DA, Marcus RN, et al. Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2007;68(1): 111–119
15. Currier GW, Citrome LL, Zimbroff DL, et al. Intramuscular aripiprazole in the control of agitation. J Psychiatr Pract 2007;13(3):159–169
16. Daniel DG, Zimbroff DL, Swift RH, et al. The tolerability of intramuscular ziprasidone and haloperidol treatment and the transition to oral therapy. Int Clin Psychopharmacol 2004;19(1):9–15
17. Andrezina R, Josiassen RC, Marcus RN, et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. Psychopharmacology (Berl) 2006;188(3):281–292
18. Brook S. Intramuscular ziprasidone: moving beyond the conventional in the treatment of acute agitation in schizophrenia. J Clin Psychiatry 2003;64(suppl 19):13–18
19. Tulloch KJ, Zed PJ. Intramuscular olanzapine in the management of acute agitation. Ann Pharmacother 2004;38(12):2128–2135
20. Wagstaff AJ, Easton J, Scott LJ. Intramuscular olanzapine: a review of its use in the management of acute agitation. CNS Drugs 2005;19(2): 147–164
21. Zimbroff DL, Allen MH, Battaglia J, et al. Best clinical practice with ziprasidone IM: update after 2 years of experience. CNS Spectr 2005; 10(9):1–15
22. Mendelowitz AJ. The utility of intramuscular ziprasidone in the management of acute psychotic agitation. Ann Clin Psychiatry 2004; 16(3):145–154
23. Arana GW, Goff DC, Baldessarini RJ, et al. Efficacy of anticholinergic prophylaxis for neuroleptic-induced acute dystonia. Am J Psychiatry 1988;145(8):993–996
24. Arya DK. Co-prescription of anticholinergic drugs with neuroleptics [letter]. Br J Hosp Med 1992 Feb–Mar;47(4):304
25. Keepers GA, Clappison VJ, Casey DE. Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. Arch Gen Psychiatry 1983;40(10):1113–1117
26. Citrome L. Comparison of intramuscular ziprasidone, olanzapine, or aripiprazole for agitation: a quantitative review of efficacy and safety. J Clin Psychiatry 2007;68(12):1876–1885
27. Bagnall A, Lewis RA, Leitner ML. Ziprasidone for schizophrenia and severe mental illness. Cochrane Database Syst Rev 2000;(4):CD001945
28. Belgamwar RB, Fenton M. Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses. Cochrane Database Syst Rev 2005 Apr;(2):CD003729
29. Allen MH. Managing the agitated psychotic patient: a reappraisal of the evidence. J Clin Psychiatry 2000;61(suppl 14):11–20
30. Allen MH, Currier GW, Carpenter D, et al. The expert consensus guideline series. Treatment of behavioral emergencies 2005. J Psychiatr Pract 2005 Nov;11(suppl 1):5–108
31. Allen MH, Currier GW, Hughes DH, et al. Treatment of behavioral emergencies: a summary of the expert consensus guidelines. J Psychiatr Pract 2003;9(1):16–38
32. Battaglia J. Pharmacological management of acute agitation. Drugs 2005;65(9):1207–1222
33. Buckley PF, Noffsinger SG, Smith DA, et al. Treatment of the psychotic patient who is violent. Psychiatr Clin North Am 2003;26(1):231–272
34. Lukens TW, Wolf SJ, Edlow JA, et al. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. Ann Emerg Med 2006;47(1):79–99
35. Marco CA, Vaughan J. Emergency management of agitation in schizophrenia. Am J Emerg Med 2005;23(6):767–776
36. McAllister-Williams RH, Ferrier IN. Rapid tranquillisation: time for a reappraisal of options for parenteral therapy. Br J Psychiatry 2002;180: 485–489
37. Petit JR. Management of the acutely violent patient. Psychiatr Clin North Am 2005;28(3):701–711
38. Huf G, da Silva Freire Coutinho E, Fagundes HM Jr, et al. Current practices in managing acutely disturbed patients at three hospitals in Rio de Janeiro-Brazil: a prevalence study. BMC Psychiatry 2002;2:4
39. Red Book 2007: Pharmacy's Fundamental Reference. Philadelphia, Pa: Thompson Scientific; 2007
40. Raveendran NS, Tharyan P, Alexander J, et al. Rapid tranquillisation in psychiatric emergency settings in India: pragmatic randomised controlled trial of intramuscular olanzapine versus intramuscular haloperidol plus promethazine. BMJ 2007 Oct;335(7625):865
41. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
42. Barnes TR. The Barnes Akathisia Rating Scale—revisited. J Psychopharmacol 2003;17(4):365–370
43. Murlow CD, Oxman AD. Cochrane Collaboration Handbook. 4th ed. Oxford, UK: Update Software; 1997
44. Review Manager (RevMan [computer program]. version 4.2.). Copenhagen, Denmark: The Cochrane Collaboration; 2003
45. Alexander J, Tharyan P, Adams C, et al. Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting: pragmatic randomised trial of intramuscular lorazepam v haloperidol plus promethazine. Br J Psychiatry 2004 Jul;185:63–69
46. Meehan KM, Wang H, David SR, et al. Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: a double-blind, randomized study in acutely agitated patients with dementia. Neuropsychopharmacology 2002;26(4):494–504
47. Kapur S, Arenovich T, Agid O, et al. Evidence for onset of antipsychotic effects within the first 24 hours of treatment. Am J Psychiatry 2005; 162(5):939–946
48. Jones B, Taylor CC, Meehan K. The efficacy of a rapid-acting intramuscular formulation of olanzapine for positive symptoms. J Clin Psychiatry 2001;62(suppl 2):22–24
49. TREC Collaborative Group. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. BMJ 2003 Sep;327(7417):708–713
50. Barak Y, Mazeh D, Plopski I, et al. Intramuscular ziprasidone treatment of acute psychotic agitation in elderly patients with schizophrenia. Am J Geriatr Psychiatry 2006;14(7):629–633
51. Daniel DG, Potkin SG, Reeves KR, et al. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. Psychopharmacology (Berl) 2001;155(2):128–134
52. Huf G, Coutinho ES, Adams CE. Rapid tranquillisation in psychiatric emergency settings in Brazil: pragmatic randomised controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine. BMJ 2007 Oct;335(7625):869–876
53. Lesem MD, Zajecka JM, Swift RH, et al. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. J Clin Psychiatry 2001;62(1):12–18
54. Meehan K, Zhang F, David S, et al. A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. J Clin Psychopharmacol 2001;21(4):389–397
55. San L, Arranz B, Querejeta I, et al. A naturalistic multicenter study of intramuscular olanzapine in the treatment of acutely agitated manic or schizophrenic patients. Eur Psychiatry 2006;21(8):539–543
56. Centorrino F, Meyers AL, Ahl J, et al. An observational study of the effectiveness and safety of intramuscular olanzapine in the treatment of acute agitation in patients with bipolar mania or schizophrenia/ schizoaffective disorder. Hum Psychopharmacol 2007;22(7):455–462
57. Zimbroff DL, Marcus RN, Manos G, et al. Management of acute agitation in patients with bipolar disorder: efficacy and safety of intramuscular aripiprazole. J Clin Psychopharmacol 2007;27(2):171–176
58. Preval H, Klotz SG, Southard R, et al. Rapid-acting IM ziprasidone in a psychiatric emergency service: a naturalistic study. Gen Hosp Psychiatry 2005;27(2):140–144
59. Damsa C, Adam E, De Gregorio F, et al. Intramuscular olanzapine in patients with borderline personality disorder: an observational study in an emergency room. Gen Hosp Psychiatry 2007;29(1):51–53
60. Pascual JC, Madre M, Soler J, et al. Injectable atypical antipsychotics for agitation in borderline personality disorder. Pharmacopsychiatry 2006;39(3):117–118
61. Fulton JA, Axelband J, Jacoby JL, et al. Intramuscular ziprasidone: an effective agent for sedation of the agitated ED patient. Am J Emerg Med 2006;24(2):254–255
62. Kohen I, Preval H, Southard R, et al. Naturalistic study of intramuscular ziprasidone versus conventional agents in agitated elderly patients: retrospective findings from a psychiatric emergency service.

Am J Geriatr Pharmacother 2005;3(4):240–245
63. Miceli JJ, Wilner KD, Swan SK, et al. Pharmacokinetics, safety, and tolerability of intramuscular ziprasidone in healthy volunteers. J Clin Pharmacol 2005;45(6):620–630
64. Brook S. A pilot study of intramuscular ziprasidone in the short-term treatment of patients with acute exacerbation of schizophrenia. Hum Psychopharmacol 2000;15(7):521–524
65. Bushe CJ, Taylor M, Mathew M. Intramuscular Olanzapine: a UK case series of early cases. Ann Gen Psychiatry 2007 Apr;6:11
66. Greco KE, Tune LE, Brown FW, et al. A retrospective study of the safety of intramuscular ziprasidone in agitated elderly patients. J Clin Psychiatry 2005;66(7):928–929
67. Barzman DH, DelBello MP, Forrester JJ, et al. A retrospective chart review of intramuscular ziprasidone for agitation in children and adolescents on psychiatric units: prospective studies are needed. J Child Adolesc Psychopharmacol 2007;17(4):503–509
68. Khan SS, Mican LM. A naturalistic evaluation of intramuscular ziprasidone versus intramuscular olanzapine for the management of acute agitation and aggression in children and adolescents. J Child Adolesc Psychopharmacol 2006;16(6):671–677
69. Staller JA. Intramuscular ziprasidone in youth: a retrospective chart review. J Child Adolesc Psychopharmacol 2004;14(4):590–592
70. Hazaray E, Ehret J, Posey DJ, et al. Intramuscular ziprasidone for acute agitation in adolescents. J Child Adolesc psychopharmacol 2004;14(3): 464–470
71. Rosenheck RA. Open forum: effectiveness versus efficacy of second-generation antipsychotics: haloperidol without anticholinergics as a comparator. Psychiatr Serv 2005;56(1):85–92
72. Khanna R, Das A, Damodaran SS. Prospective study of neuroleptic-induced dystonia in mania and schizophrenia. Am J Psychiatry 1992; 149(4):511–513
73. Baker LA, Cheng LY, Amara IB. The withdrawal of benztropine mesylate in chronic schizophrenic patients. Br J Psychiatry 1983;143:584–590
74. Addonizio G, Alexopoulos GS. Drug-induced dystonia in young and elderly patients. Am J Psychiatry 1988;145(7):869–871
75. Aguilar EJ, Keshavan MS, Martinez-Quiles MD, et al. Predictors of acute dystonia in first-episode psychotic patients. Am J Psychiatry 1994;151(12):1819–1821
76. Geyer HL, Bressman SB. The diagnosis of dystonia. Lancet Neurol 2006; 5(9):780–790
77. Swett C Jr. Drug-induced dystonia. Am J Psychiatry 1975;132(5):532–534
78. Sunderland T, Tariot PN, Cohen RM, et al. Anticholinergic sensitivity in patients with dementia of the Alzheimer type and age-matched controls: a dose-response study. Arch Gen Psychiatry 1987;44(5):418–426
79. Saraf S, Chandra PS. Tardive dyskinesia and second-generation antipsychotics. Am J Psychiatry 2005;162(2):404–405
80. Sramek JJ, Simpson GM, Morrison RL, et al. Anticholinergic agents for prophylaxis of neuroleptic-induced dystonic reactions: a prospective study. J Clin Psychiatry 1986;47(6):305–309
81. Baldessarini RJ, Cohen BM, Teicher MH. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. Arch Gen Psychiatry 1988;45(1):79–91
82. Olanzapine for injection: new formulation. No advantage in agitated patients. Prescrire Int 2004;13(71):92–93
83. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? a multicenter, prospective, double-blind, emergency department study. Am J Emerg Med 1997 Jul;15(4):335–340
84. Gillies D, Beck A, McCloud A, et al. Benzodiazpines alone or in combination with antipsychotic drugs for acute psychosis. Cochrane Database Syst Rev 2005 Oct;(4):CD003079
85. Battaglia J, Houston JP, Ahl J, et al. A post hoc analysis of transitioning to oral treatment with olanzapine or haloperidol after 24-hour intramuscular treatment in acutely agitated adult patients with schizophrenia. Clin Ther 2005;27(10):1612–1618
86. Daniel DG, Currier GW, Zimbroff DL, et al. Efficacy and safety of oral aripiprazole compared with haloperidol in patients transitioning from acute treatment with intramuscular formulations. J Psychiatr Pract 2007; 13(3):170–177
87. Wright P, Meehan K, Birkett M, et al. A comparison of the efficacy and safety of olanzapine versus haloperidol during transition from intramuscular to oral therapy. Clin Ther 2003;25(5):1420–1428
88. Hugenholtz GW, Stolker JJ, Heerdink ER, et al. Short-acting parenteral antipsychotics drive choice for classical versus atypical agents. Eur J Clin Pharmacol 2003;58(11):757–760
89. Volavka J, Czobor P, Nolan K, et al. Overt aggression and psychotic symptoms in patients with schizophrenia treated with clozapine, olanzapine, risperidone, or haloperidol. J Clin Psychopharmacol 2004;24(2): 225–228
90. Krakowski MI, Czobor P, Citrome L, et al. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 2006;63(6):622–629
91. Miller DD, McEvoy JP, Davis SM, et al. Clinical correlates of tardive dyskinesia in schizophrenia: baseline data from the CATIE schizophrenia trial. Schizophr Res 2005;80(1):33–43
92. Battaglia J, Lindborg SR, Alaka K, et al. Calming versus sedative effects of intramuscular olanzapine in agitated patients. Am J Emerg Med 2003; 21(3):192–198
93. Canas F. Management of agitation in the acute psychotic patient: efficacy without excessive sedation. Eur Neuropsychopharmacol 2007 Mar;17(suppl 2):S108–S114
94. National Institute of Clinical Excellence. The short-term management of disturbed/violent behaviour in inpatient psychiatric settings and emergency departments. London, England: National Institute of Clinical Excellence; 2005
95. Huf G, Alexander J, Allen MH. Haloperidol plus promethazine for psychosis induced aggression. Cochrane Database Syst Rev 2005 Jan;(1):CD005146
96. Shatzberg AF, Nemeroff CB. Textbook of Psychopharmacology. 3rd ed. Arlington, Va: American Psychiatric Publishing; 2005
97. Starke PR, Weaver J, Chowdhury BA. Boxed warning added to promethazine labeling for pediatric use. N Engl J Med 2005 Jun;352(25):2653

For the CME Posttest for this article, see pages 2004–2006.