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

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Abstract

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, EMBASE, and the Cochrane Registry for studies published in English of intramuscular SGAs and intramuscular haloperidol alone or in combination with an anticholinergic agent. 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 SGAs to haloperidol alone were identified. However, we found only one RCT of haloperidol plus an anticholinergic. In the second analysis, we identified 18 studies, including four using haloperidol combined with promethazine (an antihistamine with anticholinergic properties).

DATA EXTRACTION—The primary outcome measure was acute dystonia; secondary outcomes included akathisia, parkinsonism, or additional anticholinergic medication. For RCTs, risk ratios (RR) and 95% confidence intervals (CI) 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, CI 0.10-0.39), akathisia (RR 0.25, CI 0.14-0.45), and anticholinergic use (RR 0.19, CI 0.09-0.43) compared with haloperidol alone. When all trials were considered (N=3425), rates of acute dystonia were higher for haloperidol alone (4.7%) than SGAs (0.6%) or haloperidol plus promethazine (0%).

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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.

Keywords

antipsychotic drugs; extrapyramidal symptoms; dystonia; agitation; intramuscular

INTRODUCTION

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 extra-pyramidal symptoms (EPS) such as dystonia.[5] Such symptoms can be distressing, painful, or even life-threatening, and may erode patient trust and compliance.[6]

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 three 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 qualiative 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 cost an order of

magnitude more than 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.

METHODS

Search Strategy

We searched MEDLINE (1950-Present), EMBASE, and the Cochrane Registry of Controlled Trials (last search 1/16/2008) 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 above search were re-checked to ensure that they met the inclusion criteria. One reviewer (T.S.) assessed methodological quality of the included studies according to the randomization procedure, blinding, intervention details, and outcome measures (described below).

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 chronic 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 sub-therapeutic doses. Patient populations were not restricted to any particular diagnosis; any study where 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 (SAS)[41] or the Barnes Akathisia Scale (BAS).[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 two studies. We found only one 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 below. In the case of studies where 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 below. For all outcomes, a risk ratio with 95% confidence intervals was calculated using a fixed effect model. Heterogeneity was assessed using a Mantel-Haenszel chi-squared 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, two sensitivity analyses were conducted. First, RCTs were excluded if they were not double-blind, there were other methodological concerns, or there was ambiguity in the reporting of the outcomes. Another sensitivity analysis excluded trials with greater than 24 hours of antipsychotic exposure where event frequencies were corrected by the method described above. 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 above, 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 where 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 non-randomized, 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 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 Corell 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 seen below, 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 above, 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 was pooled across studies with a weighted average in order to calculate the absolute risk of occurrence of acute dystonia for each of the three treatment 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 above. 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 above, 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 seven studies were included; all of the intramuscular SGAs were represented in the analysis, including ziprasidone (three studies, N=725), olanzapine (two studies, N=268), and aripiprazole (two studies, N=353). Notably, all trials were double-blind except for the three ziprasidone trials. Two of these trials[10, 16] were open label, while in one[11] patients were not blinded but all assessments were blinded to treatment assignment. Two trials included treatment arms with sub-therapeutic 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 three 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 55-92%), with a mean age range of 32.8-41.9 years old.

Outcomes Included—Included RCTs reported the specified outcome measures to a varying degree. Six of the seven 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 (Josiassen, personal communication). Five studies reported the occurrence of akathisia;[10, 11, 13, 14, 16] five 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 SAS and BAS 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 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 non-significant amount of heterogeneity among studies (Chi-squared p=0.72, I-squared=0%), so a fixed effects model was employed. 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) 0.10-0.39 (Figure 1); NNTH 25.0, 95% CI 20-50. When the three ziprasidone trials[10, 11, 16] were excluded in a sensitivity analysis, the results did not change significantly.

Akathisia—Five trials with a total of 1418 patients reported on akathisia.[10, 11, 13, 14, 16] Of patients who received intramuscular SGAs, 18 of 1038 developed akathisia, while 27 of 380 patients who received haloperidol experienced this adverse event. There was a non-significant amount of heterogeneity among studies (Chi-squared p=0.49, 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, CI 0.14-0.45; NNTH 20.0 CI 12.5-33.3). In the sensitivity analysis that excluded the three ziprasidone trials,[10, 11, 16] the results did not change significantly.

Anticholinergic Use—Anticholinergic use was reported in five studies.[9-11, 13, 16] However, all ziprasidone studies were excluded: the precise number events were not reported for Daniel et al. 2004[16] and it was not possible to distinguish between anticholinergics given during the intramuscular versus oral phase of Brook et al. 2000 and 2005.[10, 11] Thus, the analysis included 434 patients from the two 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 (Chi Squared p=0.29, I-squared 10.9%) between studies, and the fixed-effects model employed found a

significant advantage for intramuscular SGAs (RR 0.19, CI 0.09-0.43; NNTH 7.7, CI 5.3-14.3; Figure 3).

Risk of Acute Dystonia in All Trials

Study Characteristics—Beyond the RCTs directly comparing SGAs and haloperidol identified above (and also included here), eleven 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, eight had intramuscular SGA treatment arms, while four 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=1370) or single-blind randomized trials (N=1433); two studies were randomized open label (N=438)[10, 16] and three were non-randomized open-label (N=187).[50, 55, 56] Notably, all four trials of haloperidol in combination with promethazine were randomized but were not 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, 56]

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] three studies were excluded because they did not last at least 24 hours;[58-61] five studies were excluded because they included insufficient numbers of subjects;[62-66] and four were excluded because the patients were under 18 years old.[67-69]

Acute Dystonia—There was a marked difference in the risk of acute dystonia between the three groups. Among 2021 patients treated with intramuscular SGAs, only 12 experienced a dystonic reaction (0.6%)—much less than the 40 of 844 (4.7%) patients 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 seven 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 three 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 either 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 of 844) of patients given intramuscular haloperidol alone experienced a dystonic reaction, in contrast to only twelve of 2021 (0.6%) patients given SGAs and *zero* of 560 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 plus promethazine is no more likely to precipitate dystonia than SGAs.

This finding is important for two 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, than 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 20mg $11.76, aripiprazole 10mg $13.61, olanzapine 10mg $26.16; haloperidol 5mg $0.87, promethazine $0.63, diphenhydramine $0.59)[39] this decision may have financial implications. However, it is important to note that not all anticholinergic agents are inexpensive; a 2mg 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.[70]

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-naïve. 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 chronic psychotic disorders who have received antipsychotics in the past may be less susceptible to acute EPS than first episode patients,[71] 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 chronic anticholinergic medication at baseline. Abrupt withdrawal of such treatment can itself cause EPS,[72] which might bias reported rates of events. These factors may limit the ability to generalize our findings to antipsychotic-naïve patients experiencing a first episode of psychosis.

Second, most studies included in this review enrolled non-elderly adults, with men more heavily represented than women. Dystonia is more common in men;[6, 73, 74] the higher proportion of men in this analysis could lead to an overestimation of the risk of dystonia. More importantly, with the exception of two studies that explicitly considered the agitated elderly,[46, 50] all other studies mainly enrolled non-elderly patients. As acute dystonia is far more common in young people,[73, 74] 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, 75, 76] 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.[77]

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 have suffered 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. could be applied to our second analysis. Most saliently, Saraf and Chandra[78] 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 this data to other extrapyramidal syndromes.

Fifth, the average haloperidol dose for studies included in the review (6.5mg-10mg) was higher than the 5mg dose typically used in clinical practice.[3] Given that higher doses of haloperidol could lead to more frequent dystonic reactions,[6, 79, 80] these doses might exaggerate the difference between haloperidol and comparison drugs.[81] 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 5mg 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.[82] and a recent review on the topic[83] 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. 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, 84-86] This may be an important advantage given that the availability of intramuscular preparations has been demonstrated to influence the choice of a maintenance agent,[87] and maintenance treatment with oral SGAs may be superior to haloperidol at

reducing aggression.[88] However, the advantage for SGAs in preventing aggression may be primarily carried by clozapine,[88, 89] 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.[90] Finally, some authors have claimed that intramuscular SGAs produce a specific calming effect rather than non-specific sedation,[91, 92] 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 four trials[40, 45, 49, 52] have been noted to be of very high methodological quality,[93] 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.[94] Promethazine is a sedating antihistamine with anticholinergic properties; it is also a phenothiazine with a low D2 affinity.[95] 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.[96] 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.,[52] “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.” 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,[70] 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 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.

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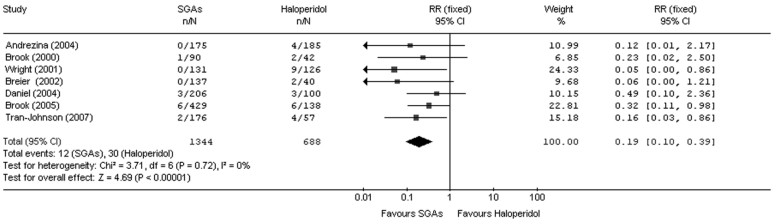

FIGURE 1.

Fixed-effect model of risk of acute dystonia in randomized controlled trials of second-generation antipsychotics versus haloperidol

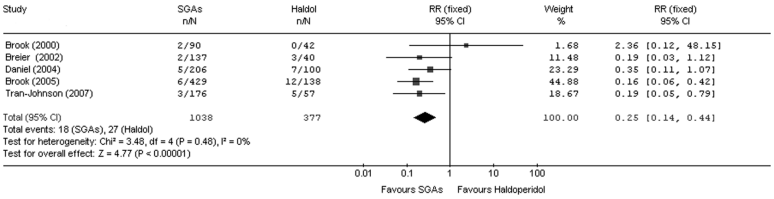

FIGURE 2.

Fixed-effect model of risk of acute akathisia in randomized controlled trials of second-generation antipsychotics versus haloperidol

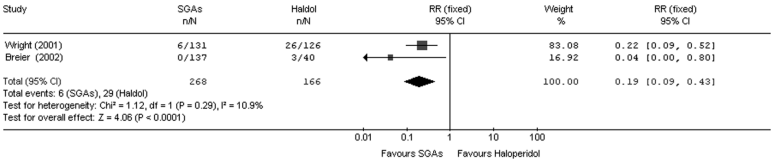

FIGURE 3.

Fixed-effect model of risk of anticholinergic use in randomized controlled trials of second-generation antipsychotics versus haloperidol

TABLE 1

Characteristics of Randomized Controlled Trials Comparing Intramuscular SGAs and Intramuscular Haloperidol

Study	Drug	Dose (mg)	N	Male (%)	Age (mean)	Blinding	Symptoms Required	Outcomes Reported
Andrezina et al. 2006[17]	Aripiprazole	9.75	175	63	41.9	Double-blind	PEC[a] scores 15-32; two 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	PEC 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[b]>40	Dystonia, akathisia
	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	1, 5.25, 9.75, 15	178	60	41.6	Double-blind	PEC scores 15-32; two items >4	Dystonia, akathisia
	Haloperidol	7.5	57	65	40.0			
Wright et al. 2001[9]	Olanzapine	10	131	*c*	38.2[c]	Double-blind	PEC score >14, one item >4	Dystonia, akathisia, anticholinergics
	Haloperidol	7.5	126		38.2			

[a] PEC: Positive and Negative Syndrome Scale Excited Component

[b] BPRS: Brief Psychiatric Rating Scale

[c] Wright et al (2001) did not report the proportion of male and female subjects, or the mean age of each treatment arm

TABLE 2

Characteristics of Additional Studies Included in Analysis of All Trials

Study	Drug	Dose (mg)	N	Male (%)	Age (mean)	Study Design	Diagnosis	Severity
Alexander et al. 2004[45]	Haloperidol + Promethazine	5 or 10 + 25 or 50	100	55	30.9	Single-blind, randomized controlled trial	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	Agitation with presumed mood or psychotic disorder	Requiring IM medications for agitation
Daniel et al. 2001[51]	Ziprasidone	20	41	78	39.9	Double-blind, randomized controlled trial	Any psychotic disorder	PANSS[a] >3 on 3 agitation items
Huf et al. 2007[52]	Haloperidol + Promethazine	5 or 10 + 25 or 50	160	59	40.2	Single-blind, randomized controlled trial	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, randomized controlled trial	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, randomized controlled trial	Bipolar I, manic or mixed state	PEC[b] >14, one item >4
Meehan et al. 2002[46]	Olanzapine	2.5 or 5	137	39	77.6	Double-blind, randomized controlled trial	Age >55 and probable dementia with agitation	PEC >14, one item >4
Raveendran et al. 2007[40]	Olanzapine	5 or 10	150	65	30.4	Single-blind, randomized controlled trial	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, randomized controlled trial	Agitation	Requiring IM medications for agitation

[a]PANSS: Positive and Negative Syndrome Scale

[b]PEC: Positive and Negative Syndrome Scale Excited Component

TABLE 3

Risk of Dystonia Across All Trials

Treatment	N	Dystonic Events	Risk of Dystonia
Haloperidol	844	40	4.7%
Haloperidol + Promethazine	560	0	0%
SGAs	2021	12	0.6%