A meta-analysis of the risk of acute extrapyramidal symptoms with intramuscular antipsychotics for the treatment of agitation
Satterthwaite T D, Wolf D H, Rosenheck R A, Gur R E, Caroff S N

CRD summary
The authors found that, for acute anxiety, intramuscular second-generation antipsychotics had a lower risk of acute extrapyramidal symptoms than haloperidol alone. These findings appear reliable. The authors also concluded that the extrapyramidal symptoms risk associated with second-generation antipsychotics and with haloperidol plus promethazine is comparable. This conclusion may not be reliable, as it was based on indirect comparisons.

Authors' objectives
To evaluate the risk of acute dystonia and other extrapyramidal symptoms associated with second-generation antipsychotics versus intramuscular haloperidol with or without an anticholinergic agent in the treatment of agitation.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched. Search dates spanned 1950 to January 2008. Search terms were reported. The references of retrieved studies, other relevant studies and major textbooks were hand searched. The search was limited to studies published in English.

Study selection
Randomised controlled trials (RCTs) comparing short-acting intramuscular second-generation antipsychotics to haloperidol, with or without an anticholinergic agent, for the treatment of agitated or acutely psychotic patients were eligible for inclusion. Trials were required to have a minimum of 20 participants and 24 hours' follow up. The primary outcome of interest was acute dystonia. Secondary outcomes included akathisia, parkinsonism and anticholinergic medication requirement. Total rates of extrapyramidal symptoms were not included as an outcome.

Participants in the included trials were diagnosed with schizophrenia or related disorders. Trial eligibility was determined by above-threshold scores on symptom rating scales (where reported). Very few participants had not received a previous antipsychotic. The mean age range was 33 to 42 years and most participants (55% to 95%) were male.

Only one of the studies identified compared intramuscular second-generation antipsychotics to haloperidol in combination with an anticholinergic agent, so the authors widened the inclusion criteria of the review. For this second analysis, studies of any design were eligible provided that participants received either intramuscular second-generation antipsychotics or haloperidol plus an anticholinergic (regardless of comparator). The sole outcome of interest was acute dystonia. In other respects inclusion criteria were as for the first analysis.

Across all the included studies, the intramuscular second-generation antipsychotics used were ziprasidone, olanzapine and aripiprazole. Haloperidol doses ranged from five to 10 milligrams (mgs). The anticholinergic drug used in combination with haloperidol was promethazine (25 or 50 mgs). Data were included in the review only if the comparison or outcome was reported by more than one study.

The authors did not state how the papers were selected for the review or how many reviewers performed the selection.

Assessment of study quality
The following aspects of study validity were assessed: randomisation, blinding, intervention details and outcome measures. A single reviewer conducted the validity assessment.

Data extraction
For the first analysis, risk ratios and 95% confidence intervals were calculated from the number of events in the two
groups occurring in the first 24 hours. If a study included multiple drug doses, only subjects who received a therapeutic dose were included in analysis. For the second analysis event rates were extracted from study arms receiving intramuscular second-generation antipsychotics, haloperidol plus an anticholinergic, or haloperidol alone. If necessary the 24-hour event rate was estimated from the total number of events and median duration of antipsychotic exposure. Data were extracted in duplicate. Primary study authors were contacted for additional information as necessary.

Methods of synthesis
For the first analysis, studies were combined using a Mantel Haenszel fixed-effect model to calculate pooled risk ratios and 95% confidence intervals. Heterogeneity was assessed with the $\chi^2$ test and $I^2$ statistic, with significance thresholds of 0.10 for $\chi^2$ and 50% for $I^2$. Numbers-needed-to-harm were also calculated, with 95% confidence intervals. A sensitivity analysis was conducted excluding studies where there were methodological concerns (e.g. not blinded, outcomes reporting ambiguous) and where the 24-hour event rate had been estimated by the reviewers.

For the second analysis, data were pooled across study arms to calculate individual weighted mean event rates for each type of intervention.

Results of the review
Eighteen studies were included (n=3,425), eight double blind randomised controlled trials (RCTs), five single blind RCTs, two unblinded (open-label) RCTs, and three observational studies.

Risk of acute dystonia in RCTs: Seven RCTs (n=2,032 patients) compared intramuscular second-generation antipsychotics to haloperidol alone. The second-generation antipsychotic group was at significantly lower risk of dystonia (risk ratio 0.19, 95% confidence interval (CI): 0.10 to 0.39) with a number-needed-to-harm of 25 (95% CI: 20 to 50) based on seven RCTs. The second-generation antipsychotic group was also at significantly lower risk of akathisia (risk ratio 0.25, 95% CI: 0.14 to 0.44) with a number-needed-to-harm of 20 (95% CI: 12.5 to 33.3) based on five RCTs (n=1,415 patients). In addition, the second-generation antipsychotic group was significantly less likely to need anticholinergics (risk ratio 0.19, 95% CI: 0.09 to 0.43), with a number-needed-to-harm of 7.7 (95% CI: 5.3 to 14.3), based on two RCTs (n=434 patients). No significant heterogeneity was found and the sensitivity analyses did not change the statistical significance of any of the findings.

Rate of acute dystonia in all studies: When all eighteen studies (n=3,425 patients) were pooled, the rates of dystonia were 4.7% (40 of 844 patients) for haloperidol alone, 0.6% (12 of 2,021 patients) for second-generation antipsychotics, and 0% (none of 560 patients) for haloperidol plus promethazine.

Cost information
Intramuscular second-generation antipsychotics cost over ten times as much as haloperidol plus an antihistamine with anticholinergic properties (though not all anticholinergics are inexpensive). The cost of continuing a second-generation antipsychotic for maintenance therapy could be considerable.

Authors’ conclusions
Intramuscular second-generation antipsychotics had a lower risk of acute extrapyramidal symptoms than haloperidol alone, for acute anxiety. However, the extrapyramidal symptoms risk associated with second-generation antipsychotics and with haloperidol plus promethazine was comparable.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies, although the restriction to published studies in English means that the review was prone to language and publication biases. It was unclear whether steps were taken to minimise reviewer bias and error by having more than one reviewer independently select studies. Only one reviewer was involved in validity assessment and no details were reported about some important aspects of study quality (e.g. allocation concealment, follow-up rates). However, potential biases in the included studies, particularly with respect to participant selection, were well addressed in the text. For the first analysis (comparing second-generation antipsychotic to haloperidol), appropriate statistical techniques were used to combine the randomised
controlled trials, assess for heterogeneity and explore differences between these studies. The results of this analysis were consistent and appear likely to be reliable. However, the results of the second analysis (comparing second-generation antipsychotic to haloperidol plus anticholinergic) appear unlikely to be reliable because the comparisons were indirect, as the authors pooled single arms of studies and randomisation was broken.

Implications of the review for practice and research

**Practice:** The authors stated that the reduced risk of extrapyramidal symptoms associated with intramuscular second-generation antipsychotics should not be the main factor in choice of an antipsychotic for agitation. In acute care settings, this choice should be tailored to the individual and should take account of multiple factors. It may be advisable not to treat agitation with haloperidol alone.

**Research:** The authors stated that industry-sponsored trials may provide only limited evidence of the risk of extrapyramidal symptoms associated with intramuscular antipsychotics, and may not apply to very agitated patients. Future studies should consider comparing intramuscular second-generation antipsychotics with haloperidol plus an agent to prevent extrapyramidal symptoms, rather than haloperidol alone. Combinations of haloperidol and benzodiazepine could also be investigated. Studies should use a standard 5 mg dose of haloperidol in order to enhance clinical relevance. Ideally large head-to-head trials should assess the differential risk of extrapyramidal symptoms among intramuscular second-generation antipsychotics.

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