Tolerability of paliperidone: a meta-analysis of randomized, controlled trials

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CRD summary
The review concluded that a 50% reduction in treatment emergent psychosis was observed in patients with schizophrenia treated with paliperidone, but this was about equal to the occurrence of an adverse event with paliperidone. A lack of reported procedure, uncertain quality of included studies and concern with the pooling of data means that these conclusions should be interpreted with caution.

Authors' objectives
To determine an adverse effects profile for the atypical antipsychotic paliperidone.

Searching
EMBASE and MEDLINE were searched up to March 2010. ClinicalTrials.gov was searched for completed or ongoing trials. Manufacturers' clinical trial reports were included. Index terms were given for the clinical trials database, but not MEDLINE or EMBASE. The search was restricted to articles written in English.

Study selection
Randomised controlled trials (RCTs) that compared paliperidone with placebo in adults and reported the incidence of adverse events were eligible for inclusion. Trials that used the injection (paliperidone palmitate) form of the drug were excluded, as were trials where the focus was pharmakineti.

Paliperidone doses ranged from 1.5mg/day to 15mg/day. Concurrent treatment included Parkinson's therapy, beta-blockers, benzodiazepines and antidepressants. Trial duration ranged from two to six weeks. Trial populations included schizophrenia (unspecified), acute schizophrenia, acute schizoaffective disorder, chronic schizophrenia (with or without insomnia) and bipolar I disorder. One trial included only elderly participants. A wide range of adverse events were reported and included incidence of extra-pyramidal symptoms, tachycardia and weight gain as well as treatment of emergent psychosis and other attributable benefits.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they systematically assessed the quality of the included trials, but commented that RCT quality was assessed in a previous study that was updated by their review.

Data extraction
Data were extracted to enable calculation of risk difference or attributable risk (AR) and associated 95% confidence intervals (CIs). Overall incidence (as a percentage) was reported for each adverse event. Trials were pooled if at least two trials reported the adverse event and there was a total population of at least 500 persons. Attributable risk was calculated by subtracting incidence in the placebo group from that in the drug group and was reported as the number of adverse events per 100 persons exposed.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Summary risk ratios (RRs) and attributable risks were estimated using the Mantel-Haenzel method. The authors stated that a random-effects model was used. Statistical heterogeneity was assessed using $X^2$ and the $I^2$ statistic. Sensitivity analyses for dosage (3mg to 6mg, 3mg to 9mg, 3mg to 12mg and inclusion of 15mg doses) and indication (schizophrenia-only population) were conducted.

Results of the review
Fifteen studies were included in the review (3,779 participants, range 42 to 1,205). Two studies combined data from other included trials.
Significantly greater risk of extra-pyramidal symptoms (EPS) (RR 1.98, 95% CI 1.65 to 2.38; $I^2=0\%$; 10 studies),
tachycardia (RR 1.79, 95% CI 1.29 to 2.49; $I^2=0\%$; nine RCTs) and weight gain (RR 2.02, 95% CI 1.37 to 2.96; $I^2=0\%$;
ev) were found with paliperidone compared with placebo. Evidence of a significant attributable risk was found for most of the adverse events reported, the greatest of which were for any EPS (AR 10, 95% CI 6 to 14; $I^2=63\%$),
tachycardia (AR 4, 95% CI 1 to 6; $I^2=64\%$) and weight gain (AR 4, 95% CI 2 to 6; $I^2=17\%$).

A significant reduction in risk of emergent psychosis events among patients in USA with schizophrenia was found in favour of paliperidone compared with placebo (RR 0.50, 95% CI 0.34 to 0.72; $I^2=8\%$; eight RCTs). No significant reduction of attributable risk was shown for emergent psychosis (AR 8, 95% CI -14 to 1), although substantial heterogeneity was found ($I^2=91\%$). Heterogeneity was reduced ($I^2=42\%$) when patients with schizoaffective disorder were excluded and attributable risk was reduced to five per 100. No significant between-group differences were found for the other attributable protective outcomes.

Sensitivity analyses by indication did not significantly alter the results found for attributable risk, but reduced heterogeneity for any adverse event (0%), EPS symptoms (51%) and tachycardia (47%) and increased heterogeneity for weight gain (37%). A dose response was found for all adverse events except weight gain. Inclusion of a 15mg dose reduced episodes of acute psychosis and increased EPS symptoms.

**Authors’ conclusions**

A reduction in treatment emergent psychosis (up to 50% reduction in patients with schizophrenia) was found with paliperidone, but was about equal to the occurrence of an adverse event. Paliperidone increased the risk of the most troublesome adverse events in schizophrenia, although many effects (EPS was an exception) could be reduced by using low doses ($\leq$6mg).

**CRD commentary**

The review question was clearly defined in terms of study design and intervention and more broadly supported in terms of population and outcomes. Relevant databases were searched and effort was made to locate unpublished trials. The search was restricted to trials written in English and so language bias could not be ruled out. The authors did not report whether they took steps to reduce risks of error and bias in study selection and data extraction. The quality of the included trials was not assessed systematically, which limited interpretation of the results.

The authors stated that they used a random-effects model to pool trials and also stated that they used the Mantel-Haenzel method (which assumes a fixed-effect model); this made it unclear which meta-analytic method was used to pool trials. It appeared that some data may have been included more than once in at least one analysis (risk ratio of EPS symptoms); two abstracts were included and their combined data was included in a third trial. The authors acknowledged that results were confounded by concomitant medication and that the short durations of the included trials precluded assessment of the longer term effects of paliperidone.

A lack of reported procedure, uncertain quality of the included studies and some concern with the pooling of data means that the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**

The authors did not state any implications for practice or research.

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