Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia

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CRD summary
This review suggested that paliperidone extended-release was an effective and well-tolerated atypical antipsychotic agent in patients with schizophrenia and had a similar profile to some other commonly used atypical antipsychotic agents. Although this review had some limitations with regard to reporting and analysis, the conclusions were consistent with the data presented.

Authors' objectives
To assess the effectiveness and tolerability of paliperidone extended-release in comparison to other atypical antipsychotic drugs in the management of schizophrenia.

Searching
MEDLINE, EMBASE, The Cochrane Library, PsycINFO and CINAHL were searched for eligible studies. There were no language restrictions. Search dates were not provided. Search terms were indicated. Reference lists of included studies were searched. Manufacturers of all drugs considered were approached for further published and unpublished studies.

Study selection
Studies were eligible if they were double-blind randomised placebo-controlled trials that evaluated the atypical antipsychotic drugs risperidone, olanzapine, quetiapine, aripiprazole and paliperidone extended-release in adults with schizophrenia. Studies had to include at least 20 patients and use at least one dose within the product's label range. Included dose ranges were fixed or mean doses within currently recommended, effective or target dose ranges for each agent. Dose ranges included in the analysis were: risperidone 4mg/day to 8mg/day (4mg/day to 6mg/day for tolerability), aripiprazole 10mg/day to 30mg/day, olanzapine 10mg/day to 20mg/day (5mg/day to 20mg/day for tolerability), quetiapine 150mg/day to 750mg/day and paliperidone extended-release 3mg/day to 12mg/day. Studies with patients who changed therapies during the study and studies that did not report quantitative data were excluded. Studies had to include information on withdrawals and drop-outs and had to have a minimum Jadad score of 3. The included trials had a duration of between four and eight weeks. Most studies had more than two study arms (up to six). Ten studies compared different doses of a single drug and five studies compared different drugs. Mean age ranged from 37 to 39 years. The proportion of women was 16% to 39%. Reported baseline body mass index (BMI) was between 26kg/m² and 27kg/m². Baseline scores on the Positive and Negative Syndrome Scale (PANSS) suggested a highly symptomatic population. Baseline scores were generally similar across the different antipsychotic drugs. Baseline scores on the Clinical Global Impression-Severity Scale (CGI-S) ranged from 3.7 to 5.2 (mean 4.8).

Two reviewers independently performed study selection.

Assessment of study quality
Two reviewers independently assessed study quality using the Jadad scale of randomisation, blinding, withdrawal and drop-outs to award a score up to a maximum of 5. Quality was a selection criterion and only studies with a minimum Jadad score of 3 were included.

Data extraction
All articles that met the inclusion criteria were reviewed to find out which outcomes were sufficiently common to enable data extraction and analysis. Data for particular outcomes were extracted if data for that outcome were available for more than one of the five drugs and if data in at least two studies were reported with a consistent definition of the outcome. Based on this assessment, the efficacy outcomes assessed included PANSS, CGI-S, withdrawal due to lack of efficacy and withdrawal for any reason. Safety outcomes assessed included withdrawal due to adverse events, incidence
of clinically significant weight gain (7% or more compared to baseline), somnolence and agitation. Data were extracted in order to calculate effect sizes and 95% confidence intervals (CI) for continuous outcomes and odds ratios and 95% CI for dichotomous outcomes.

Data were independently extracted by two reviewers. Any discrepancies were resolved by referring to the original publication.

Methods of synthesis
Effect sizes and odds ratios (and their 95% CIs) were combined in a meta-analysis using the DerSimonian and Laird method. Heterogeneity was assessed using Cochran’s Q. Publication bias was assessed using a funnel plot analysis. Random-effects meta-regression was used to estimate the influence of patient mean age, sex, duration of therapy, baseline PANSS score and type of drug. Different doses for each drug in a given study were considered separately.

Results of the review
Twenty studies were included (outcome data for 5,313 participants, n=1,634 placebo, n=553 risperidone, n=642 olanzapine, n=605 quetiapine, n=1,028 aripiprazole and n=851 paliperidone extended-release). Sample sizes in the individual studies ranged between 69 and 630. Six studies examined risperidone, six examined olanzapine, four examined quetiapine, six examined aripiprazole and three examined paliperidone.

All of the atypical antipsychotic drugs significantly improved total PANSS scores (overall effect size -11.6, 95% CI -13.3 to -10.0). Effect sizes for the individual agents ranged from -14.9 (95% CI -17.6 to -12.3) for olanzapine to -9.5 (95% CI -11.7 to -7.2) for aripiprazole. PANSS positive score was significantly improved (overall ES -2.4, 95% CI -2.9 to -2.0). Effect sizes for individual agents ranged from -4.3 for risperidone and olanzapine (risperidone 95% CI -5.7 to -2.8 and olanzapine 95% CI -5.3 to -3.4) to -2.6 (95% CI: -3.4, -1.7) for aripiprazole. There was significant improvement in PANSS negative score (overall effect size -2.4, 95% CI -2.9 to -2.0). Effect sizes for individual agents ranged from -3.4 (95% CI -4.2 to -2.7) for olanzapine to -1.3 (95% CI -2.6 to -0.07) for quetiapine. One study on olanzapine included patients with a lower mean PANSS total score than in other studies and its exclusion reduced the effect size for olanzapine.

Improvement on CGI-S score with atypical antipsychotic agents was -0.5 overall (95% CI -0.6 to -0.4). Effect sizes for individual agents ranged from -0.8 (95% CI -1.1 to -0.5) for risperidone to -0.3 (95% CI -0.4 to -0.2) for aripiprazole.

Paliperidone extended-release, olanzapine and risperidone tended to have lower rates of withdrawals due to lack of efficacy than all atypical antipsychotic agents together (compared to placebo, OR overall 0.39, 95% CI 0.34 to 0.45). Rates tended to be higher than the mean for aripiprazole and quetiapine.

Overall withdrawal for any reason had an odds ratio of 0.52 (95% CI 0.46 to 0.58) compared to placebo. Rates were clearly lower than the mean for paliperidone extended-release and risperidone and higher than the mean for quetiapine and aripiprazole.

There was no significant difference in rates of withdrawals due to adverse events for all the atypical antipsychotic agents taken together compared to placebo. Results were similar for the individual agents except olanzapine, which had higher withdrawal rates due to adverse events; the extent to which this result was significant was unclear.

Atypical antipsychotic drugs led to significant weight gain compared to placebo (OR 2.84, 95% CI 2.3 to 3.5). Odds of weight gain were lowest with paliperidone extended-release (OR 1.75, 95% CI 1.29 to 2.37) and highest with olanzapine (OR 4.56, 95% CI 3.46 to 6.01). There was no obvious influence on this outcome of any of the assessed confounders (age, sex and duration of therapy).

Atypical antipsychotic drugs were associated with increased odds of somnolence compared to placebo (OR 1.7, 95% CI 1.39 to 2.09). Odds of somnolence were lower than the mean with paliperidone extended-release and aripiprazole and higher than the mean with risperidone and olanzapine.

Overall, there was no significant difference in agitation between atypical antipsychotic drugs and placebo. Agitation was claimed to be lower than placebo for paliperidone extended-release and for quetiapine, but the significance of the
result was uncertain.

Results for all safety outcomes were consistent when lower effective dose ranges were included.

**Authors' conclusions**
Paliperidone extended-release was an effective and well-tolerated atypical antipsychotic agent that provided new treatment options for people with schizophrenia. Because of heterogeneity between the different atypical antipsychotic agents, information on individual benefit/risk profiles of the drugs was necessary for selecting an appropriate treatment for each patient.

**CRD commentary**
This systematic review addressed a clearly stated research question. Appropriate inclusion criteria were defined. Measures were taken to avoid the introduction of error and bias during the review process. The literature search included various relevant databases. Search terms were indicated. Supplementary searches were carried out. Methodological quality was assessed and used as a basis of study selection; details of study quality were not reported. Only outcomes that could be summarised in a meta-analysis were reported. Meta-regression analyses were carried out based age, sex, duration of therapy, baseline PANSS score and type of drug. Analyses of drug tolerability were carried out for different dosage ranges. Information on patients included in the trials was somewhat limited. Individual trial results were not given. No defined statistical analysis was used to compare between drugs. Differences were suggested (based on absolute numbers) that were unlikely to have been significant. Evidence of significant heterogeneity in some analyses was not explained completely by the analysis of confounders. Most of the between-study variability appeared to be due to use of different study drugs. No analyses were shown for testing for significant differences between the different drugs.

The review was funded by Johnson & Johnson (manufacturer of paliperidone extended release).

Taking into account the limitations mentioned, the authors' conclusions followed from the data presented in that paliperidone extended-release performed similarly to the other atypical antipsychotic agents.

**Implications of the review for practice and research**
The authors made no specific recommendations for practice.

**Research:** The authors stated that better outcome reporting and longer term data were required in trials of atypical antipsychotic agents.

**Funding**
Johnson & Johnson Pharmaceutical Services, LLC.

**Bibliographic details**
Jones MP, Nicholl D, Trakas K. Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia. International Journal of Clinical Pharmacology and Therapeutics 2010; 48(6): 383-399

**PubMedID**
20497747

**Original Paper URL**
http://www.dustri.com/nc/journals-in-english?artId=7610

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
AccessionNumber
12010004765

Date bibliographic record published
22/12/2010

Date abstract record published
06/07/2011

Record Status
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