Off-label use of atypical antipsychotics: an update

CRD summary
This review concluded that atypical antipsychotics were used for a range of off-label conditions with varied results and it may not be appropriate to assume class effects. The conclusions of this broad review should be considered carefully for each individual condition bearing in mind the acknowledged presence of publication bias, potential language bias and unexplained heterogeneity.

Authors’ objectives
To review the safety and efficacy of atypical antipsychotic medications commonly used in off-label conditions.

Searching
This review was an update of a previous report (see Other Publications of Related Interest). PubMed, EMBASE, CINAHL, PsycINFO, DARE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to May 2011. Search terms were reported. Additional searches included regulatory documents from the US Food and Drug Administration and Health Canada, ClinicalTrials.gov and references from relevant reviews and included papers. Only papers published in English were considered for inclusion.

Study selection
Controlled trials that compared atypical antipsychotic medication with either placebo, another atypical antipsychotic drug (excluding clozapine) or other medication for treatment of off-label conditions were considered eligible for inclusion. Large observational studies with a sample size of over 1,000 patients were included to assess adverse events. Studies of adults and children were eligible (only adult studies were reported). Outcomes were not pre-specified. Included studies reported on atypical antipsychotic medications (including aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) for treatment of anxiety, dementia/severe geriatric agitation, depression, insomnia, obsessive-compulsive disorder (OCD), personality disorders, post-traumatic stress disorder (PTSD), eating disorders, attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome. Further details of the included studies were summarised by condition and presented in the full report. No trials were found for off-label uses of paliperidone, asenapine and iloperidone.

Studies were selected by two independent researchers. Disagreements were resolved by consensus.

Assessment of study quality
Validity of the controlled trials was assessed using the Jadad scale of randomisation, blinding, allocation concealment and loss to follow-up. The Newcastle-Ottawa scale was used to assess the validity of observational studies.

The overall strength of evidence for intervention efficacy was rated using guidance suggested by AHRQ (Agency for Healthcare Research and Quality) for its Effective Health Care Program in terms of high, moderate and low confidence that the evidence reflected the true effect.

Two reviewers independently conducted the study quality assessment.

Data extraction
Two reviewers independently extracted study details from the controlled trials. Two reviewers extracted and a third checked the study details extracted from the observational studies. A statistician extracted numerical data for efficacy and effectiveness outcomes.

Event counts and sample sizes by group were extracted for outcomes that reported count data. Sample size, mean difference and standard deviations were extracted for continuous outcomes. Studies were excluded from analysis if mean differences by outcome were not reported and could not be calculated from the given data. Where trials did not report a follow up standard deviation, this was imputed.
Methods of synthesis
Continuous outcome data were summarised using weighted mean differences within each comparison. Where different outcome scales were used a standardised mean difference was calculated using the Hedge's g effect size. Dichotomous data were summarised using relative risk (RR). Random-effect meta-analysis was used to pool effect sizes or relative risks across trials. A minimum of three trials was required to perform meta-analysis. Decisions were made by a psychiatrist, a statistician and the project team jointly.

Where adverse events occurred in two or more trials, exact conditional inference was used to estimate the pooled odds ratio (OR) and 95% confidence intervals (CI) and the number needed to harm (NNH) was calculated. Adverse events data were grouped according to three comparisons: atypical antipsychotic versus placebo; atypical antipsychotics versus other atypical antipsychotics; and atypical antipsychotics versus another active drug.

Publication bias was assessed using the Begg and Egger tests. Heterogeneity was assessed using the Q-test and $I^2$ test.

Results of the review
One hundred and seventy trials contributed to the efficacy review 168 of which provided unique data. Most were placebo-controlled rather than direct comparisons of atypical antipsychotics. One hundred and twenty-nine studies were included that reported adverse events data. Key results are presented below.

**Dementia** (38 RCTs): There was a positive significant difference between the atypicals as a class and placebo for all three outcome measures (total/global scores SMD 0.17, 95% CI 0.08 to 0.25, psychosis SMD 0.12, 95% CI 0.04, 0.19 and agitation SMD 0.20, 95% CI 0.12 to 0.27). $I^2$ values indicated moderate heterogeneity (74.6%). No publication bias was present in the risperidone analysis. Further results grouped by medication and dosage were given in the full report.

**Anxiety** (14 placebo RCTs): Pooled analysis of three trials for generalised anxiety disorder reported a statistically significant difference in favour of quetiapine versus placebo (RR 1.26, 95% CI 1.02 to 1.56). Heterogeneity was present ($I^2$=78.2%). There was no evidence of publication bias. Trials of olanzapine, risperidone and ziprasidone were too heterogeneous to pool and reported mixed results.

**Obsessive-compulsive disorder** (16 RCTs): Analyses that compared quetiapine (five trials, $I^2=61.3\%$) and olanzapine (two trials) found no statistically significant benefit versus placebo. Pooled analysis of risperidone versus placebo (three trials, $I^2=0\%$) found a significant effect of treatment (RR 3.92, 95% CI 1.26 to 12.13). Tests suggested that publication bias was present for this last analysis. Further comparisons were reported.

Analyses were also conducted for depression (36 trials), ADHD (four trials), eating disorders (six trials), personality disorder (12 trials), PTSD (10 trials), insomnia (one trial) and substance abuse disorders (33 trials).

**Safety**: In elderly patients, adverse events included an increased risk of death (NNH=87), stroke (for risperidone, NNH=53), extrapyramidal symptoms (for olanzapine NNH=10 and risperidone NNNH=20) and urinary symptoms (NNH from 16 to 36). In non-elderly adults, adverse events included weight gain (particularly with olanzapine), fatigue, sedation, akathisia (for aripiprazole) and extrapyramidal symptoms.

**Authors’ conclusions**
Benefits and harms varied among atypical antipsychotics for off-label usage. For symptoms associated with dementia in elderly patients, small but statistically significant benefits were observed for aripiprazole, olanzapine and risperidone. Quetiapine was associated with benefits in the treatment of generalized anxiety disorder and risperidone was associated with benefits in the treatment of OCD; adverse events were common.

**CRD commentary**
This review addressed a very broad topic area with only partially defined inclusion criteria. The searches were comprehensive and built on an earlier review. Exclusion of papers in languages other than English may have introduced language bias. Study selection, data extraction and quality assessment processes were likely to have minimised reviewer error and bias. Use of a simple summary score to assess quality may have missed additional important elements. The analyses appeared appropriate, although the breadth of the topic and lack of pre-specified primary outcomes made it difficult to interpret the results. Heterogeneity was assessed, but did not seem to be taken into account when interpreting the results. The quality assessment did not appear to impact on the overall conclusions.
The conclusions should be considered carefully for each individual condition bearing in mind the acknowledged presence of publication bias, potential language bias and unexplained heterogeneity.

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

**Practice:** The authors did not make any specific recommendations about practice.

**Research:** The authors stated that it may not be appropriate to assume class effects for atypical antipsychotics. Each drug required trials to demonstrate efficacy for each off-label indication and head-to-head trials were required to compare drug effects. Further research should explore dosage recommendations and duration of treatment.

**Funding**


**Bibliographic details**


**Original Paper URL**

http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&amp;productid=786

**Other publications of related interest**


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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.