Risk of treatment-emergent diabetes mellitus in patients receiving antipsychotics

CRD summary
This review concluded there was no evidence of an increased risk of diabetes mellitus during treatment with second-generation antipsychotics compared with first-generation antipsychotics. Despite the poor reporting of review methods, the authors’ cautious conclusion reflects the methodological weaknesses of the included data.

Authors' objectives
To determine the risk of emergent diabetes mellitus in patients receiving treatment with antipsychotics.

Searching
MEDLINE and PsycINFO were searched for English language studies published in peer reviewed journals between 1966 and 2005. Search terms were reported. The reference lists of review articles were also screened for additional references.

Study selection
Cohort studies that assessed the risk of diabetes mellitus with exposure to antipsychotic monotherapy, using first- and second-generation drugs, were eligible for inclusion in the review.

All but one of the included studies assessed new cases of diabetes mellitus in patients treated with antipsychotic drugs. Most studies included patients who had healthcare plans or commercial insurance. The majority of the studies were carried out in the USA and were funded by pharmaceutical companies. The studies varied in how they defined the development of diabetes and what methods they used to identify new cases. Where stated, the length of follow-up ranged from less than one year to 25 months. Included antipsychotics were first-generation antipsychotics, clozapine, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone.

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

Assessment of study quality
The authors stated that studies were assessed for their susceptibility to common sources of bias referenced in two published studies. No further details of the criteria were reported. The authors did not state how the validity assessment was performed.

Data extraction
The numbers of cases of diabetes mellitus were extracted and used to calculate the incidence, attributable risk between agents and the number-need-to-harm, expressed per 1000 patients with 95% confidence intervals. Where available, any adjustments made for any risk factors known to be associated with the development of diabetes were extracted, including weight, race/ethnicity, diabetogenic drugs and psychiatric diagnoses.

The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
Studies were combined in a narrative synthesis, with data tables quantifying the risk of newly emergent diabetes mellitus in those studies comparing first- and second-generation antipsychotics.

Results of the review
Twenty-five retrospective studies were included in the review, including nineteen cohort studies (261,698 patients receiving antipsychotics), four case-control studies (over 81,889 patients receiving antipsychotics), one cross-sectional study (38,632 patients receiving antipsychotics) and one combined cohort and case-control study (19,637 patients receiving antipsychotics). Details of study quality were not reported. None of the studies controlled for familial history.
levels of physical activity or diet, which are known to be risk factors for the development of diabetes mellitus.

Fifteen cohort studies were included in the assessment of attributable risk. The studies failed to show a consistent advantage for first- (not specified) or second-generation antipsychotics (clozapine, risperidone, olanzapine and quetiapine). Nine studies reported a lower risk of developing diabetes for those patients treated with a second-generation drug than those treated with a first-generation drug. All but one study comparing the risk of diabetes with first-generation antipsychotics versus clozapine, reported a higher risk with clozapine (number-needed-to-harm ranged from 19 to 179 per 1000 patients). Effect sizes for the other second-generation drugs were inconsistent, small and rarely statistically significant. The number-needed-to-harm for each study and drug were presented.

**Authors’ conclusions**
The review did not demonstrate an increased risk of diabetes mellitus during treatment with second-generation antipsychotics in comparison with first-generation antipsychotics.

**CRD commentary**
This review answered a clear review question, using broadly defined criteria for study design and patient population. Inclusion criteria were only stated for the fifteen comparative studies, so the decision to include and tabulate the non-comparative studies appeared puzzling. Searches were carried out for studies published in English in two databases, so relevant studies may have been missed and the review may be at risk of language and publication bias. No details of the study methods were reported, making it difficult to assess the risk of reviewer error and bias. Also details of the assessment of study quality were not reported, so it was also difficult to assess the reliability of the data. No randomised controlled trials were identified, and none of the included retrospective studies adjusted their analysis to take into account major confounding variables such as familial risk and level of physical activity. Studies used heterogeneous definitions and methods to assess the development of diabetes; few followed patients beyond one year. Effect sizes were also usually small, inconsistent and rarely statistically significant. The data are unlikely to be reliable and a cautious interpretation is advised, as acknowledged by the authors. Overall, despite the poor reporting of the review methods, the authors’ cautious conclusion reflects the methodological weaknesses of the included data.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that prospective, long-term longitudinal studies are required, which account for the multifactorial nature of diabetes mellitus pathogenesis. They also stated that there is a need for a randomised controlled trial comparing antipsychotic use and the new onset of glucose dysregulation.

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