Do certain atypical antipsychotics increase the risk of diabetes: a critical review of 17 pharmacoepidemiologic studies
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CRD summary
This review assessed the excess risk and relative risk of type 2 diabetes associated with atypical antipsychotics. Olanzapine was associated with a greater risk of diabetes than untreated psychiatric illness and risperidone. Risperidone did not increase risk compared with non-treatment or conventional antipsychotics. The authors' conclusions should be viewed with caution as there were a number of methodological limitations.

Authors' objectives
To assess the excess risk and relative risk of type 2 diabetes associated with atypical antipsychotic drugs (APs).

Searching
MEDLINE was searched from January 1996 to June 2003; the search terms were reported. The reference lists of retrieved articles were checked. In addition, posters and abstracts of U.S. and European psychiatry meetings were searched from January 2000 to June 2003.

Study selection
Retrospective studies assessing the risk of diabetes associated with exposure to atypical APs, which included a population of untreated patients with major psychiatric illness as a reference group and reported hazard ratios (HRs), relative risks (RRs) or odds ratios (ORs) for individual APs, were eligible for inclusion. Prospective clinical studies were excluded. The included studies evaluated risperidone, olanzapine, clozapine and quetiapine compared with no APs, conventional APs, or each other. Some studies were restricted to patients with schizophrenia, but most had a population with a variety of psychiatric disorders. Where reported, the mean duration of AP exposure varied (conventional: 2.25 months to 5.6 years; atypical 3 months to 2.2 years).

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 authors assessed study validity with regard to methodological issues such as the selection of treatment and comparison groups, overall study design, definition of outcome measure, selection and inclusion of covariates, and the statistical methods used.

The authors did not state how the validity assessment was performed.

Data extraction
RR, OR and HRs were extracted, along with their 95% confidence intervals (CIs) for each comparison.

One reviewer extracted the data, which all authors then independently evaluated.

Methods of synthesis
The studies were grouped narratively by treatment. Differences between the studies could be examined in the tables of study details.

Results of the review
Seventeen studies were included in the review: 12 cohort studies, 4 case-control studies and 1 prevalence study. The number of participants was difficult to determine, but there appeared to be >203,077 treated with atypical APs, 61,338 with conventional APs and >14,678 untreated.
Atypical APs compared with no treatment (3 cohort and 1 case-control): treatment with olanzapine resulted in a significant increase in the risk of diabetes (4 studies), but no increased risk was observed with risperidone (4 studies) or quetiapine (1 study). The results for clozapine were mixed, with 1 study reporting an increased risk and another reporting no difference in risk between the groups.

Atypical APs compared with conventional APs (7 cohort and 1 case-control): the results were conflicting. Nine comparisons showed a significant increase in the risk of diabetes with atypical AP: two of risperidone, two of quetiapine, three of olanzapine and two of clozapine. However, most comparisons reported no increased risk of diabetes: eight of risperidone, five of olanzapine, two of clozapine and three of quetiapine. Of the 5 studies that reported the risk of diabetes comparing any atypical AP with any conventional AP, only one reported a significant increase in risk. The only study that compared risperidone to different doses of conventional AP showed an increased risk with the low dose of conventional AP.

Of the 9 studies comparing olanzapine with risperidone (6 cohort, 2 case-control and 1 prevalence study), six reported a significant increase in the risk of diabetes with olanzapine.

**Authors' conclusions**

Olanzapine therapy poses a higher risk of diabetes than untreated major psychiatric illness. Olanzapine is associated with a greater risk of diabetes than risperidone. It is unclear whether clozapine is associated with a greater risk of diabetes than untreated major psychiatric disorder.

**CRD commentary**

The review question was broad but well-defined. The inclusion criteria were clear with regard to the intervention, outcome, study design and participants. It is not known whether any language restrictions, which can lead to language bias, were applied. The searches for published studies were restricted. Though the authors attempted to identify unpublished studies, publication bias may be present since only one database was searched. While the data extraction was performed by one reviewer and checked by another, thereby reducing the risk of bias and error, the processes by which studies were selected and validity assessed were not reported. The authors excluded prospective studies but did not justify this decision. The outcome measures were also unclear: the authors appeared to use the OR and RR interchangeably, which may not have been appropriate depending on the prevalence of the outcome measured. The validity of the included studies was assessed, but some important aspects of the assessment were not reported. The studies were appropriately synthesised in a narrative, as the studies were heterogeneous, and the methodological limitations (e.g. confounding and temporal relationships) of retrospective cohort and case studies used in this review were taken into consideration. Nonetheless, it is unclear whether the results are generalisable to all patients with psychotic disorders or whether they can be applied to any specific psychotic disorder, as there was a lot of heterogeneity across the studies, particularly in the patient population. The inconsistencies in reporting, inadequate validity assessment, potential for missed studies, selection bias and reliance upon retrospective data mean that the authors' conclusions should be viewed with caution.

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

**Practice:** The authors stated that clinicians should consider the patients' individual risk factors for diabetes when choosing an antipsychotic. Patients with additional risk factors for diabetes, particularly those that take olanzapine and possibly clozapine, should be monitored quarterly.

**Research:** The authors stated that further studies comparing the risk of diabetes in patients taking olanzapine with risperidone are needed.

**Funding**

Janssen Pharmaceutica Products, L.P.

**Bibliographic details**

Record Status
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.