Reviewer's report

Title: Association between second-generation antipsychotics and newly diagnosed treated diabetes mellitus: does the effect differ by dose?

Version: 1 Date: 21 June 2011

Reviewer: Lars Kessing

Reviewer's report:

The purpose of this study was to examine whether any association between SGAs (aripiprazole, clozapine, olanzapine, risperidone, quetiapine, ziprasidone) and diabetes mellitus differs according to dose using administrative and healthcare claims data from three United States sites. The authors conclude that the risk of diabetes for persons exposed to olanzapine, risperidone, and quetiapine was elevated and dose-dependent whereas aripiprazole and ziprasidone were not associated with significant risk of diabetes and dose dependent relationships were not apparent.

Major Compulsory Revisions

A number of limitations may make the conclusion of the paper less valid.

1. Most prescription data bases do not include data on the prescribed daily dose of the drugs but only on the name, dose of medication and the number of tablets prescribed. Did the authors have information on the prescribed daily dose of the drugs? There are different ways to retrospective estimate the prescribed daily dose of the drugs but each method has some drawbacks. It is not clear how the authors overcame this central issue.

2. Besides the above potential flaw, the main problem is the reduced statistical power related to the analyses for aripiprazole and ziprasidone as revealed by the wide 95% confidence intervals. The authors do not present the number of patients taking each type of antipsychotic (this should be presented in Table 2). It is very likely that the negative finding of no dose effect of these drugs may simply be due to the low statistical power in these analyses. In this way the authors will not be able to examine whether association between SGAs and diabetes mellitus differs according to dose (the purpose). The problem with varying/low statistical power makes the study findings difficult to interpretate.

Other issues:

1. Individuals were excluded from analyses if they had evidence of diabetes before the index date. The exclusion period must have been short, but the lengths is not given?

2. It is not clear how “add on of another antipsychotic” was handled in the analyses.

3. Was there an effect of the duration of treatment and of polypharmacy of
antipsychotic drugs as found in a recent paper by Kessing et al, 2010.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

Lars Vedel Kessing has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZenica, Pfizer, Wyeth, Servier, Janssen-Cilag.

I declare that I have no other competing interests.