

- Second Messenger -

Relatively Speaking, How Odd Can Hazards be?

Interpreting the odds ratio

Second-generation antipsychotics may be associated with diabetes more so than first-generation antipsychotics.

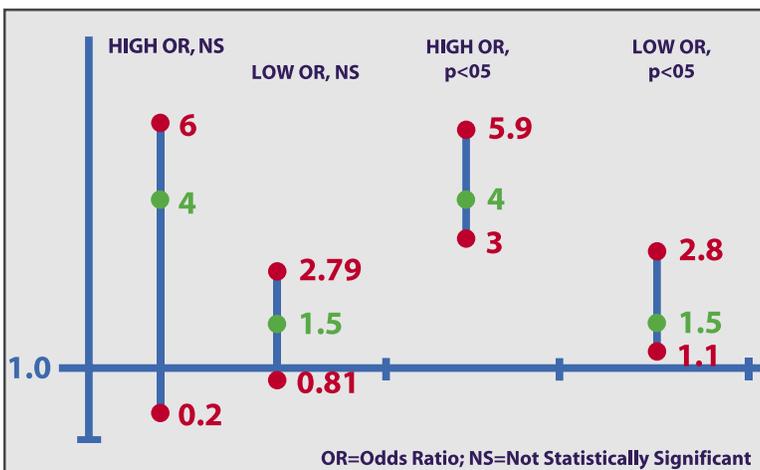
The association of second-generation antipsychotics with new onset type 2 diabetes mellitus is a hot topic. We hear statistics such as patients taking olanzapine having a 4.2 times elevated risk of developing diabetes than those taking conventional antipsychotics.¹ Reported in that paper, a case-control epidemiological study, were *odds ratios* (OR). Here the OR represents the likelihood that persons with diabetes have been exposed to a particular antipsychotic (say, Drug A), compared to another (Drug B). If the OR is 1.0, then the likelihood is the same. If the OR is 3.0, then the likelihood is three times as great. If the OR is 0.5, then the likelihood is half as great. But how can we properly interpret this figure?

Enter the confidence interval

First, we need to look at the *confidence interval* (CI). The CI consists of two numbers: the *lower bound* and the *upper bound*. A 95% CI means that there is a 95% probability that the actual OR falls in between the lower bound and the upper bound. If the number 1.0 falls in between the lower bound and the upper bound, then included in the 95% probability is the possibility that there is no difference in risk, and we say that the result is not statistically significant. This can result in situations where one can calculate a very high OR (for example 20.0) and yet it would not be statistically significant if the 95% CI was 0.10–100. Also possible is a very low OR (for example 1.1) that would be statistically significant if the 95% CI were 1.05–1.15. Figure 1 represents several possibilities for ORs and their 95% CI. Coming back to our example,¹ the 95% CI for the OR of 4.2 was quite “wide” at

Figure 1: How Odd Can Odds Ratios Get?

Strength of the association may be high, but statistical significance may not be reached (if confidence interval includes 1.0)⁵



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1.5 to 12.2. This may be explained by the relatively small number of patients receiving olanzapine compared to conventional antipsychotics (970 versus 18,443) and thus, the small number of incident cases (9 among patients receiving olanzapine and 382 among patients receiving conventional antipsychotics).

Our own group’s case-control study² took place in a different treatment context (state hospitals in New York rather than outpatients in the United Kingdom) in a later period of time (2000–2002 rather than 1987–2000 when second-generation antipsychotic utilization was far less common). Our CIs were narrower, but yielded unexpected results. Statistically significant elevations in risk were observed for patients receiving more than one second-generation antipsychotic (OR=2.86, 95% CI=1.57–5.2), clozapine (OR=2.06, 95% CI=1.07–3.99) or quetiapine (OR=3.09, 95% CI=1.59–6.03), compared to exposure to first-generation antipsychotics alone. Although not statistically significant, odds ratios for olanzapine (OR=1.57, 95% CI=0.87–2.82) and risperidone (OR=1.50, 95% CI=0.81–2.79) were also elevated. How could this be and what does it mean?

Risk, bias, and confounds, oh my!

Figure 2 shows the odds ratios calculated in our study, and one can readily note that the confidence intervals overlap considerably. Thus, no conclusions can be made about the comparative risk of directly pitting one second-generation antipsychotic against another. One can conclude that there may be something to the notion that second-generation antipsychotics may be associated with diabetes more so than first-generation antipsychotics. Other points include the possibility of *treatment-assignment bias*, which occurs if a clinician favors one drug over another in patients at high risk for developing diabetes, because of family history and age for example. The latter risk factors happen to be quite important and the patient may develop diabetes regardless, leading to erroneous attribution of risk to the preferred antipsychotic. Yet another bias is *surveillance bias*, where if one orders more plasma glucose tests for patients on one medication versus another, the likelihood of finding problems would be higher the greater the number of tests done. Conversely, the fewer tests, the fewer chances of finding a problem. In our sample, we found that patients receiving conventional antipsychotics received fewer plasma glucose tests than patients receiving clozapine, olanzapine, or more than one second-generation antipsychotic.

A rule of thumb

Because of these and other confounds, many epidemiologists will be less likely to accept an OR of less than 3.0 at face value, and almost never an

OR of less than 2.0. Increases in risk of less than 100% (i.e., an OR of less than 2.0) are difficult to interpret because of the possibility of confounding factors that have not been accounted for.³

Attributable risk was found to be 2% for clozapine and less than 1% for the other second-generation antipsychotics. A more intuitive way of explaining this is to calculate the *Number Needed to Harm*

Attributable risk can answer the clinically relevant question of, "How many more cases of diabetes will I be likely to see if I treat my patients with a second-generation antipsychotic instead of haloperidol?"

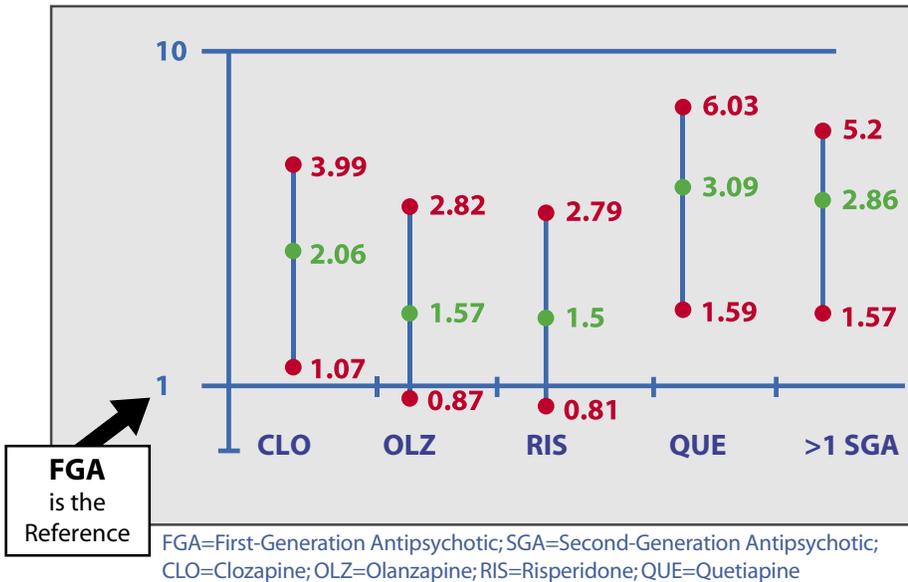
Other useful terms

The *relative risk ratio* (RR) is another way of comparing risk of association. It is a product of a cohort epidemiological study. *Hazard ratios* (HR) can also compare risk and are the output of statistical analyses of survival data. RR, OR, and HR can be interpreted in a similar fashion together with their CIs, but these three *risk ratios* are calculated very differently. None of these risk ratios tell us much about *attributable risk*. Attributable risk can answer the clinically relevant question of, "How many more cases of diabetes will I be likely to see if I treat my patients with a second-generation antipsychotic instead of haloperidol?" Attributable risk was calculated in a recently published study of diabetes among patients treated by the US Department of Veterans Affairs.⁴

(NNH). NNH is simply the reciprocal of the attributable risk. By calculating NNH we see that one would need to treat 49 patients on clozapine, 125 on quetiapine, 159 on olanzapine, or 2,000 on risperidone before seeing an extra case of diabetes above and beyond what we would expect with conventional antipsychotics.

The bottom line—When you hear an OR, RR, or HR, ask for the CI. If the CI includes 1.0, walk away. Be wary if the CI is unduly wide—ask how many cases there were. If the risk ratio is over 3.0 and has a narrow CI, pay more attention. Regardless of the risk ratio, you will need to know the attributable risk in order to place this into a clinically relevant context. The concept of NNH is helpful in this regard. ☒

Figure 2: Antipsychotics and New Onset Diabetes Mellitus
Age-Adjusted Odds Ratios vs. FGAs²



References

1. Koro CE, Fedder DO, L'Italien GJ, L'Italien et al. *British Medical Journal* 2002;325(7358):243-247.
2. Citrome L, Jaffe A, Levine J, Allingham B, Robinson J. *Psychiatric Services* 2004;55(9):1006-1013.
3. Braithwaite W, Cole P, Feinstein AR et al. <http://www.annapoliscenter.org/Reports/epidemiology.pdf>.
4. Leslie DL, Rosenheck RA. *American Journal of Psychiatry* 2004;161(9):1709-1711.
5. Citrome L. ISCTM Meeting, 2005.

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