Editorial: Metabolic effects and antipsychotics

Stephen R. Saklad, Pharm.D., BCPP[1]

[1]Clinical Pharmacist, San Antonio State Hospital
Clinical Associate Professor, College of Pharmacy, The University of Texas at Austin

KEYWORDS

antipsychotics, monitoring, side effects

The invention and use of antipsychotics has transformed the prognosis for persons with serious and persistent mental illness from that of a lifetime of incarceration to a potentially manageable illness. The outcomes now include a few with virtually complete success and a few that have clinically insignificant benefits. Most persons with serious and persistent mental illness have some clinical improvement, but not restored to their previous level of function.

Chlorpromazine was a "wonder drug" of the 1950s that aided the most helpless in the mental hospital: those with schizophrenia. There was no animal model of psychosis, so researchers found a surrogate to screen for new agents. The ***inclined screen*** or ***rotarod*** were the assays used to detect the surrogate markers of rigidity and slowed movement in rats. These assays led to many similar "D_2-Me_{T00}" agents with similar efficacy and mostly comparable adverse effects. Of course, because of the surrogate used in their discovery, all of these agents caused extrapyramidal symptoms (EPS), including pseudoparkinsonism acutely and as it was later discovered, tardive dyskinesia.

Clozapine changed that picture in the 1980s. Now we had a silver bullet: an antipsychotic that could be efficacious without significant EPS. In fact, clozapine appeared to have increased efficacy compared to older agents. All was good … almost.

Clozapine was launched by Sandoz in several European countries beginning in 1972. In 1975, clozapine was available in Finland. Within six months, 17 cases of agranulocytosis were found among the three thousand patients exposed.[1]

Agranulocytosis due to clozapine occurs at a rate of about 0.5% and deaths were mitigated with an unprecedented mandatory monitoring program that involved pharmacists. Soon, we realized that there were additional issues with clozapine.

Clozapine increased weight, triglycerides, and glucose dysregulation. This led to or worsened the metabolic syndrome thereby increasing the risk of cardiovascular disease. Additionally, large increases in clozapine dose or high doses lowered seizure threshold. I have observed this on several occasions when clozapine treated patients at San Antonio State Hospital returned from Thanksgiving pass and were restarted on their previous clozapine dose. They would seize on Tuesday afternoon.

Other antipsychotics soon followed clozapine. All tried to mimic the "atypical" antipsychotic efficacy profile that clozapine showed: antipsychotic efficacy with low rates of extrapyramidal symptoms. They all worked to avoid the known problem of agranulocytosis. Initially, the metabolic effects were not identified as problems, however it was later discovered that the first series of these "atypical" antipsychotics have similar, and sometimes worse, metabolic effects. Later "second generation" or "new generation" antipsychotics tended to have cleaner metabolic profiles, but still focused on the apparently unique pharmacologic profile of clozapine: dopamine D_2 and serotonin (or 5-OH tryptamine: 5-HT) 2_A antagonism.

Although second generation antipsychotics were hoped to have clinical efficacy that was superior to the first generation agents, recent studies have demonstrated efficacy that is statistically similar to the first generation agents. Adverse effects continue to differ between all of the antipsychotics. All of the studies use measures of central tendency, such as analysis of variance (ANOVA), to do statistical comparisons between groups. While the ANOVA technique was developed to measure grain yields,[2] it has been used as the gold standard test for differences between groups.

Unfortunately, we really don't care about ***groups of people*** do we? Clinicians care about ***individuals***, not ***groups***. The mean of the test group may have shown no difference from the mean of the control group in a study. However, mixed in either group in a study are some individuals that worsened, some with no clinical change, and some that improved tremendously. We should be using statistical tests to examine these outliers. How

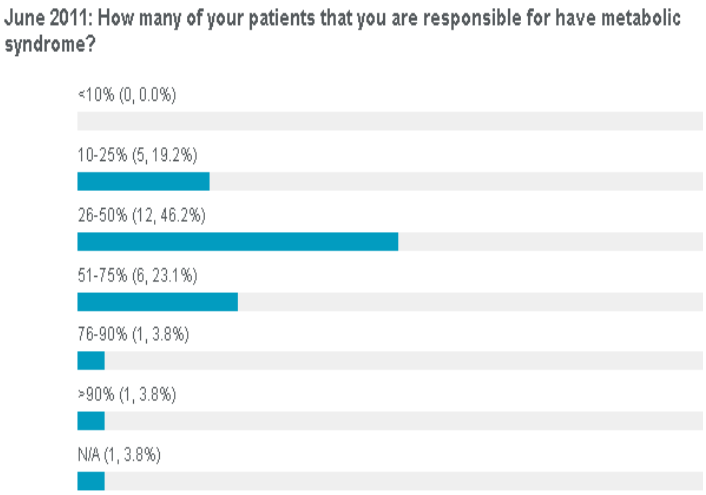
many of each group being studied had clinically important benefits or adverse effects? Unfortunately, most statistics research has been done to remove outliers, not to identify them and determine how they differ from the rest.

While statistical study design is unlikely to be an area of fascination to most CPNP members, finding and helping the outliers with metabolic problems is a common activity of a pharmacy clinician. The June CPNP poll shows that most of our members report that have between 25-75% of their patients have metabolic syndrome (Figure 1). Our role in antipsychotic monitoring that was codified for clozapine's clinical use has now expanded to include metabolic effects.

Most of us are likely to monitor weight, and many will also track fasting glucose or hemoglobin A1C, lipids, and blood pressure. Some of you may measure waist circumference, but in my experience this is still rare. If I want to know someone's waist circumference, I usually need to measure it personally ... it is not in the chart.

This first issue of MHC explores some of the ways that CPNP members have attempted to monitor, track, and reverse metabolic effects of antipsychotic medications. The members of the MHC Editorial Board are excited to present this new publication and welcome your feedback.

Figure 1: CPNP Poll on Metabolic Syndrome



REFERENCES

1. Idänpään-Heikkilä J, Alhava E, Olkinuora M, Palva IP. Agranulocytosis during treatment with clozapine. Europ J Clin Pharmacol. 1977;11:193-198.
2. Fisher RA. Studies in Crop Variation. I. An examination of the yield of dressed grain from Broadbalk. J Ag Science. 1921;11:107-135.

How to cite this editor-reviewed article
Saklad SR. Editorial: Metabolic effects and antipsychotics. Ment Health Clin [Internet]. 2011;1(1):1-2. Available from: http://dx.doi.org/10.9740/mhc.n74795