**Presentation by Dr. John Newcomer: Sept 19, 2001, CAMH**
**Impaired Glucose Regulation, Diabetes, Schizophrenia, and Antipsychotic Medication**

- Discussion of diabetes and glucose regulation and weight gain – background.
    - Age, adiposity and ethnicity are 3 key factors.
    - Prevalence of diabetes increases with age – most of the age effect comes from increasing adiposity
- All antipsychotics cause weight gain, but it's a question of degree. "Clozapine and olanzapine end up on the top of the pile."
- Incidence of type 2 diabetes is 12-36% for clozapine and 6-35% for olanzapine using WHO or American Association of Diabetes criteria. Noted that Lilly states number is 3.1%, but this is based on random blood glucose and 160 as a cut-off.
- Showed summary of case reports:

| | **New Onset DM/IGT** | **DKA** |
|---|---|---|
| **Clozapine** | 72 | 10 |
| **Olanzapine** | 82 | 14 |
| **Quetiapine** | 2 | 1 |
| **Risperidone** | 1 | 1 |

- Stated that risp has been on market much longer than olz but many fewer case reports. Acknowledged that you can find these reports for any antipsychotic but it's a question of degree and frequency.
- Discussion of Diabetic Ketoacidosis (DKA). Stated that DKA can kill you (mortality rate of 2-10% or higher). Worried that psychotic patients may take longer to recognize DKA which may increase mortality in this group.
- Impaired glucose regulation can lead to increased risk of macrovascular disease – even if do not meet cut off for diabetes. Progressive relationship between glucose and cardiovascular risk.
- Detailed review of his study of medication-related abnormalities in glucose regulation in schizophrenia using oral 50g dextrose challenge. **Now in press in Archives of General Psychiatry (Newcomer et al.).** All patients were non-diabetic at baseline and matched for adiposity. Cross sectional study and had unchanged medication regimen for at least 3 months. Used 75 mins because this was length of cognitive battery in study. (*Stated that 2 hours is a random time frame anyway and was chosen purely out of convenience. Said the longer time period you wait, the <u>more</u> the groups separate.*) Some patients were taking concomitant meds (including SSRIs and depakote), but when these patients were taken out of the analysis, this did not change the results. Olz and cloz pts' blood glucose were each significantly higher compared to typical antipsychotics. No sign difference found for risp vs typicals. No

differences were found among the atypicals but small sample size. Insulin levels still rising at 75 mins for olz and cloz but falling for risp.

- Showed HOMA (homeostasis model assessment) data for insulin resistance in treated patients with schizophrenia. Showed sign diffs between olz and typicals and cloz and typicals but no diff for risp vs typicals.
- IVGTT (Henderson et al, 2000, NCDEU) data for antipsychotic-associated differences in insulin sensitivity: Said worried that numbers aren't accurate since risp numbers are "remarkable" and lie outside the general population (ie, risp looked too good to be true.)
- Showed Newcomer et al. (No source noted) graph of insulin resistance in treated patients: Pooled olz and cloz data (no reason noted why) and found sign diffs between pooled group and BMI controls and also vs Lean Controls.
- Ended with discussion of consequences of weight gain and elevated blood glucose/diabetes. Implied that mortality due to weight gain may be as great as lives saved from decreased suicide rate with treatment: Estimated 492 suicides/100K in schizophrenia prevented by clozapine, at a cost of 416 additional deaths secondary to weight gain.
- Encouraged regular monitoring of blood glucose and weight.
- Treatment-associated changed in glucose regulation may interact with treatment-induced weight gain to further disturb glucose regulation.
- Some discussion of potential mechanisms.