Joslin Diabetes Center Continuing Medical Education Event- Schizophrenia, Bipolar Disorders and Diabetes: Interrelationships and Interventions

Summary by A. Potts
Boston: March 2, 2004
Approx 150 attendees

I. **Schizophrenia, Bipolar Disorders, Diabetes and Metabolism: Interrelationships (Speaker: Dr. John Newcomer, Washington Univ School of Medicine)**

- Introduction and framework for symposium
  - Discuss ADA Consensus Guidelines and evidence supporting guidelines
  - Discuss FDA request for label changes
- Epidemiologic overlap of schizophrenia, bipolar disorders, and metabolic defects – managing multiple risks
  - Mentioned that issue of diabetes and mental illness has existed well before second generation antipsychotics
  - Obesity complicating schizophrenia and bipolar disorders
  - The metabolic syndrome
- Overview of second-generation antipsychotic agents (SGAs)
  - Similar efficacy across newer antipsychotics so boils down to adverse event debate (one exception is clozapine)
  - Showed one year weight gain data for various SGAs
    - Included data from Kinon with all doses of olanzapine (stated this included 2.5 mg doses) and showed about 6 kg weight gain at 1 year
    - Said Charlie Nemeroff did analysis of Lilly's olanzapine data from pivotal clinical trials for doses of 12.5-17.5 mg and found greater than 10 kg weight gain at 1 year.
  - Weight gain is dose related for some drugs (ex: risperidone, olanzapine) but not others
  - Not everyone gains weight but it's difficult to tell who will
  - Mentioned that Henderson has an article in press looking at hypertension in schizophrenia
  - Discussed even higher rates of weight gain in adolescents with SGAs (*Ratzoni 2002*)
  - ADA Guidelines: found differences among the SGAs in contrast to FDA that concluded it's a class effect
    - Compelling evidence – olanzapine, clozapine
    - Equivocal evidence – risperidone, quetiapine
    - No clear evidence – aripiprazole, ziprasidone
  - Review of evidence for ADA Guideline conclusions
    - FDA Medwatch Reports – need to look at prescription years and consider denominator (olanzapine had twice the number of cases but half the number of prescription years as risperidone)
    - Evidence for dyslipidemia with clozapine, olanzapine, quetiapine and risperidone but no evidence with aripiprazole or ziprasidone
    - Epidemiology studies – Koro is "best of the lot". Same result was found by 75% of the other epidemiology studies. In general, higher weight gain resulted in higher risk for diabetes. Koro database was only one that had blood levels – found that there was a higher risk for dyslipidemia for olanzapine but not for risperidone. Less than 25% of studies had results similar to Buse study that found there was a high risk for all SGAs studied.
    - Controlled studies: (*Note – Newcomer did not mention or review any of the Lilly clamp studies*)

- Haupt and Newcomer clamp study - gold standard. Found that as fat mass increased, insulin sensitivity decreased.
- Newcomer et al Arch Gen Psych – found differences among the drugs independent of fat.
    - Henderson also found similar result when comparing olanzapine vs risperidone vs clozapine) – some patients get diabetes on SGAs without gaining weight.
- Pfizer study on fasting triglycerides found improvement of lipids with ziprasidone and risperidone but increase in triglycerides with olanzapine and quetiapine
- Ira Glick (Pfizer funded) study looked at ziprasidone vs olanzapine at 6 weeks. Found no difference in efficacy at 6 weeks but differences in adverse effects.
    - Discussed Lilly poster presented at ACNP 2003 that compared olanzapine vs ziprasidone after 26 weeks. Said that this poster showed adverse effect differences that were very similar to Glick poster.
    - BMS supported randomized study of olanzapine vs aripiprazole vs placebo 26 week looked at time to achieve criteria for metabolic syndrome. See *L'Italien et al in Preventative Medicine in Managed care December Supplement*.
        - Looking at this data and more, ADA and APA sponsored guidelines emphasized that weight gain is a critical factor. Concluded that there is compelling and consistent evidence for diabetes risk and dyslipidemia for olanzapine and clozapine.
- Optimizing treatment of schizophrenia and bipolar disorders
    - Good summary of safety concerns can be found in Nasrallah (2001) Ann Clin Psychiatry including discussion of Adverse events such as blood pressure, sedation, EPS, prolactin.
    - Important to consider morbidity vs mortality (need to pay more attention to the adverse events that are killing people)
        - Ex: prolactin is uncommon with SGAs and is largely reversible
        - Ex: QTc – is it really clinically significant with ziprasidone? So far no QTc related deaths have been reported for ziprasidone. Need to look at theorectical risks (ex: QTc) vs real risks (Ex: metabolic syndrome)
            - There has been a shift in perception
- Managing medical risks in the setting of mental health care delivery
    - *Steve Marder et al (in press, American J of Psychiatry*) published guidelines for monitoring weight, diabetes, and lipids
- Summary

II. **Schizophrenia, Bipolar Disorders, Diabetes, and Metabolic Disease: Medical Interventions (Speaker: Dr. Richard Beaser, Executive Director of CME at Joslin Diabetes Center in Boston)**

- Metabolic syndrome, diabetes, and DKA in the patient with schizophrenia, bipolar disorders, or other severe psychoses
    - Classification of diabetes has recently been updated by ADA – see *Diabetes Care 2004; 27(suppl 1):S5-S10*. (Ex: Normal fasting plasma glucose was just lowered from upper limit of 110 mg/dL to 100 mg/dL.)
    - Recognizing the insulin resistant patient
    - Challenges of treating Type 2 Diabetes in patients with severe mental illness
        - If we can't change behaviors then we have to rely more heavily on pharmacologic interventions
        - Need to assess self-care capabilities

        - Antipsychotic medication and antidiabetic medication selections are important
    - *Sernyac 2003 J Clin Psych; 64:5* study of clozapine
        - Found 77% of patients had normal glucose levels, 18% Impaired fasting glucose, and 5% diabetes.
- Importance of controlling diabetes and components of the metabolic syndrome
    - Discussed risks related to diabetes (ex: Diabetes is a cardiac risk equivalent – if you have diabetes, it's as if you came out the the ICU after treatment for M.I.)
    - BMI increases the risk of Type 2 DM (especially if BMI > 30) therefore treatment choice for schizophrenia is very relevant.
    - Discussed visceral adiposity and use of CT Scan to detect (but no discussion of Ryan and Thakore articles)
    - Key factor is that diabetes often goes undetected for a long time.
    - Changes in Beta cell function occur over time – on-going process so critical factor if you give patient a medication that causes weight gain since this speeds up the process and metabolic derangements.
- Clinical components of the metabolic syndrome
- Summary: preventive strategies and standards of care for people with diabetes and the metabolic syndrome
    - Aerobic exercise improves insulin sensitivity, but people don't like to exercise
    - Smoking increases risk of Type 2 DM
    - Discussion of risks/benefits of treatments for DM
    - Discussed DKA – etiology and clinical presentation
    - Goals for chronic diabetes management
    - Cardiovascular disease in diabetic patients is worst in women
    - ADA Consensus Guidelines – provided website to access
        - Considers a very important publication with good and powerful recommendations
        - Encourages baseline screening (stressed importance of determining family history)
        - Second generation antipsychotics are associated with increased risk of diabetes – risk differs among SGAs (summarized table from ADA Guidelines)
        - Ended with similar to that by George Orwell: "All antipsychotics are equal, but some are more equal than others."

Question and Answer Period:

Newcomer was challenged on his claim that all SGAs have equal efficacy (including a question from me). He responded that all meta-analyses (except the Glick/Davis meta-analysis which has methodological problems) have found the same thing – similar efficacy across all SGAs with the exception of clozapine. He concluded by asking "why start with a drug that has the highest risk for weight gain?"