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 theoretical 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
  o Sernyac 2003 J Clin Psych; 64:5 study of clozapine
    o 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
  o 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.)
  o BMI increases the risk of Type 2 DM (especially if BMI > 30) therefore treatment choice for schizophrenia is very relevant.
  o Discussed visceral adiposity and use of CT Scan to detect (but no discussion of Ryan and Thakore articles)
  o Key factor is that diabetes often goes undetected for a long time.
  o 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
  o Aerobic exercise improves insulin sensitivity, but people don’t like to exercise
  o Smoking increases risk of Type 2 DM
  o Discussion of risks/benefits of treatments for DM
  o Discussed DKA – etiology and clinical presentation
  o Goals for chronic diabetes management
  o Cardiovascular disease in diabetic patients is worst in women
  o 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?”