Summary of April 4, 2002 Massachusetts General Hospital Meeting

Attendees:
MGH: David Henderson, Don Goff, Enrico Cagliero, David Nathan
Lilly: Missy Sowell, Robert Baker, Starr Grundy, Alison Potts

Overview/Key points:

- **Review of hyperglycemic clamp study by Sowell**
  - *Presentation*: Small increase in insulin in healthy volunteers on both olanzapine and risperidone. When data were adjusted for weight, neither agent was correlated with significant change from baseline.
  - *Discussion*: Data relevant for most of the population (i.e., there is no "big, bad effect") but does not address mechanism of DKA in specific, presumably rare, individuals
- **Review of cross sectional study of Bergman's minimal model data by Henderson**
  - *Presentation*: Found insulin resistance in patients treated with clozapine (largest), followed by olanzapine, but found the data from patients treated with risperidone were better than norms for general population. Higher olanzapine blood level correlated with higher insulin resistance.
  - *Discussion*: Limitations discussed: (1) cross sectional and not random assignment to antipsychotics; (2) patients equated for present weight but no accurate measure of weight gain history after start of present antipsychotic; (3) unknown whether patients are similar in history of treatment resistance (patients may not be equated on all important variables.); (4) not clear that results on olanzapine are different than anticipated in normal controls.
- **Review of DKA data by Cagliero**
  - *Presentation*: MGH database examined from Jan 1995 – Jan 2001 for cases of DKA in patients also diagnosed with schizophrenia. Found 6 cases where diagnosis was confirmed and no history of pre-existing diabetes. At time of DKA, four of these patients were taking olanzapine (10-20mg), one was taking clozapine (200mg) and one was taking clozapine (550mg) plus risperidone (2mg). Estimated incidence of DKA in their population of patients with schizophrenia was approximately 0.2%. Plan on expanding database to include patients from the Brigham.
  - *Discussion*: Limitations discussed: (1) possibility of selection bias of patients coming to MGH for treatment of DKA vs schizophrenia (i.e., would lead to overestimate of incidence of DKA among patients with schizophrenia), (2) what is the appropriate denominator for these cases; (3) length of time on the medications is unknown.
- **Discussion of next steps**
  - Henderson, Cagliero, Goff and Nathan proposed potential studies to continue follow up of DKA issues. Dr. Nathan said they want to understand mechanism of DKA and determine whether certain patients are at risk. Future studies could include: (1) follow up with patients in MGH and Brigham databases to determine more about patient history, (2) analyze the DNA of these DKA patients, (3) rechallenge these DKA patients with antipsychotic and complete clamp study and blood glucose, lipid, etc measures after short term antipsychotic exposure. Want to use

olanzapine as probe in these patients to determine how they differ from general population.
  - Henderson will take the lead on following up with letter(s) of intent related to these follow up studies.

Discussion Details

Hyperglycemic clamp study review – Missy Sowell

- Reviewed data from hyperglycemic clamp study of healthy volunteers. Found small increase in insulin in both olanzapine and risperidone treated volunteers. These changes were correlated with weight changes. When the data were adjusted for weight, neither agent was correlated with significant changes from baseline.
- *Nathan*: Fluid retention may have contributed to weight gain.
- *Sowell*: Clozapine case of DKA related to patient who had gained weight and then lost the weight. Weight gain could be an issue in cases of DKA even if patients are not overweight at time of DKA. In many of the case reports of DKA, we do not have all of the relevant data.
- *Nathan*: Appears to be no specific olanzapine-related decreases in insulin. However, need to look at patients who develop DKA and determine how they are different from the general population. Data from the clamp study are relevant for most of the population and rule out a generalizable or "big bad" adverse effect of olanzapine, but do not answer the question of mechanism of the rare event of DKA.
- *Sowell*: Discussed ZDF rat studies that showed pair-fed animals (where food intake is matched) do not have accelerated pancreatic failure on olanzapine.
- *Henderson*: Need to understand underlying differences for patients who develop DKA since not cases of DKA had gained weight. Need this information to protect patients and avoid lawsuits. Described patient on olanzapine who developed DKA. Father of patient is a judge. Father had requested that his son be put on olanzapine. Henderson said he discussed risks of hyperglycemia and DKA with the father and the patient. The patient later developed DKA. Henderson said his upfront discussion with the patient and his father helped them identify DKA and avoid a lawsuit.
- *Nathan*: Is there an interaction between olanzapine and a diabetogenic gene? Need further research. Similar pattern to cases of Flatbush diabetes since patients can have a full remission of diabetes symptoms after the medication is stopped.
- *Goff*: Two outstanding issues: (1) is there an increased risk of diabetes on atypical antipsychotics, (2) issue of DKA risk.

Review of cross sectional study of Bergman's minimal model data – David Henderson

- Reviewed his own data from cross sectional study of patients taking clozapine, olanzapine, or risperidone. Used Bergman's minimal model analysis to interpret a frequently sampled intraveneous glucose tolerance test.
- Said patients were equated at baseline for weight (mean BMI = 25), age, amount of exercise, and were all at low risk for diabetes. The patients were not randomly

assigned to antipsychotic and had at least 6 months of exposure to the medication prior to entering the study.

- Henderson only has retrospective data on weight gain from patient self-report but said there don't appear to be differences in this group of patients. Has not yet examined differences in diet among the groups.
- In this study said he found evidence for insulin resistance in patients taking clozapine (worst) and olanzapine but none for risperidone. Measures for the patients taking risperidone actually appeared to be better than norms from the general population.

- **Data:** (Note: I can't promise accuracy of the numbers. I wrote them down during verbal presentation of data. -*AP*)

Means	**Clozapine**	**Olanzapine**	**Risperidone**
Triglyceride	193	205	73
HOMA (took mean of 3 fasting values)	2.73	2.4	0.86
Fasting insulin	11.0	10.63	4.33
Fasting glucose	97	95	88
Insulin sensitivity	3.21	4.54	11.72

- From these data, Henderson concluded that clozapine and olanzapine may be blocking the glucose transporter compared to risperidone. He is assuming that glucose effectiveness is a surrogate for insulin resistance; on the other hand argued that some discrepancy between these noted in olanzapine patients may represent direct interference by olanzapine with glucose metabolism.
- Discussed that insulin sensitivity of patients taking olanzapine was found to be significantly different from patients on risperidone. However, noted that the risperidone patients had a mean that is better than that found in the general population (7.56 for adult males.)
- Henderson found that higher blood level of olanzapine correlated with higher insulin resistance (although there was not a significant correlation with dose.) There was not a similar significant correlation with clozapine blood levels but they have not yet looked at correlations with metabolites.
- *Goff:* We do not have population norms for insulin sensitivity in patients with schizophrenia for comparison to the above data, in fact results for olanzapine may not differ from anticipated results in normals.
- *Baker:* Patients prescribed olz or clz may be different before receiving drug…possibility of illness severity effect on insulin sensitivity/glucose homeostasis. The clozapine and olanzapine patients may be different from those in the risperidone group in terms of treatment resistance.
- *Goff:* Some studies have found a correlation of weight gain and response to treatment. (*Baker*: May be due to likelihood of staying on drug and length of treatment/exposure to medication.) If real effect, then could be common pathway between weight gain and efficacy. If we limit the study to patients who have not

gained weight on the medications (as they tried to do in this min mod study), we may be looking at a very different (perhaps treatment resistant) population.

- *Goff:* Can't recommend anything to clinicians on basis of these data. Thiese arecross sectional data, not prospective, patients were not randomized to medication, small sample, patients may not be same at baseline. We need to look at convergence of data from all relevant studies.
- *Henderson:* Find these data less limited and more important to clinicians. Data from min mod study raises concern that there are direct differences among the medications. Thinks there is a direct drug effect on insulin resistance – especially with olanzapine.
- *Sowell:* No evidence in normals in the hyperglycemic clamp study for direct drug effect. However, shorter duration of drug exposure.
- *Goff:* Can't assume correlation means causality.
- *Cagliero:* Insulin resistance appears to be feature of clozapine and olanzapine. Expects to see substantial increase in Type II diabetes over time (months or years) in patients on these drugs.
- *Sowell:* Euglycemic clamp study in healthy volunteers over 3 weeks ongoing now.
- *Goff:* Clozapine study found linear increase in diabetes but cases of DKA occurred early on. Effect was not weight related – weight gain did not predict "survival". Something else must be going on.
- *Cagliero:* We may be seeing acceleration of effects (acceleration of progression to diabetes in patients at risk for disorder) due to medications.

Diabetic Ketoacidosis – Enrico Cagliero

- Described case of patient on olanzapine 10mg bid, carbamazepine, lamotrigine, lithium, etc. Olanzapine was stopped in ER after patient presented with DKA. Patient's olanzapine dose was increased from 5mg bid to 10mg bid one month prior to DKA. Patient was switched to risperidone 3mg, topirimate, etc. All levels including triglycerides dropped to the normal range over the following months.
- Studying MGH database from Jan 1995 – Jan 2001 for cases of DKA in patients also diagnosed with schizophrenia. (Noted limitation: would not capture cases if diagnosis of schizophrenia is not noted in chart.) Over 3,000 patients with schizophrenia were identified in database. Found 11.2% prevalence of diabetes in this group. Found 362 cases of patients who were hospitalized due to DKA. Of the 15 DKA cases with diagnosis of schizophrenia, screened out 1 patient where diagnosis couldn't be confirmed plus 8 patients who had pre-existing diabetes (Type I or II.) Identified 6 cases where diagnosis was confirmed and no pre-existing diabetes. At time of DKA, four of these patients were taking olanzapine (10-20mg), one was taking clozapine (200mg) and one was taking clozapine (550mg) plus risperidone (2mg).
- Four of these DKA patients were Caucasian, 1 African American, 1 Hispanic. Age range: 23 – 40 years of age. Length on medications unknown.
- From this data, the estimated incidence (risk per year) of DKA in their population of patients with schizophrenia was 10.6 per 10,000. They compared this rate to data published in literature 46 per 10,000 in patients with diabetes and 1.4 per 10,000 in the general population.
- *Baker*: From this study data, risk of DKA in patients with schizophrenia is 0.2%. Order of magnitude higher than that estimated by the FDA. Is there a selection bias of patients coming to MGH for DKA versus schizophrenia. I.e., as a tertiary

medical care facility, expect a large portion of Boston's acutely severely ill patients (DKA) to be sent to MGH, versus a smaller portion of those treated for schizophrenia, as many competing locales for these patients. Or is the denominator the factor?

- *Goff*: Does not think there is a selection bias since 3,000 patients with schizophrenia found in the database and this would be good estimate of number of patients with schizophrenia in the catchment area of MGH. But would they not expect patients with DKA from outside this catchment area to be routed to MGH?
- Five of the 6 patients were off insulin at follow up visit. Don't have other important information on these patients including whether medications were stopped or changed. Said one patient was taken off olanzapine for a couple of months and was put back on olanzapine by another doctor – patient had another episode of DKA one month after being restarted on olanzapine. *Henderson* – that patient then died. *Cagliero* – Death was not due to diabetes.
    - Cagliero is presently working to expand this DKA database to include patients from the Brigham and increase the sample size. Also waiting for IRB approval to speak to patients to gain additional information.
    - *Cagliero:* All of the six identified cases of DKA discussed above had high A1C at time of event. Indicates that screening could help identify patients at risk for DKA.

There was no consensus on how long patient would have to be re-exposed (few days to 6 months suggested, latter not feasible) in order to feel comfortable that there is no drug contribution.

General Discussion/Next Steps:

- *Goff:* Said DKA in schizophrenia is reminiscent of clozapine and agranulocytosis since it occurs in less than 1% of patients. Wonders about mechanism – same as Flatbush diabetes group?
- *Sowell:* How to interpret dechallenge cases…possibility that awareness of diabetes made contribution to improved glucose plus natural history of "Flatbush" diabetes…Henderson felt awareness of diabetes by patient unlikely to have altered patient behavior, i.e., feels that behavioral interventions are difficult in schizophrenia…Can benefit from diagnosing patients with diabetes since changes in lifestyle, diet and exercise can be impactful.
- *Cagliero:* Olanzapine probably isn't directly affecting pancreatic beta cells considering the results of the clamp study. Suggested that a nationwide registry could be useful to raise awareness and capture cases of DKA in patients with schizophrenia.
- *Henderson:* Recommends that doctors monitor all patients and get baseline measures (including fasting blood glucose, lipids, etc.) Difficult to determine when a doctor should take a patient off a medication versus intervene with diet and exercise. We need to study patients who develop DKA and determine why this occurs. If patients have risk factors for diabetes, the doctor needs to take this into account when selecting medications.
    Does he believe that these data should shift overall risk-benefit equation to often avoiding olanzapine? Answer not clear – Dr. Henderson suggesting that indeed this is the case, Dr. Goff that olanzapine in many ways remains their favored choice for schizophrenia.
- *Missy:* Reviewed Clinical Trials Database (TED) related to random blood glucose measures from Lilly clinical trials. Discussed that diabetes was not exclusionary.

- *Nathan:* Need to examine cases of DKA since these are rare events. Interested in whether there is interaction between patient predisposition and medication. Said olanzapine is a good drug but doesn't want to expose patients to unnecessary risk. Wants detailed phenotyping of these DKA patients. Could acutely rechallenge these DKA patients identified in database to help understand mechanism of action and phenotype – are these patients different from Flatbush diabetes cases?
- *Nathan*: Their group wants to study patients with DKA history and is looking for financial support to complete these studies. Is considering rechallenging these patients and using olanzapine as a probe to determine whether there is a rare defect in these individuals. (*Goff/Baker* – reluctant to rechallenge unless more clear that risk is low and outcome likely to be conclusive). Wants to look at all of the DKA plus schizophrenia cases whether or not there is a history of diabetes. Most interested in mechanistic issues. Are there any effects on the immune system (like agranulocytosis)? Is there a transporter change?
- *Goff*: Olanzapine, clozapine and quetiapine are all in the same class – interested in whether there is a similar mechanism of action on the immune system.
- *Nathan*: Would like to collect DNA from these DKA/schizophrenia patients. Could do a clamp study during acute rechallenge with olanzapine (baseline and then after 4-5 days of drug exposure may be sufficient for steady state.) Compare to control group of patients on olanzapine but with no history of DKA. Said he wants to explore specific patient characteristics using olanzapine as a probe.

Follow up required: Per request of Henderson, A. Potts to send Letter of Intent form for IIT to Henderson. (Complete: Sent via email April 9, 2002.)