Discussion from the August 17, 2000 Weight Gain and Hyperglycemia Steering Committee

Hosted by Alan Breier and Norma Ascroft

Attendees:
Dan Casey, MD
Don Goff, MD
David Allison, PhD
David Henderson, MD
John Newcomer, MD
Jogin Thakore, PhD

Internal Attendees
Norma Ascroft, PharmD
Charles Beasley, MD
Chris Bomba
Alan Breier, MD
Jamie Dananberg, MD
Peter Feldman, PhD
Mike Griffeth
Suni Keeling
John Krueger
Mark Milliken, PharmD
Vin Rampey, PhD
JR Richards
Surajah Roychowdhury, PhD
Simean Taylor, MD, PhD
Anna Thornton, PharmD
Skip Vignati, MD

Overall Summary of Day's Discussion:

Reactions to what each of the consultants have seen today?

Allison

- Weight gain is a marketing and health issue, separate from glucose. This issue will not kill the drug but is more of a marketing issue. The glucose story is dangerous and could be quite damaging to the product and needs to be addressed quickly. The competitive environment is brutal.
- For the current analysis of Lilly's hyperglycemia database, Lilly needs to take a look at the statistical analysis and make it a stronger story.
- For hyperglycemia, a large study is fine but the smaller clinical and nonclinical studies are equally important to publish quickly and get information out there; from a regulatory and legal point of view, sponsors need to prepare for worst case scenario – the Lilly has on hand with clinical or preclinical data, the better.

- Zyprexa team is tracking in the right direction with weight gain by showing that the patient or health care profession can treat/ manage the weight gain; intervention studies are a good approach.
- Overall with both issues, be honest and put out good information that is driven by science.
- How much danger will Zeldox be? Zeldox may prove not be as effective but may definitely have the ability alter the olanzapine message and creates perception(s).
- Continue to explore interesting aspects of weight gain with this drug such as the "disinhibition" CNS theory that possibly effects peoples eating habits (see discussion under weight gain below)

Goff

- Emphasize in your message that not all patients gain weight. It seems the Zyprexa team has been managing this relatively well so far. The Competition is always hard to manage. Having options is the key. Be able to recommend to treating physicians at what point will you recommend treatment or interventions; provide treatment options; admit that there may be certain amount of weight gain and patients will have to way out options with their clinicians.
- An algorithm approach to provide to clinicians? Be very cautious of this approach. This is often done with weight intervention in "normals" and is *not* successful. It is difficult to be able to exactly predict the sensitivity and specificity of candidates to follow a laid out plan or algorithm.

Thakore

- (His) Experience already shows that schizophrenia patients already gain greater amount of visceral fat –increases risk already of DM, CA, etc; so don't do algorithms ("if this, then that") but put everything into perspective with scientific sharing of data. Algorithms are complicated and competitors can take advantage of this – turn them the wrong way.

Casey

- On the right track to search and provide answers to clinicians whom are definitely looking for answers for both issues. There are other signals that Lilly needs to be paying attention to now such as *lipids* that should be addressed early versus playing the defense mode like we are now for hyperglycemia. For example, (he) has heard rumors that some clinicians are recommending patients sign an ICD before olanzapine therapy due to the health risks.
- Overall, there are health risks in this patient population. A sponsor can really impact this area and put this issue of weight control and glycemic control, along with healthier living and increased education, (e.g., smoking sessation, lipid monitoring, hypertension management, prolactin and bone density) into perspective. This builds credibility
- Lilly can deflect the issues as not only olanzapine-related. This is most likely a class issue. Comment by group: have to manage this carefully that we do not blame the disease.

Newcomer

- Impressed with the level of the science and honesty today; do see an upside to the studies (like the HGIM) study. Lilly needs to relay the message(s) appropriately.
- A line of defense is providing information that these issues are not unique to olanzapine; agrees the hyperglycemia issue from a scientific, regulatory and legal point of view is the most important.
- In general, whatever Lilly can do to provide information regarding diabetes/hyperglycemia to clinicians and patients, because we are dealing with individuals outside of the endocrine world, can really help (educate). Lilly already has the expertise in this area within the company to do this.
- Lilly needs to focus on treatments for hyperglycemia. Need to think about this in psychiatric population (proof of principle).

Other Gaps?

- Lipids: start monitoring them more rigorously
- Need to get a better handle on the acidosis without alarming people (get better quality data) across all drugs; (Charles) - this is tough due to the rarity of the event (in our own data of 7000, only 3 named incidences in our database that are still muddled with the information given); Casey recommends a "swat" team approach – have a template set up of what you are looking for as soon as an event comes and have someone go out and look at the patient chart in a timely manner – work with the clinicians.
- No animal models on DM; may need to invest in primate studies.

An Interpretation/Transcript of the Day's Dialogue

Hyperglycemia Discussion

Beasley (see presentation slides) -the questions are, does Olanzapine cause or contribute to the development of diabetes? We are aware of 2 positive de-challenge-re-challenge cases (not related to weight gain in these 2 cases) Does Olanzapine cause/contribute to diabetes through some direct mechanism? Can overall rate be distinguished from overall background weight?

Animal Data: original oral development of the compound: 14 week, 6 mo and 1 yr 1 endpoint only for collection; large doses for the rat; (See Charles slides for detail of information shared) no definitive statements and these animals did not gain weight.

Dog study 3 mo, 6 mo, 1 year; young adult beagle dogs = variability across these sets of dogs; Dan – randomness may be due to a single animal. Would be helpful to graph it out against the Control group and plot against the data points.

Dan – if you look at means – appears not much going on; example of a sub-group of people that clearly change and they are accounting for all the increases in the whole. This (events of hyperglycemia) occurs independent of weight gain.

In human case incidences, for example with haldol, some incidences have shown to occur but not as many lately; are the haldol people being sampled at the same rate of newer agents based on awareness? Based on the biases against atypicals?

Are tests being run in the correct species? Rat -yes -but different strains of rats have different susceptibilities (Fishers 334's are not the best). Recommendation to try different species.

Are atypicals causing some kind of stress on these patients receiving therapy (similar to the PG analysis) or are we more aware of DM as a whole?
What is the rate of undiagnosed DM – 10% of the pts at 60 years of age have met the criteria of DM (half of the patients with DM, 50% have gone undiagnosed but will be picked up with glucose monitoring with atypicals)

How much of this is now a vicious cycle by just awareness – which will automatically increase the overall % of pts found with DM taking atypicals?

Really need to do age/weight /race match patients with incidence.

Summary of Human Data:
Slightly over 61,000 glucose assays that went into the data analysis – with 5,500 patients with data. Data from Lilly clinical trials are all random glucoses; ADA guidelines (see slide of methodology); all of the pts not directly compared – what is shown is from the survival analysis that were direct comparisons.

Taylor - Problems with these cutoffs (as many people trending up as they are trending down) any downward trend has to be random – so what you are looking for is any excess of an upward trend. The data that Charles has analyzed does show this excess (from baseline to lowest value of patients on drug)

Taylor - based on the data presented, it seems that olanzapine may be a little worse than haldol but not significant as far as affect on DM; as far as placebo – the chances for the 2.4 + year follow up will be difficult. Need to be aware of the extension time of the 2 treatment groups (the CI reflects that the 2 arms were comparable in this sense as well as the numbers that made it up to 2 years)

Allison -skeptical of the data and the statistical analysis. These data are not compelling at this time. Like to see Cox regression, analysis of the means, etc before making a more definitive assumption. Other questions : fasting vs not fasting and how long they were followed are big issues. We only have random data (these were not fasting).

Alan – how do we get at data that would be compelling?

Allison – certainly we can use this data along with smaller well-controlled studies and preclinical data – with rigorous statistical analysis = more compelling.

Taylor – never going to be able to totally rule out the % of pts who will develop.

Charles – There is variability but provoking enough.

Taylor – there is room for other, smaller studies that are more controlled.

Thakore – data are unreliable just by the nature of the patients that one is dealing with in these large trials; encourage a small study with a very controlled environment (overnight stay with controlled diets and collections).

Shall we go forward with providing this information that we have actively in the field?

Casey – be careful with this because you may be saying "there is no difference or problem". Which is the opposite direction of what clinicians feel is happening with their patients and may be more damaging = "denial"

Dananberg – team has really tried hard to put forth best initial way with controlled data to begin the exclusion of a *major* effect and then we can go to the next step of clarifications with the small controlled trials but be careful of putting darts at the data.

Consensus – ok as long as you are honest; explain your deficiencies or caveats up front with the data and that you are rigorously still pursuing the study of the issue.

Allison – the message is that we think it's ok to present this data – not that it is bad data but that the "spin" is acutely sensitive; encouraging that Lilly should be cautious.

Alan – summary is that the data has limitations but adds value to shedding the light on the issue and continue to explore

Casey – do not publish as it is today; does not think it will helpful

Alan – challenge – understand that we will need to redo analysis; we do intend to publish.

Casey – if your conclusion is that there are no difference, need to be careful.

Alan – if we are cautious in our interpretation, state up front what the deficiencies are, is it then ok to publish?

Casey – still be cautious – it may cause question to all the other material presented.

Consensus- take a close look at the statistical analysis

Alan – if our competitors that are already presenting data that is weaker than this and bringing a spotlight to this issue against olanzapine that it causes DM; we agree that we need to improve, but we cannot just sit here.

Allison – agree. Lilly should publish it b/c it is better than what is currently out there; It will not be to Lilly's advantage to counter with equally sloppy data against our competitors so analyze it well first; maybe distance yourselves from the data – hiring a CRA? and expert panel to publish it.

In the weight gain paper – co-investigators were involved.

Casey – not saying that we should bury it but work with it some more so that you are not vulnerable b/c of analysis.

Newcomer – the most that can come out is to put a size on the affect -- what is the largest affect that could be hiding in the placebo group and haldol group; look at that noise in those 2 control groups – "affect size study". Currently we cannot distinguish how many is schizophrenia vs a drug affect so this data will help provoke more thought and discussion. For marketing benefit: Lilly needs to put a cap on it , also educate the psychiatric world on endocrine effects so they know what to expect and will not be as alarmed with the data-- shows Lilly is not burying the problem.

Prevalence of DM in middle age men s 3%; our data show 2% In this population.
It is just too hard to distinguish from the "noise" in the data if we have no control on their diets.

Dananberg (presentation)- This discussion: focuses on what we saw out of Lilly's spontaneous database – 419 cases to date of "hyperglycemia events"; about 50% is "mild", other 50% is high: 600 mg/dl or hospitalized – not sure what is the actual event (DKA, hyperosmolar coma).
Goal of upcoming studies (ie, HGIM) help us to start to answer the question: do atypical (olanzapine vs risperidone vs placebo) antipsychotics cause a direct effect on increase of glucose (secretion)? – broadly then there are issues related to the use of atypicals ; or if it random enough that it is related to patient population / genetic predisposition.

More studies will start to test insulin *secretion* in patients and in normals. If negative results, may want to look at pts with abnormal glucose tolerance.

Taylor - need to be aware that you may not see results expecting due to the calorie restriction (in real world , they are eating a lot more calories).

How does one conduct a study to look at glucose metabolism in patients with schizo?

If Study HGIM is negative – need go to high risk pt (with impaired glucose in schizo patients); does it make sense to start with normals and then go patients *then* to high risk patients(altered glucose metabolism as well as schizo)? Yes (Newcomer)

For control use risperidone, not haldol (out of date) however, haldol may be closest to a placebo arm. Provides a more definitive statement otherwise you may contribute to class effect.

Weight Gain Discussion

Preclinical

Heiman (see presentation slides) - haloperidol sc 0.1 and 0.3 (higher dose tends to sedate) and food consumption - indirect calorimetry with Sprague Dolleys (200 grams / 2 month – ad lib food; take into acct that this age is high in growth phase) food is 20% protein with moderate carb and fat; seems to be the most sensitive model (with female being more sensitive model with weight over the males); may have to due to leptin sensitivity

Leander – not all models will react similarly across all the antipsychotics.

Continued haldol study – body weight gain highest on the higher doses; RQ after 3 days of administration increases the RQ. This means a preference to metabolize carb instead of fat; haldol will spare fat and trend toward use of carbs; we also measured energy expenditure – is maintained across the controls as well as the 2 doses of haldol – a bit of a surprise since at the higher doses tend to sedate the animals – ambulatory movt is less so will need to look at thyroid and check temperature (initially these drugs decrease temp then will increase in temp – increase in calorie use by using large amounts of heat), fidgeting

Apparent energy balance – pos energy balance due to above; similar to risperidone sc; with the olanzapine sc – did not see anything in the beginning; suspected due to half life (shorter in the rat than in the other agents); switched to the pamoate at 160 mg/kg over 14 and started to see increase in food intake, decrease in fat utilization and increase in carb utilization; opm does not cause much sedation.

With changes in diet to test fat utilization: moderate carb/ low fat diet. We saw a significant decrease in the utilization of fat. Testing other diets.

Sibutramine study– Day 1 intervention being studied; only given 1 injection so blood level starts to drop about day 1. Is there tolerance to sibutramine? Most likely a prevention of starvation in neurotransmission – body tries to bring back to body set point – can look like tolerance; saw a huge rebound once sibutramine is dropped.

Fat and Lean mass measurements– after 3 days of treatment and after 14 days of treatment: controls are gaining lean mass and fat mass; with opm, see slight decrease in lean and significant increase in fat mass; sibutramine prevents this either alone or in combination with opm.

Leander (see presentation slides) – effects of olanzapine in drinking water at various doses with rodents and maintained on ad lib diet; showed 0.1 as the optimal dose to show weight gain. Weight of female showed increase in 160 mg/kg sc opm = model.

Amantadine – dosed after weight gain (note that daily of mice causes decrease in weight also); at 100mg/kg daily; when amantadine was stopped, increase in weight occurred immediately. Full mechanism is still unknown (partial dopamine effects).

Maintained rats at 160 mg/kg while monitoring food intake – shows nice suppression with amantadine in early study; effect of mCPP on food intake the effects was enhanced compared to the vehicle.

Where do these effects come from? Could be binding affinities of olanzapine (and other antipsychotics) for neuronal receptors ; H1 does not seem to be the most potent effect ; changing the dose of olanzapine does not seem to effect the weight in patients that are already gaining weight in the clinical setting ; therefore the D2 effect may be responsible for some of these effects.

H1 affinity shift becomes more potent in the rat to human with olanzapine; same with clozapine; not as much of the case with risperidone (don't know about active metabolites and the effect it can have on weight gain in several of the compounds)

Allison – try cafeteria feeding
Check the strains (try Osborne Mendels sp) – can obtain through NIH – susceptible to weight gain particularly on high fat diets.
Consider switching to mice – leptin sensitivity

Discussion: Publish this animal data - shows that Lilly cares and that we are doing research on it – will trigger interest of research in other antipsychotics as well as TCA's, etc; will trigger investigators (clinical) to become interested. Would be good science overall. What may be more interesting in the gene therapy area is the array in addition to the SNP mapping.

Clinical
Breier (see presentation slides)- Presented olanzapine associated weight change in patients (2-year observation). There is an exaggerated response of weight gain in children with olanzapine as well as risperidone; plan on looking at other psychiatric populations (bipolar, elderly, etc).

Allison – overall weight gain in patients could be the additional effect of lifestyle and feeling better (eg, olanzapine causes everyone to gain a minimum weight but the 25 pounds is due to other additional factors).

Comments – in clinical experience, not seeing big difference between no gainers and gainers in lifestyles or diet.

Casey – anyone who gains 5 kg +, clinician will start to get concerned with health risks, even more so at 10 kgs.

Allison – Educate out in the field - need to take in consideration that normal population will gain 1-1.5 pounds per year after the age of 30 years; given how schizophrenic patients eat, majority will gain that plus more, easily. In normals, lean people will gain more weight over time than those that are already large.

Breier - Weight is not associated with dose (5-20 mg range) curious to see if this would be not true in 40 mg. A good response also correlates with weight gain; an additional bias may be built in that people are being followed more rigorously as a whole who are good responders.

Allison – could olanzapine be a "disinhibitor" to relax people to eat? The normal person tends to have a certain amount of discipline and self control with overeating. Studies show that in the normal population, if they are disinhibited by a milkshake or alcohol, for example, these people will eat more and gain more over time.

Review of predictors by Breier – BMI, appetite, and clinical response

Breier - Continuing to look at interventions:

- Behavior – diet (high protein, low carb); will test in animal model first.
- Weight Watchers program (lifestyle modifications)
- Pharmacologic – Axid, sibutramine, mazindole, amantadine, topiromate, orlistat (still questioning orlistat); Wellbutrin -open label funding is ongoing; animal model is not effective. Mazindole– cheap, available (excepted widely).

Henderson – ongoing study of olanzapine plus sibutramine; no major side effects seen to date, majority of patients that have lost 5-30 pounds.

Allison- also has study with amantadine (?). Also doing orlistat study (only one approved that is not centrally acting)

END

(SEE PAGE ONE FOR SUMMARY COMMENTS)

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