Robert W Baker
10/09/2000 03:28 PM

To: Thomas M Brodie/AM/LLY@Lilly
cc: Christopher C Bomba/AM/LLY@LILLY, Jack E Jordan/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly
Subject: Re: meeting with endocrinologic consultants

Thanks Tom. I appreciate your generosity with your board's time Although obviously concerning, it was helpful to see their reaction. My take was that they remained skeptical because of the number of reported adverse events and by the substantial weight increase with olanzapine. Moreover, like this group we believer that definitive research has not yet been done and may not be readily doable. In light of these facts, the finding that olanzapine did not seem worse than haloperidol in terms of inducing hyperglycemia likely appeared counterintuitive, provoking questions about whether methodlology of analysis is hiding real treatment difference. I don't think that that is the case, but did suggest to the product team members working on analysis that they are fair criticisms that should be addressed. Meanwhile, Chris and I agee that we in the US will benefit by continuing to work with endocrine moving forward.

Best,

R
Thomas M Brodie

Thomas M Brodie
10/09/2000 03:10 PM

To: Robert W Baker/AM/LLY@Lilly
cc: Eugene R Thiem/AM/LLY@LILLY

Subject: Re: meeting with endocrinologic consultants

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Regards,
Tom

ZY 2224 232

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cc: Eugene R Thiem/AM/LLY@LILLY
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10/09/2000 03:42 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly
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cc: Eugene R Thiem/AM/LLY@LILLY

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ZY 2224 233

To:	CN=Ernie Anand/OU=EMA/O=LLY@Lilly
CC:	CN=Charles M Beasley Jr/OU=AM/O=LLY@Lilly; CN=Patrizia Cavazzoni/OU=AM/O=LLY@Lilly; CN=Patrick Jonsson/OU=EMA/O=LLY@Lilly; CN=Jared G Kerr/OU=AM/O=LLY@Lilly; CN=Mark D Millikan/OU=AM/O=LLY@Lilly; CN=Andrea K Smith/OU=AM/O=LLY@Lilly; CN=Margaret O Sowell NONLILLY/OU=AM/O=LLY@Lilly; CN=Padraig Wright/OU=EMA/O=LLY@Lilly
Date:	03/26/2001 10:39:32 AM
From:	CN=Anna Thornton/OU=AM/O=LLY
Subject:	Re: Olanzapine and Cardiovascular risk

Hi Emie,

Thank you for the information. Mark Millikan is working with Andrea and Charles on a "Standby Statement".

Anna
(x77076)

Ernie Anand

03/25/2001 01:57 PM

To:	Charles M Beasley Jr/AM/LLY@Lilly
cc:	Patrizia Cavazzoni/AM/LLY@Lilly, Patrick Jonsson/EMA/LLY@Lilly, Andrea K Smith/AM/LLY@Lilly, Margaret O Sowell NONLILLY/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly, Padraig Wright/EMA/LLY@Lilly
Subject:	Re: Olanzapine & cardiovascular risk

Dear Colleagues

You may find the just published editorial by Liu & Manson from Boston of interest , especially with respect to this dialogue :

What is the optimal weight for cardiovascular health ?
Liu & Manson (2001) ; Brit J Med , vol 322 , pp 631-632

ps - theres a preceeding editorial to Liu & Hanson as well :

Obesity genes
Sorensen & Echwald (2001) ; Brit J Med , vol 322 , pp 630-631

Regards,Ernie

From: Charles M Beasley Jr on 15/03/2001 14:36

To: Andrea K Smith/AM/LLY@Lilly
cc: Ernie Anand/EMA/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, Margaret O Sowell NONLILLY/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly

Subject: Re: Olanzapine & cardiovascular risk

Unfortunately, I believe it will be a while before we have a clear, ***definitive*** position developed regarding hyperglycemia, hyperlipidemia, obesity, the metabolic syndrome long-term cardiovascular risk and olanzapine. We have 2 physicians primarily dedicated to these issues and a host of others working on them as well. One thing that we can say definitively is that olanzapine causes weight gain and for approximately 50% of patients in trials who remained on the drug for >6 months, the amount of gain was >10 pounds. Some patients, in clinical trials gained as much as 80+ pounds. Lacking empirical data to the contrary, it would be ludicrous to state that such a patient is not at long-term, increased cardiac risk relative to prior to gaining that weight, especially, if in temporal association with that weight gain the patient developed an increase in fasting glucose and lipid levels. Therefore, much research is ongoing.

Charles

Andrea K Smith
03/12/01 03:26 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly
cc:
Subject: Olanzapine & cardiovascular risk

Here's the note from Ernie. As I told Anna, I've tried to draft the standby to address this and other CV issues.

Andrea

—— Forwarded by Andrea K Smith/AM/LLY on 03/12/2001 03:25 PM ——

Ernie Anand
03/12/2001 10:36 AM

To: Andrea K Smith/AM/LLY@Lilly
cc: Patrick Jonsson/EMA/LLY@Lilly, Suni Keeling/AM/LLY@Lilly
Subject: Olanzapine & cardiovascular risk

Dear Andrea

Do we have a standby statement to clarify our position here eg :

That Zyprexa can cause cardiovascular complications due to weight gain/diabetes , which are clinically recognised risk factors

We have an EU planners meeting coming up in 2 weeks time & it would be valuable to have our position on this clarifled.

Thanks,Ernie

---------- Forwarded by Ernie Anand/EMA/LLY on 12/03/2001 15:32 ----------

Ernie Anand
11/03/2001 12:44

To: Patrick Jonsson/EMA/LLY@Lilly, John C Saunders/EMA/LLY@Lilly, Valerie Simmons/EMA/LLY@Lilly, Padraig Wright/EMA/LLY@Lilly
cc:

Subject: Olanzapine & cardiovascular risk

Dear All

Thought you'd like to be aware of this article.

In my opinion its yet another example of how we are becoming quickly associated into this whole arena of cardiovascular risk due to cholestrol/ weight gain / diabetes as key causative factors ;comments that have also been made in the last 2 week from very independant sources as well eg Prof Nicolas Moore at the Feb 28 Diabetes Adv Board meeting in London & Prof John Camm at the March 7 QTc meeting organsied by LillyUK , also in London.

Its very clear to me that our whole cardiovascular message needs to be further refined to help differentiate positioning vs QTc , hypotension/bradycardia & obeseity/weight as CVS risk factors.

Welcome your thoughts/comments.

Regards,Ernie

Assessing atypical antipsychotic CV risk: bodyweight alone not enough.

PUBLICATION DATE: 5 MARCH 2001 (20010305)

SUMMARY TEXT:
The assessment of metabolic variables predictive of cardiovascular (CV) disease, rather than just the measurement of bodyweight alone, may be necessary to fully assess the CV risk associated with atypical antipsychotics, according to researchers from Canada.
The researchers conducted an interim analysis of a cross-sectional multicentre study in which morphological indices of adipose tissue distribution and obesity, and a fasting metabolic risk profile, were assessed in 44 men, aged 28.9 +- 8.5 years. These men had received either olanzapine 12.8 +- 4.4 mg/day for 17.9 +- 8.1 months (22 patients) as their first atypical antipsychotic treatment agent, or risperidone 2.8 +- 1.8 mg/day for 17.4 +- 8.8 months.
The men treated with olanzapine had a poorer metabolic CV risk factor profile than those treated with risperidone as predicted by 4 of the metabolic variables investigated [see table]; total cholesterol, fasting glucose and insulin levels were not significantly different between the 2 treatment groups. Moreover, despite similar bodyweights and body mass index

values, men treated with olanzapine were more likely than those treated with risperidone to be characterised by the atherogenic metabolic triad* (32 vs 5% of patients).

The researchers warn that the results of their study need to be interpreted cautiously, as the data were not based on changes from baseline. However, they say that their findings 'raise concerns about potentially deleterious effects of olanzapine on cardiovascular health' even though a cause and effect relationship could not be established. They add that further studies to investigate such a relationship need to be conducted with urgency.

* includes hyperinsulinaemia, elevated apolipoprotein B level and small dense low-density lipoprotein particles

Table: Metabolic variables predictive of cardiovascular risk in patients treated with olanzapine or risperidone

Metabolic variable	Olanzapine-treated patients	Risperidone-treated patients
Plasma triglyceride levels	2.1 +- 1.3 mmol/L	1.3 +- 0.7 mmol/L
Very low-density lipoprotein cholesterol levels	0.9 +- 0.6 mmol/L	0.5 +- 0.4 mmol/L
Total cholesterol/HDL* cholesterol ratio	5.3 +- 1.7**	4.3 +- 1.4
HDL cholesterol level	0.95 +- 0.2 mmol/L**	1.06 +- 0.2 mmol/L

* high-density lipoprotein

** The difference between the treatment groups was not significant, but a trend was noted.

REFERENCES:

Bouchard RH; Demers M-F; Simoneau I; Almeras N; Villeneuve J; et al. Atypical antipsychotics and cardiovascular risk in schizophrenic patients. Journal of Clinical Psychopharmacology 21 : 110-111, FEB 2001 (English, Study (Canada))

Robert W Baker
10/10/2000 09:00 AM

To: Charles M Beasley Jr/AM/LLY@Lilly
cc: Paul Berg/AM/LLY@Lilly, Alan Breier/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly, W Scott Clark/AM/LLY@Lilly, John H Holcombe/AM/LLY@Lilly, Jack E Jordan/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, Alvin H Rampey Jr/AM/LLY@Lilly, Roy N Tamura/AM/LLY@Lilly, Paula T Trzepacz/AM/LLY@Lilly, (bcc: Robert W Baker/AM/LLY)
Subject: Re: meeting with endocrinologic consultants

Dear Charles:

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Regarding the marketing side, I agree that we heard a sentiment (though not sure it is unanimous) that we should not aggressively defend ourselves; in fact I thought we were getting suggestions to more vocally tell clinicians that olanzapine may well have a diabetes problem, based again largely on weight issues. To me, this reinforces the need to take an appropriately cautious tone with our findings. On the other hand, data are data and I do not feel impelled to state the case more negatively than it appears to us; our competitors are handling that quite nicely. I do think that what to say pending more "proof" is a key area for medical and marketing discussion.

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10/10/2000 08:33 AM

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ZY 2224 239

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10/09/2000 03:42 PM

To: Charles M Beasley Jr/AM/LLY@Lilly, Alan Breler/AM/LLY@Lilly
cc: Christopher C Bomba/AM/LLY@LILLY, Patrizia Cavazzoni/AM/LLY@Lilly, Suni Keeling/AM/LLY@LILLY

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ZY 2224 240

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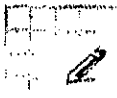

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Charles

Robert W Baker

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10/10/2000 10:09 AM

To: Robert W Baker/AM/LLY@Lilly, Charles M Beasley Jr/AM/LLY@Lilly
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Subject: Re: meeting with endocrinologic consultants

Charles and Robert,
Let me add my 2 cents worth. I know our endocrine advisory group well, and I might be able to help interpret their reactions to the data presented.

First, I have attached two simple tables that the ADA uses for diagnostic cutoff points for glucose values. I show this so that we are all on the same page. The tables represent the 'world' of diagnoses in the eyes of our consultants, so we had a mismatch between the analysis (>160 for IGT) and the diagnostic criteria, while >200 is diagnostic of diabetes IF symptoms are also present. At any rate, the ADA says that a blood glucose 140 or greater should be further evaluated. As you know, the consultants wanted to see ALL glucose values at baseline and over time. Showing a large number of values of >140 at baseline will underscore the likelihood that diabetes may already be present in many patients with schizophrenia, which is another point we want to further explore and emphasize. From the data shown, the group did not agree with the premise that DM has a higher than normal prevalence in schizophrenia.

Secondly, only one endo referred to Rezulin, while others said that the present analysis had nothing in common with that drug. The point was that Lilly has to be forthcoming with the data to gain and maintain our just credibility. Showing our advisory group a slightly modified analysis with ALL glucose values would be a vital step forward here.

Thirdly, our analyses with the reference ranges from Covance raised some concern, such as a glucose of > 200 being "within the reference range for random glucose of normal individuals". I don't recall the specific value, but the 99th centile cutoff point you mentioned in the reference range was a glucose value that is 'diabetic' by any standard. I am looking into the glucose reference ranges at Covance as a result of the meeting, as clearly people with diabetes are included in the normal reference ranges.

Lastly, as others have pointed out, my sense was that the group was more concerned about weight gain than the hyperglycemia. In response to a consultant's question, the mention of weight gain in healthy volunteers at the end of the presentation, without showing the data, came as quite a surprise. It nearly appeared that this tidbit had to be drawn out of Lilly, which seemed to heighten the other questions.

We are at a critical point here. Our advisory group is Who's Who in diabetes. If we can bring a few of them to Lilly as consultants to the Zyprexa team, show them that we listened to their suggestions by presenting another analysis that THEY suggested, we should be able to solidify their support and understanding.

I am willing to work with your group in whatever capacity I can.

John

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