

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 Ernie,

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 :

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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:
Thornton/AM/LLY@Lilly
cc:
Subject:

Charles M Beasley Jr/AM/LLY@Lilly, Anna

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

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

Ernie Anand

03/12/2001 10:36 AM

To:
cc:
Keeling/AM/LLY@Lilly
Subject:

Andrea K Smith/AM/LLY@Lilly
Patrick Jonsson/EMA/LLY@Lilly, Suni

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 clarified.

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))

