

To: Douglas Berv <douglas.berv@yale.edu>
CC: CN=Stacey E Soules/OU=AM/O=LLY@Lilly
BCC: CN=Michael E Bandick/OU=AM/O=LLY@Lilly
Date: 07/22/2003 12:42:49 PM
From: CN=Alan Breier/OU=AM/O=LLY
Subject: Re: Zyprexa

Dear Dr. Berv,

Thank you for your letter and candid feedback. You are right that this has been a challenging area both on the science side and the communication front. Our credibility on this issue is critically important and therefore I am dismayed that you did not find my letter credible. It seems we need to work harder to establish credibility with you.

I agree with your comments about weight gain associated olanzapine and the lipid data are beginning to support a relationship between weight gain (as would be expected). I disagree with you about the FBG data. Study after study has failed to support a unique or direct causal linkage with olanzapine. Moreover, a difference in FBG with olanzapine has not been found when compared to other agents including drugs with far less weight gain such as ziprazidone. Four decades of research on the link between obesity and diabetes indicates that obesity is clearly a risk factor for diabetes but it alone requires a very long time (usually years) to precipitate diabetes and most individual who become obese do not develop diabetes. The DM associated with olanzapine and other antipsychotics is occurring relatively early in treatment (weeks or months). This leads to the possibility the agents themselves are impacting on insulin function directly (and the clamp studies I describe in the letter suggest that this is not the case) or the patients themselves have other, baseline risk factors and are being pushed over the edge by increase food intake or DM is occurring spontaneously in these at risk patients. This point of patients with risk factors being the ones developing DM irrespective of drug assignment is being borne out in a number of studies.

We advocate doing exactly what you are doing - closely monitor your patients and intervene appropriately. The data indicate however that this approach is warranted with all of the antipsychotics because of the reasons I state above and in the letter and not just olanzapine.

Thank you again for the feedback. We are eager to get this important topic right - accurate, transparent (no spin) and scientifically sound. Any other thoughts/recommendations you have for us please let us know.

Alan Breier, M.D.

Douglas Berv
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Zyprexa MDL 1596: Confidential-Subject to Protective Order

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edu> cc: soules_stacey-e@lilly.com
07/22/2003 10:02 AM Subject: Zyprexa

Dear Dr. Breier:

Your sales rep Stacey Soules today presented me copy of your letter regarding Zyprexa and Diabetes. While Stacey's discussion with me was reasonable, thoughtful, and appropriate, your letter was a disappointment. It could have been written by a Washington spin doctor. I think that in the long run your letter will only make Lilly's problems with Zyprexa worse.

Zyprexa is a great medication. It works well and fast. I find it more reliable than its competitors. I, and my colleagues who routinely follow our patients' FBG and lipids, however, find that Zyprexa causes increased FBG and/or lipids in at least 20% of our patients. Additionally, it causes much more weight gain than the other second generation antipsychotics except Clozaril.

Your statements that "available data do not establish a causal link between diabetes and Zyprexa," "Zyprexa did not decrease pancreatic insulin release, or....have a direct effect on insulin sensitivity," might be technically correct, but they are misleading and remind me of President Bush's 16 words. I and my colleagues have seen time and time again increases in FBG and lipids in patients on Zyprexa, and have seen these increases reverse when Zyprexa is discontinued. There have been documented deaths from ketoacidosis in patients placed on Zyprexa.

Lilly is under great pressure right now, but a cover-up will only make things worse. I suggest Lilly state the obvious:

Zyprexa is a highly effective medication. Increases in FBG, lipids, and weight may occur in patients placed on Zyprexa. Lilly recommends baseline and follow-up FBG, lipids, and weight in all patients placed on Zyprexa. If changes in these parameters occur the clinician should evaluate the risks and benefits of all options and

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take remedial action.

Sincerely,

Douglas Bcrv, MD

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