To: CN=Craig A Hartman/OU=AM/O=LLY@Lilly
CC: CN=Albertus vandenBergh/OU=AM/O=LLY@Lilly
Date: 08/01/2002 04:10:41 PM
From: CN=Patrizia Cavazzoni/OU=AM/O=LLY
Subject: Re: PLEASE REVIEW : Antipsychotics and Diabetes
Attachments: A Pharmacoepidemiological Study of DM.pdf

CraigJust one minor suggestion IN BOLD. Also, Jared has sent you the Koller-risperidone abstract, which reinforces the message that, while more cases have been reported with olanzapine and clozapine, conclusion as to causality can ultimately only be made on the basis of prospective studies or systematic studies of relative risk. We have done studies in both areas, which have shown to cosistent meaningful difference between olanzapine and various comparators.

I am quoting the conclusions from the Koller- RISPERIDONE abstract

These data, along with similar reports of hyperglycemia with olanzapine, clozapine and quetiapine, suggest that antipsychotic use may unmask or precipitate diabetes in psychotic patients. Causality cannot be ascertained because of the nature of these data and absence of control groups. While the number of such cases in the literature and in Medwatch attributed to clozapine or olanzapine are greater than those with risperidone, no conclusions can be made until direct prospective studies of causality and relative risk are done. Awareness of these associations may enhance the ability of clinicians to use these drugs effectively.

let me know if there is anything else I can do

Patrizia

Craig A Hartman

08/01/2002 02:09 PM

To: Patrizia Cavazzoni/AM/LLY@Lilly, Albertus vandenBergh/AM/LLY@Lilly
cc:
Subject: PLEASE REVIEW : Antipsychotics and Diabetes

Bert and Patrizia:

I plan to send this and fax the CLAMP study to Mario in response to his Note so that he has all of the information and understands our position. I think that we have not definitively said publically that there could be a class label change (at least not as clearly laid out as I have it below). We need to be thoughtful about our public stance on this...we will live with what we say here for some time as you probably know. Mario is not a major analyst, but we have improved our dialog with him recently. He had rated us a sell for several years and he has upgraded us twice now to hold status. Your thoughts are greatly appreciated.

Craig

Mario:

The conclusion that the FDA's studies into the relationship between antipsychotics and diabetes could potentially lead to label changes for the class of antipsychotic medications is ~~reasonable~~ **understandable**. However, I would like to provide you with some important points.

The incidence of diabetes is growing at epidemic proportions in the U.S. and diabetes is significantly more prevalent in people with serious mental illness (2-4 times greater than the general population). Dr. Koller's study rightly draws attention to the comorbidity of diabetes in patients with serious mental illness.

The relationship among diabetes, psychiatric illness and antipsychotic medications is unclear. The risk factors for people with serious mental illness for diabetes are as follows: family history, ethnic background, diet, weight gain, level of physical activity, etc. These risk factors turn out to be exactly the same risk factors identified by the ADA. We also know that prior to the introduction of antipsychotic medications, high incidences of diabetes and hyperglycemia were reported for people with serious mental illness.

We agree with Dr. Koller's statement that further research is needed. She has already published the results of a study of comorbid diabetes clozapine and a study of risperidone, prior to the publication you referenced on Zyprexa. We are leveraging our internal expertise in diabetology by actively engaging our internal endocrinologists and we are also working with numerous external researchers to aprise them of the facts as we know them, including the studies we have conducted and the findings. Our objective is to find out if there are any other possible studies we should be conducting in this area, above and beyond what we already have planned (a "leave no stone unturned" approach). In a perfect world, we would simply conduct "the definitive trial" to find out the answer. Unfortunately, that does not exist. We will continue to conduct well controlled clinical studies and embrace the outcomes.

In any case, we believe it is vitally important for prescribers to understand the very high prevalence of diabetes in this population and that good clinical practice should prevail. Treating the risk of diabetes or diabetes is not difficult. The difficult part for psychiatrists is treating schizophrenia. Our position is that physicians should be aware of this risk (which is a documented risk that existed prior to the use of antipsychotic agents) follow ADA guidelines and choose the best drug for the treatment of each patient's schizophrenia.

One other thought about the Koller study. Dr. Koller points out herself that spontaneous adverse event surveillance can neither establish causality nor determine true incidence and prevalence. In addition the article notes that distortions in reporting may occur over time as

prescribers become aware of a particular adverse event from various sources. Experts in drug safety caution against over interpreting reporting rates within the FDA database that Dr. Koller used because small diferences in the population using the drug, publicitiy surrounding its use and the diligence a manufacturer exercises in gathering, recording and reporting adverse reactions could result in one product wrongly appearing to be associated with a higher risk than another's.

The following study shows the risk of diabetes is comparable between Zyprexa and haldol and Zyprexa and risperdal. I am faxing you a copy of the CLAMP study as well.

A Pharmacoepidemiological Study of DM.pdf

Regards,
Craig Hartman
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