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To: Lori M Vance/AM/LLY@Lilly  
cc: Kenneth C Kwong/AM/LLY@Lilly, Anna Thornton/AM/LLY@Lilly  
Subject: Re: HCAM manuscript

Interest in a temporal association between olanzapine administration and alterations in glucose homeostasis, as well as such a relationship between antipsychotic agent in general and alterations in glucose homeostasis was precipitated by ongoing review of spontaneous adverse event reports for marketed olanzapine as well as academic literature discussing these subjects.

With regard to marketed olanzapine spontaneous adverse event reports, the following summarize our experience:

- 1) In first 2 years of marketing, an estimated 1.581 million persons were treated with marketed olanzapine.
- 2) During this interval, Lilly received 197 spontaneous adverse event reports for marketed olanzapine which may have involved a hyperglycemic event, based on COSTART terms used to code events.
- 3) The degree of hyperglycemia varied considerably as did the clinical presentations described in these reports.
- 4) Where adequate information was available to characterize the presentation (n = 143), 23 presented with glucose <300 mg/dl, 47 presented with glucose  $\geq$ 300 mg/dl and <600 mg/dl, and 73 (>50% of total characterized) presented with glucose  $\geq$  600 mg/dl or DKA or hyperosmolar coma. Among the latter group, many patients experienced glucose >1000 mg/dl, and the highest reported glucose was 1825 mg/dl (survived).
- 5) Among the patients with presenting glucose <600 mg/dl, 84% had a history of diabetes or hyperglycemia. A majority of the patients, whether with a diabetic history or not, had risk factors for diabetes.
- 6) Among the 3rd group of patients, where data were available, 70% **did not** have a history of diabetes. Where known, a majority of these patients did have risk factors for diabetes.
- 7) Among the 3rd group of patients, where data were available, and **including patients with both a history and no history of diabetes**, 25% presented within 26 days of initiation of olanzapine.
- 8) Available demographic data did not reveal a pattern suggestive of at risk patients.

With regard to medical literature:

- 1) Multiple case series/reports have been published (total cases may now exceed those reported for clozapine).
- 2) One reported case was of resolution on dechallenge and recurrence on rechallenge.

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