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Testimony before a Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Regarding the Neuropsychiatric Effects of CHANTIX (varenicline), ZYBAN (bupropion), and Nicotine Replacement Therapy

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September 14, 2016

My name is Sammy Almashat, and I am a physician and researcher with Public Citizen's Health Research Group. I have no financial conflicts of interest. I will primarily be addressing the fundamental flaws in the EAGLES clinical trial that rendered it incapable of definitively detecting an increased risk of neuropsychiatric adverse events in varenicline-treated subjects.

The boxed warning was placed on varenicline in 2009 due to a deluge of post-marketing adverse event reports of suicidality and neuropsychiatric events.[1] Since its approval in 2006, at least 4,701 neuropsychiatric adverse events in patients on varenicline have been reported to the FDA.[2,3]

The EAGLES trial was powered to detect absolute differences in event rates between varenicline and placebo of 2.63% to 5.25% for non-psychiatric and psychiatric subjects, respectively.[4] These represent exceedingly high estimates of the incidence of neuropsychiatric events. There were 17.1 million patients who received varenicline prescriptions from 2006 through 2015.[5] Even assuming, as is standard, that the 4,701 neuropsychiatric adverse events with varenicline reported to the FDA through 2015 represented only 10% of the true number of events, that would translate to an incidence of just 0.03%. This is the same order of magnitude of excess risk on which the FDA based its requirement for warnings of the risk of suicidality to be added to the labels of antiepileptic drugs (0.19% excess risk relative to placebo).[6]

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[1] Food and Drug Administration. Briefing Document for the September 14, 2016, Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee: Serious Neuropsychiatric Adverse Events with Drugs for Smoking Cessation, **[hereafter referred to as "FDA Briefing Document"]** at PDF p.12. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM520103.pdf. Accessed September 13, 2016.

[2] **2,925 events** through Sept. 2010: Moore TJ, Furberg CD, Glenmullen J, Maltsberger JT, Singh S. Suicidal behavior and depression in smoking cessation treatments. *PLoS One*. 2011;6(11):e27016.

[3] **1,776 events** from 2011 through 2015: FDA Briefing Document, at PDF p. 172-173. (62% of the 2,864 adverse events [equal to 1,776 events] reported for varenicline from 2011 through 2015 had a psychiatric or neurologic component.)

[4] FDA Briefing Document, at PDF p. 35.

[5] FDA Briefing Document, at PDF p. 194 (Figure 3).

[6] Food and Drug Administration. Statistical Review and Evaluation. Antiepileptic Drugs and Suicidality, at PDF p. 6. May 2008.

In a blinded trial, the risk of bias is reduced, but there still exists the potential for non-differential misclassification. As you know, non-differential misclassification refers to the erroneous classification of outcomes by study investigators, at a more or less equivalent rate across all study arms. This serves to minimize differences in event rates between trial arms and increase the potential for a type II error. And in a safety study such as this, in which true event rates are already exceedingly low, this is a critical concern.

The FDA reviewers found widespread inconsistencies in the detection and classification of what they deemed "ill-defined and complex"[7] neuropsychiatric events, including: 1) incorrect use of the neuropsychiatric adverse event inventory; 2) inconsistent assessment of symptom severity by investigators; 3) inconsistent accounting of subjects experiencing multiple neuropsychiatric symptoms simultaneously; 4) inconsistent coding of symptoms; 5) inconsistent handling of subjects expressing suicidality; and 6) insufficient explanatory information in many of the adverse event narratives.[8]

This led the FDA reviewers to conclude that "the exact incidence of neuropsychiatric adverse events of significance and perhaps scope of neuropsychiatric adverse events of significance was not accurately captured by the study."[9]

The trial found a numerically, but not significantly, increased risk of neuropsychiatric events in varenicline- and bupropion-treated subjects with a history of psychiatric illness, relative to placebo (6.5% and 6.7% vs. 4.9%, respectively; risk difference 1.59 [95% CI: -0.42, 3.59] for varenicline-placebo and 1.78 [-0.24, 3.81] for bupropion-placebo).[10]

In a trial investigating rare adverse events, the erroneous misclassification of – or failure to detect – a relatively small number of events can have a pivotal effect on final outcomes. A few more events in the varenicline or bupropion arms not initially detected, or slightly fewer erroneously included events in the placebo arm, could have made these increased risks significant.

Finally, the committee must consider the context in which this trial is being considered. As the FDA noted, "the determination of whether to remove a boxed warning is a decision for which there is limited precedent."[11] Two years ago, these same two committees voted 17-1 that evidence from observational studies and a meta-analysis was not convincing enough to remove the boxed warning on varenicline and that the committees would reassess once the trial results were available.[12]

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http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforpatientsandProviders/UCM192556.pdf. Accessed September 13, 2016.

[7] FDA Briefing Document, at PDF p. 46.

[8] FDA Briefing Document, at PDF p. 46-49.

[9] FDA Briefing Document, at PDF p. 100.

[10] FDA Briefing Document, at PDF p. 50 and 52.

[11] FDA Briefing Document, at PDF p. 543.

[12] Food and Drug Administration. Summary Minutes of the October 16, 2014, Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, at PDF p. 5.

Therefore, this trial is being considered as the *sole* basis for removing a boxed warning that is in place due to thousands of reports of neuropsychiatric events in patients on varenicline. While some of these events are undoubtedly unrelated to the drug, it is inconceivable that all 4,701 FAERS reports, including numerous dechallenge and rechallenge cases,[13] were contrived or mistakenly attributed to the drug.

We urge the committees to recommend that the FDA retain the boxed warning on varenicline, as otherwise patients and their doctors will almost certainly be unaware of the risk for potentially life-threatening neuropsychiatric side effects. Thank you for your time.

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM433774.pdf. Accessed September 13, 2016.

[13] FDA Briefing Document, at PDF p. 537.