REFEREE COMMENTS

Reviewer #1

Comments:
This is a well conducted, well written, important, and timely report of a within-subject analysis in a large cohort of people to detect whether use of varenicline is associated with suicide, crime, motor vehicle accidents, or new psychiatric 'disorders'.

1. The primary substantive critique is that, while the increased risk for affective disorders, etc, in those with nicotine dependence is controlled for in this study with the within-subject design, because anxiety and depressed mood are prominent features of the nicotine withdrawal syndrome, a control group with both nicotine dependence and likely nicotine withdrawal (those attempting to quit smoking) would be important to include to clarify the likely contribution of varenicline use, per se, to this risk of affective 'disorders'. Those who used bupropion or NRT could be included as controls in an analysis expanded to include those treatments to address the concern that the finding is due to smoking cessation and not due to use of varenicline per se. This addition would vastly improve our ability to interpret the results in terms of the contribution of varenicline to the outcome.

Our response: A helpful comment. We have added new analyses comparing the risk in varenicline with that in bupropion. Specially, we have done two new between-individual analyses – one including individuals only treated with varenicline, which we have compared to a between-individual analysis of those only treated with bupropion. The latter provides a population of smokers as a control group. Our results showed that individuals treated with varenicline had a 37% decreased risk of mood conditions when compared to individuals treated with bupropion. A borderline significantly decreased risk was found for anxiety conditions. This would support the view that the increased risk of psychiatric conditions found in the within-analyses could be confounded by smoking cessation, as individuals treated with varenicline demonstrated a lower risk of psychiatric conditions when compared to other smokers.

Specifically, we have added to the **Methods**: "In further sensitivity analyses, we examined if the increased risk of psychiatric conditions could be the result of nicotine withdrawal syndrome, which is a potential time-varying confounder. We used a comparison group with nicotine dependence; individuals who had collected at least one prescription for smoking cessation medication bupropion (N06AX12) during follow-up (n=63265). In this sensitivity analysis, only individuals who had been

treated with either varenicline or bupropion were included. Individuals who had been treated with both varenicline and bupropion during follow-up (n=11386) were excluded. A between-individual Cox proportional hazards regression was then carried out, comparing average rates of mood and anxiety conditions during varenicline medication with rates during non-medication" (p. 8, last paragraph).

To the **Results,** we have added: "To test for potential confounding by nicotine withdrawal syndrome, a time-varying factor, we carried out a between-individual Cox proportional hazards regression that included only individuals treated with either varenicline or bupropion during follow-up (Table 4). Results showed that individuals treated with varenicline demonstrated significantly decreased hazards of mood conditions (HR=0.63, 0.55 to 0.74), but not for anxiety conditions (HR=0.87, 0.75 to 1.00) when compared to individuals treated with bupropion" (results section p. 10, last paragraph). We have also included a new Table showing these new results (table 4 on p. 29).

We have expanded the **Discussion** with a section discussing nicotine withdrawal as a possible time-varying confounder: "An alternative explanation is that nicotine withdrawal is a time-varying confounder. When deprived of nicotine, nicotine-dependent individuals can produce withdrawal symptoms that include depression and anxiety as nicotine includes psychoactive compounds that mimic MAO-inhibiting antidepressant effects. [56 58] To test for potential confounding by nicotine withdrawal symptoms, we compared individuals treated with varenicline to individuals treated with bupropion. Our results showed that individuals treated with varenicline had a lower risk of mood conditions, and showed no difference in risk for anxiety conditions when compared to individuals treated with bupropion. The similar or increased risks for psychiatric conditions in another cohort of smokers would support the view that the increased risk found for varenicline in the within-analyses could be confounded by smoking cessation per se. The risk for mood and anxiety conditions among varenicline users reported here should thus be regarded with caution, and need confirmation in further studies" (underlined sections added to discussion on p. 13, first paragraph).

2. Secondly, in the abstract and discussion, it should be emphasized that increased risk for affective 'disorders' was observed ONLY for those with pre-existing psychiatric illness. Again, it would be critical to interpretation of the results to understand whether this is also the case with other pharmacotherapeutic cessation aids.

Our response: We agree that this is important to clarify so that the findings are not misrepresented. So we have added to the **Abstract** (results paragraph) that a small increased risk of mood and anxiety conditions was only found in individuals with pre-existing psychiatric disorders The last sentence now reads: "However, varenicline was associated with a small increased risk of anxiety conditions (hazard ratio 1.23, 95% confidence interval 1.01 to 1.51), and mood conditions (1.31, 1.06 to 1.63), which was only found in individuals with pre-existing psychiatric disorders."

We have also expanded the **Discussion** to include, "In addition, the hazard for incidence of new psychiatric conditions was substantially attenuated (from over 2 in the between-individual analyses to 1.2 in the within-individual study), although the risk increase was limited to those with pre-existing psychiatric conditions" (please see discussion on p. 11, 1st paragraph).
And also state later: "However, the risk remained for anxiety (HR=1.27, 1.06 to 1.51) and mood (HR=1.28, 1.07 to 1.52) conditions. When stratifying on psychiatric history, associations remained only for individuals with a history of psychiatric conditions" (p. 12, 3rd paragraph).

More minor comments:
3. Introduction, second paragraph, please add 2 citations, first authors, Hong and Shim, as placebo-controlled studies of varenicline in those with serious psychiatric illness that found no evidence of worsening of psychiatric symptoms in those assigned to varenicline compared to placebo. The FDA prescribing information now cites summary data from RCT's not published and could be cited as a URL. The Kishi and Iwata meta-analysis is badly flawed in that it incorrectly summarizes the evidence for efficacy of varenicline for smoking cessation in schizophrenia and does not formally assess safety of varenicline in this population, as such it is not helpful here as a reference.

Our response: We are grateful for these useful references. We have now added the Shim 2012 reference to the introduction (reference 33), and the FDA safety update has been added to the introduction (reference 37). We agree that the Kishi reference should be deleted.

In Results
4. In the first paragraph, please clarify whether the 5.6% crime rate was the increase during treatment over the incidence before treatment.

Our response: We agree that these numbers need clarification. The 5.4% crime rate is not a risk increase during treatment. It refers to the overall number of individuals in the varenicline cohort who were suspected of a crime during follow-up November 22, 2006 to December 31, 2009. This has been

clarified in the results section, where we have also added the corresponding number of individuals in the non-medicated cohort.

Specifically, the **Results** now states: "During this time period, 5.4% were suspected of a crime, and 4.6% were diagnosed with a new psychiatric condition in the varenicline population. There were lower rates of serious traffic-related incidents (1.4%) and suicidal behaviours that attracted medical care (0.9%) in the varenicline population. In the same time-period, 4.0% in the non-medicated population were suspected of a crime, 2.2% were diagnosed with a new psychiatric condition, 1.4% received medical care for traffic-related accidents, and 0.3% received medical care for suicidal behaviours" (p. 9, 1st paragraph).

5. Use of the term 'disorders' is not optimal as operationalized for this study, as this may have been a transient phenomenon.

Our response: We agree. The term 'disorders' (i.e. psychiatric, mood and anxiety disorders) has been changed throughout the paper to the term 'conditions'.

Summary:
For the between subject hazard models, positive controls with bupropion and NRT are critical for interpretation. The between subject models do not control for the increased risks of these outcomes in persons with nicotine dependence or the increased risks for psychiatric symptoms due to the smoking cessation process /nicotine withdrawal.

See our response above to comment 1.

Reviewer: 2

Comments:
This report is very strong overall. The stepwise description of the results is clear. Addressing several points could strengthen the piece.

1. The final sentence of paragraph 2 suggests there is no literature clinicians can use to weigh the

risks and benefits of varenicline use in individuals with psychiatric illness – when really there are the cited trials (32-35). These studies are RCTs that have demonstrated safe use of varenicline in individuals with bipolar disorder, major depression, and schizophrenia. I appreciate that the authors are saying that RCTs may not pick up rare events, though so far RCTs are reassuring.

Our response: This is a very helpful comment, and we have revised the wording of the introduction to take this into account (and we have added a new reference from a BMJ meta-analysis that came out last week that support this).
Specifically, we now state, in the **Introduction** "Although there have been no safety concerns in RCTs of varenicline in individuals with bipolar disorder, major depression and schizophrenia, trials have been comprised of small samples,[31-32] resulting in limited statistical power to detect rare events" (page 3, 2nd paragraph). The new reference is: Thomas KH et al. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. BMJ 2015;350:h1109 (reference 32).

2. The analysis testing for confounding by pre-existing psychiatric disorders showed that only individuals with pre-existing psychiatric illnesses had increased HR of mood and anxiety disorders. This is an interesting point and brings up the question of what proportion of individuals with pre-existing psychiatric disorders were getting treatment for what are typically chronic problems such as recurrent major depression or anxiety disorders. It also brings up the question of whether anxiety or depression symptom recurrence is occurring here, particularly if the majority of individuals were not receiving treatment or were receiving insufficient treatment (which is unknown but a possibility). It is not stated in the Discussion that the incidence for new psychiatric disorders was only significant in the group with pre-existing psychiatric disorders. Could the authors address these points in the Discussion and contrast this finding with the RCTs (ie citation 34 by Anthenelli, et al. which showed no increase in depression symptoms among individuals with major depression treated with varenicline, though over 70% of trial participants were receiving concurrent treatment with an antidepressant medication). There may be room in the Discussion to include reflecting on these points if the authors condensed the recap of the results (ie the first paragraph of the Discussion).

Our response: This is a thoughtful comment, and one which partly corresponds with reviewer 1, #2. We agree that the discussion needs to make it clearer that it was only those with pre-existing psychiatric disorders where an increased incidence risk for psychiatric disorders was found, and have added the following sentence to the first paragraph of the **Discussion**: "In addition, the hazard for

incidence of new psychiatric conditions was substantially attenuated (from over 2 in the between-individual analyses to 1.2 in the within-individual analyses), although the risk increase was limited to those with pre-existing psychiatric conditions" (please see p. 11).
We also state later in the **Discussion** that: "When stratifying on psychiatric history, associations remained only for individuals with a history of psychiatric conditions" (p. 12, 3rd paragraph), and that "an increased risk of mood and anxiety conditions during periods of varenicline medication was found in individuals with pre-existing psychiatric disorders, which requires confirmation using other study designs" (p. 14, 2nd paragraph), and again that "…an increased risk of mood and anxiety conditions was found in individuals with pre-existing psychiatric disorders, which requires confirmation using other study designs" (p. 15, 6th paragraph).

The reviewer's point about there being no increase in depressive symptoms in RCTs does suggest one alternative explanation, which we have added to the discussion – that it is non-adherence with existing psychiatric medications that may be one explanation for this increased risk. This would need further research to clarify. Specifically, we have now added to the **Discussion**: "When stratifying on psychiatric history, associations remained only for individuals with a history of psychiatric conditions. It has been argued that varenicline is highly selective for a4b2 nicotinic receptors, and at therapeutic levels does not bind to other neurotransmitter receptors and transporters, including those implicated in mental health problems.[56 57] The within-individual analysis, however, did not take time-varying confounding factors into account, i.e. factors that were associated with both the onset of varenicline treatment and the outcome. The increased risk of mood and anxiety conditions during varenicline treatment in this group could thus be caused by time-varying factors other than varenicline; the onset of varenicline medication could mean non-adherence with other medications, which may lead to increased incidence of new psychiatric conditions. The finding that RCTs have not shown an increase in depressive symptoms among individuals who are under stable treatment for their depression would support this view.[35] " (underlined sections added to discussion on p. 13, 1st paragraph).
We have also shortened the first paragraph in the **Discussion** (on p. 11) to make space for this extra discussion