CASE REPORT
Mania induced by varenicline [version 1; referees: 1 approved with reservations, 1 not approved]

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Abstract
Varenicline is sometimes used in the treatment of smoking addiction. Side effects such as nausea, vomiting, and headaches have been well documented. In addition, depressed mood and suicidal thoughts relating to varenicline usage have been previously reported. We report a case of mania in a patient with refractory depression whose first manic episode developed under the use of varenicline in combination with original antidepressant medications.

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Case report
Mr. L., a 55-year-old male, was diagnosed with major depressive disorder based on DSM-IV TR criteria in December 2010. The presenting symptoms included depressed mood, irritability, anxiety, somatic worries, difficulty falling asleep, ideations of death, anhedonia, and an impaired working ability for two months. Therefore, we prescribed standard antidepressant treatment, and also attended psychotherapeutic intervention sessions following his visit to our outpatient department.

He showed a poor response to both antidepressant monotherapy and combination therapy with a selective serotonin reuptake inhibitor (SSRI), serotonin/norepinephrine reuptake inhibitor (SNRI) and norepinephrine/dopamine reuptake inhibitor (NDRI) combined with lamotrigine. In detail, he received sertraline monotherapy (50 mg, 3 months), venlafaxine monotherapy (112.5 mg, 4 months), duloxetine monotherapy (30 mg, 2 months) and combination therapy of bupropion and lamotrigine (300 mg/50 mg, 6 months). Repetitive transcranial magnetic stimulation was also tried with only a partial antidepressant response. Finally, he maintained mild to moderate depression with the use of a melatonergic agent (agomelatine 25 mg) and lamotrigine (50 mg).

The patient reported being addicted to smoking for the past 40 years, 1 pack per day, with a Fagerstrom nicotine dependence score of 6. In March 2013, he was prescribed varenicline 0.5 mg/day for smoking cessation. He had been treated with agomelatine (25 mg/day) for three months prior to the initiation of varenicline treatment. After six days of varenicline treatment, there was no reported nausea or other side effects. The dosage of varenicline was subsequently titrated to 2 mg/day. During the first month of varenicline treatment, persistent elevated mood, high irritability and other symptoms of mania such as hyper-talkativity, grandiosity, decreased need for sleep were reported. In addition, increased verbal and physical aggressions toward strangers were noted for one week. Thus, varenicline-related mania was diagnosed and after discontinuation of varenicline, the manic symptoms disappeared rapidly within a few days. His mood returned back to its original status between mild to moderate depression.

Discussion
The occurrence of the mania in the present case seemed to be dose-dependent and the adverse effect rapidly disappeared after discontinuation of varenicline. Depressed mood and suicidal ideation have been listed in varenicline’s black box warning. In addition, a previous case of aggressive behavior in a patient with schizophrenia induced by varenicline has been reported. However, the mechanism by which varenicline could induce mania is not clear.

A prominent reduction in the expression of mRNA for several nicotinic subunit isoforms has been reported in bipolar disorders. Nicotinic cholinergic receptors play an important role in regulating the activity of GABA inhibitory interneurons.

Selectively binding to the nicotinic acetylcholine α4β2 subunit may cause an imbalance of the inhibitory controls in the mood circuit, since the nicotinic acetylcholine receptor α7 and α4β2 subtypes have a different degree of GABAergic inhibition in target neurons. Furthermore, an increase in nicotinic receptor α7-dependent signaling has been suggested to be critically involved in the pathophysiology of bipolar disorder from a study on post-mortem patients. Varenicline seems to be safe in patients with bipolar disorders, yet a few case reports have demonstrated a hypomanic or manic relapse in patients with identified bipolar disorders. Varenicline is a partial agonist at the nicotinic acetylcholine α4β2 subunit and a full agonist at the α7 subunit. Potent α7-dependent activation and weak α4β2-dependent activation caused by varenicline might lead to a central inhibitory dysfunction that might, in turn, lead to manic symptoms in patients with bipolar disorders or bipolar diathesis. Some patients with major depression may harbor bipolar disorders later, particularly if they show high resistance to antidepressant treatment. Although central mechanisms of varenicline induced mania remain elusive, the present case report highlights the importance of monitoring for potential manic side effects with the use of varenicline in patients with major depression, especially when used in combination with antidepressants.

Consent
Written informed consent for publication of clinical details was obtained from the patient.

Author contributions
Conceived the case: Cheng-Ta Li. Analyzed the data: Ping-Tsun Chang and Cheng-Ta Li. Wrote the paper: Ping-Tsun Chang. Both authors critically revised the paper.

Competing interests
No competing interests were disclosed.

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Open Peer Review

Current Referee Status: ✗ ?

Version 1

Referee Report 10 December 2013

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Jonathan Foulds
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This article is a case report of a man who had been suffering from treatment-resistant depression who developed symptoms of mania. The main problem with this paper is that although the patient was prescribed varenicline for smoking cessation, the report contains no information on any changes in his smoking around the time he was prescribed varenicline and thereafter…none! We are left to guess about this, and it is a reasonable guess that the patient significantly reduced his smoking. In that case why are the manic symptoms being attributed to varenicline rather than to smoking cessation? Some of the symptoms described (high irritability, decreased sleep) are known symptoms of nicotine withdrawal. There is also a lack of information on other drug/substance use that may help to interpret the patient's mood changes. For example, did he consume much caffeine? Caffeine metabolism slows down significantly on smoking cessation; could that have played a role?

Overall there is insufficient provision of key information to help the reader interpret this potentially interesting case report. In addition, this report fails to cite recent key studies on large samples that are relevant to the question of whether varenicline may cause neuropsychiatric side effects (Gibbons & Mann 2013; Foulds et al, 2013; Thomas et al, 2013).

The paper needs to be revised to include a detailed description of the timing of symptoms relative to cigarette consumption and to address any other potential causes of mania.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: I act as a consultant for Pfizer (manufacturer of varenicline) and other pharma companies involved in smoking cessation.

Referee Report 19 November 2013

doi:10.5256/f1000research.2318.r2395

Eva Kralikova
First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic
Varenicline is commonly used in the treatment of tobacco dependence. Smokers have a very important and large psychiatric comorbidity. The paper presents no evidence that the status was caused by varenicline, including missing major publications on this topic - so I would evaluate it as not acceptable.

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

**Competing Interests:** No competing interests were disclosed.

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**Version 1**

**Reader Comment 19 Mar 2016**

**Omar González-Santiago,** Universidad Autónoma de Nuevo León, Mexico

It would be interesting to indicate specifically the time when the patient received each one of your antidepressants. Probably the patient is manifesting side effects of its antidepressants or may have inadequate dosing of antidepressant.

**Competing Interests:** None