Check for updates

CASE REPORT

Mania induced by varenicline [version 1; peer review: 1 approved with reservations, 1 not approved]

Ping-Tsun Chang, Cheng-Ta Li

Department of Psychiatry, Taipei Veteran General Hospital, Taipei, Taiwan

V1 First published: 13 Sep 2013, 2:183
<https://doi.org/10.12688/f1000research.2-183.v1>
Latest published: 13 Sep 2013, 2:183
<https://doi.org/10.12688/f1000research.2-183.v1>

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.

Open Peer Review

Approval Status

	1	2
version 1 13 Sep 2013	view	view
1. Eva Kralikova , Charles University in Prague, Prague, Czech Republic		
2. Jonathan Foulds , Penn State University, Hershey, PA, USA		
Any reports and responses or comments on the article can be found at the end of the article.		

Corresponding author: Cheng-Ta Li (cn5083@msn.com)

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2013 Chang PT and Li CT. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

How to cite this article: Chang PT and Li CT. **Mania induced by varenicline [version 1; peer review: 1 approved with reservations, 1 not approved]** F1000Research 2013, 2:183 <https://doi.org/10.12688/f1000research.2-183.v1>

First published: 13 Sep 2013, 2:183 <https://doi.org/10.12688/f1000research.2-183.v1>

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 warning¹. In addition, a previous case of aggressive behavior in a patient with schizophrenia

induced by varenicline has been reported². 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 interneurons³.

Selectively binding to the nicotinic acetylcholine $\alpha 4\beta 2$ subunit may cause an imbalance of the inhibitory controls in the mood circuit, since the nicotinic acetylcholine receptor $\alpha 7$ and $\alpha 4\beta 2$ subtypes have a different degree of GABAergic inhibition in target neurons⁴. Furthermore, an increase in nicotinic receptor $\alpha 7$ -dependent signaling has been suggested to be critically involved in the pathophysiology of bipolar disorder from a study on post-mortem patients⁵. Varenicline seems to be safe in patients with bipolar disorders⁶, yet a few case reports have demonstrated a hypomanic or manic relapse in patients with identified bipolar disorders⁷⁻⁹. Varenicline is a partial agonist at the nicotinic acetylcholine $\alpha 4\beta 2$ subunit and a full agonist at the $\alpha 7$ subunit¹⁰. Potent $\alpha 7$ -dependent activation and weak $\alpha 4\beta 2$ -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 treatment¹¹. 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.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

1. Food and Drug Administration. Information for Healthcare Professions: Varenicline (marketed as Chantix). 2008. [Reference Source](#)
2. Freedman R: Exacerbation of schizophrenia by varenicline. *Am J Psychiatry*. 2007; **164**(8): 1269. [PubMed Abstract](#) | [Publisher Full Text](#)
3. Benes FM: Nicotinic receptors and functional regulation of GABA cell microcircuitry in bipolar disorder and schizophrenia. *Handb Exp Pharmacol*. 2012; (213): 401–17. [PubMed Abstract](#) | [Publisher Full Text](#)
4. Alkondon M, Albuquerque EX: Nicotinic acetylcholine receptor $\alpha 7$ and $\alpha 4\beta 2$ subtypes differentially control GABAergic input to CA1 neurons

in rat hippocampus. *J Neurophysiol.* 2001; **86**(6): 3043–55.
[PubMed Abstract](#)

5. Thomsen MS, Weyn A, Mikkelsen JD: **Hippocampal $\alpha 7$ nicotinic acetylcholine receptor levels in patients with schizophrenia, bipolar disorder, or major depressive disorder.** *Bipolar Disord.* 2011; **13**(7–8): 701–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Wu BS: **Smoking and Co-occurring Disorders: Implications for Smoking Cessation Interventions for Adolescents in Residential Addiction Treatment.** *Journal of Dual Diagnosis.* 2012; **8**(2): 131–132.
7. Kohen I, Kremen N: **Varenicline-induced manic episode in a patient with bipolar disorder.** *Am J Psychiatry.* 2007; **164**(8): 1269–70.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Morstad AE, Kutscher EC, Kennedy WK, *et al.*: **Hypomania with agitation associated with varenicline use in bipolar II disorder.** *Ann Pharmacother.* 2008; **42**(2): 288–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Alhathem F, Black JE: **Varenicline-induced mania in a bipolar patient.** *Clin Neuropharmacol.* 2009; **32**(2): 117–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
10. Mihalak KB, Carroll FI, Luetje CW: **Varenicline is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nicotinic receptors.** *Mol Pharmacol.* 2006; **70**(3): 801–805.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Li CT, Bai YM, Huang YL, *et al.*: **Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: cohort study.** *Br J Psychiatry.* 2012; **200**(1): 45–51.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 10 December 2013

<https://doi.org/10.5256/f1000research.2318.r2637>

© 2013 Foulds J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Jonathan Foulds

Public Health Services, Penn State University, Hershey, PA, USA

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.

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

I confirm that I have read this submission and 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.

Reviewer Report 19 November 2013

<https://doi.org/10.5256/f1000research.2318.r2395>

© 2013 Kralikova E. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and 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.

Comments on this article

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

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research