Treatment of Depression in a Former Smoker With Varenicline? A Case Report and Discussion

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The U.S. Food and Drug Administration has warned that patients being treated for smoking cessation with varenicline may develop depression. A case of successful treatment for depression with varenicline is described. The patient's depression recurred several times with inadvertent varenicline discontinuation, then remitted again after resuming varenicline. The literature supporting the potential use of varenicline for depression is reviewed.

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CASE REPORT

The patient is a 47-year-old man who reported problems with chronic depression, of varying intensity over time. At baseline, he reported being depressed most days going back about 30 years, with periodic worsening of symptoms lasting 2 or 3 months at a time. In May 2011, he was prescribed varenicline for smoking cessation by his primary care provider. He noted an immediate improvement in his mood, and said that he felt better than he had in years. He had been in one of his more depressed phases for about 2 months prior to starting varenicline. His positive outlook and relief of depressive symptoms continued until he ran out of varenicline in August 2012. When he attempted to have it refilled, he was told that it was not possible because of institutional policy. Instead, he was prescribed venlafaxine. On venlafaxine, he experienced "extreme highs and lows." It also made him feel sick and caused him to "wake up screaming." He stopped it after a few days, and these other symptoms disappeared. He subsequently again fell into a depression, which lasted up to the time that he saw this provider in October 2012.

At the initial interview with this provider, he complained of significant depression. He lacked energy or motivation. He was out of work and did not have the ambition or energy to find a new job, despite the fact that he was behind on his rent and was considering filing for bankruptcy. He said that most days he felt "dark and gloomy," with significant anhedonia, and he experienced crying spells. He experienced guilty feelings about the past. His sleep was poor. He denied appetite problems and complained of no irritability. He denied being suicidal, although he had experienced suicidal thoughts in the past, and the family history was notable for suicide attempts by his mother. He also reported that when very depressed, he sometimes became paranoid, saw shadows under his door, and wondered if somebody was after him. He denied any recent symptoms of mania or hypomania.

The patient reported a history of alcohol and cocaine abuse, as well as excessive gambling. When drinking heavily some years previously, he usually drank in binges lasting days to a week at a time. He denied any heavy drinking for several years prior to starting varenicline, and a review of his chart did not find any inconsistences in his self-report. He was being followed regularly by his primary care provider as well as a mental health therapist, and his providers inquired about his substance use. In recent years, he had cut back on his drinking significantly, and usually drank 2 beers during the week, and a 6-pack on weekends. He had used cocaine once in the past year, after drinking 18 beers for one day only. This single binge episode in early October 2012 was related to learning that a friend had died. Prior to first starting varenicline in May 2011, he had not used any cocaine for some time. He also had refrained from excessive gambling for 3 to 4 years. Lately, he had only played the lottery on occasion, and had only spent a few dollars on lottery tickets. In the remote past, he had experimented with marijuana, LSD, crystal meth, and mushrooms.

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Upon inquiry, the patient reported a history of occasional episodes of expansive mood lasting a day to several days at a time. These episodes had tended to occur in the past when he binged on cocaine. He had not experienced any of these expansive moods for some years before being started on varenicline. Aside from the episode of extreme mood swings when taking venlafaxine as mentioned above, the patient reported one other episode of elevated mood, when he was prescribed sertraline about 15 years previously. He said that while taking it he "felt unreal with a kind of forced happiness." He noted that his mood "shot straight up. I felt like I was a flower child." The elevated mood disappeared when he stopped sertraline.

Lab values were basically within the normal range. Thyroid-stimulating hormone was slightly low at 0.31 but free thyroxine was normal. The patient was seen by endocrinology after he was found to have a benign thyroid nodule. They diagnosed him as having mild subclinical hyperthyroidism with no indication for treatment. Medical history was otherwise unremarkable, other than the patient suffering from migraine headaches.

The patient reported that the varenicline did help him with smoking cessation. He stopped smoking in June 2012, and has not smoked since that time. Prior to starting varenicline, he had been a heavy smoker for about 25 years.

The patient was tentatively diagnosed with major depression superimposed on a dysthymic disorder. Bipolar II disorder was considered. The patient was restarted on varenicline 1 mg daily. At the next follow-up session, he reported that his mood had again improved dramatically within 1 1/2 days of restarting varenicline. He denied any of the depressive symptoms of which he had complained at the initial session. There were no manic or hypomanic symptoms. There had been no major changes in his life, other than a resolution of his symptoms. He was doing well and he denied side effects. He was making efforts to work again.

At a subsequent follow-up meeting 2 months later, the patient reported that his mood had remained good with varenicline. However, he had recently run out and was again not able to get varenicline refilled for administrative reasons. There was an appeal process, and the patient was without varenicline for about 1 week until the medication was approved. At the next meeting, the patient reported that he had done well for a few days without varenicline but then had started to slip back into depression, marked mostly by a lack of motivation. During his time off of varenicline, he had started to crave alcohol and began to drink excessively. He did not use drugs and did not gamble excessively. Nor did he experience any craving to use drugs or to gamble. After restarting the varenicline, his mood improved quickly, he no longer craved alcohol, and he stopped drinking. There were no manic or hypomanic symptoms.

DISCUSSION

Presented was a case of a subject whose symptoms of depression serendipitously remitted rapidly on several occasions with the initiation of varenicline. It had initially been started for smoking cessation but then was used for primary treatment of his mood disorder. He had a longstanding history of baseline depression with episodes of worsening moods lasting months at a time. There was some evidence for an underlying bipolar II disorder, although the clinical picture was not clear. He clearly was not manic or hypomanic on examination during his period of improved mood while taking varenicline. He had a history of significant alcohol binge drinking and also using cocaine in binges. The possibility of a substance-induced mood disorder was considered but rejected in light of the fact that his mood changes with varenicline initiation and discontinuation were not related to his use of or discontinuation of substances. After initially stopping smoking with varenicline, the patient refrained from smoking, and no relationship was found to be associated with his smoking status and his mood state.

In 2011, a research article in the online medical journal PLoS One[1] reported that varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist and alpha7 full agonist, showed a substantial, statistically significant increased risk of reported depression and suicidal/self-injurious behavior. The authors had examined the U.S. Food and Drug Administration's (FDA's) Adverse Event Reporting System database from 1998 through September 2010. The FDA subsequently required that varenicline carry a "black box warning" about risks including changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions. The FDA also ordered Pfizer, the manufacturer of Chantix, to conduct a trial focusing on the safety of the drug, although the results will not be available until 2017.

Although it is prudent to be watchful for possible adverse events associated with using varenicline, clinicians

may want to keep an open mind and weigh potential benefits against the potential risks. It is well known that many patients with clinical depression fail to achieve relief with available treatments, as evidenced, for example, by the Sequenced Treatment Alternatives to Relieve Depression trial.[2] There is a need for novel therapeutic approaches to target the patients who fail to respond to standard treatments. While acknowledging the potential for negative consequences as noted above, there are reasons to consider varenicline as a potential novel antidepressant agent.

In phase III trials, varenicline attenuated symptoms of depression, irritability, anxiety, and sleep disturbances, considered in the study to likely be symptoms of withdrawal from nicotine.[3] Of note, these symptoms did not rise to the level of a clinically significant, recurrent depressive disorder, unrelated to smoking status, as described in the present case report. Further, nicotinic acetylcholine receptors (nAChRs) are involved in a variety of neurobiological systems implicated in the pathophysiology of depression.[4]

There have been a variety of preclinical studies using animal models, which show beneficial effects of varanicline on mood.[3] In the clinical realm, there have been only a few studies. Patterson and colleagues[5] studied 67 nondepressed patients undergoing smoking cessation with varenicline and found that varenicline increased positive affect and decreased negative affect. The authors suggested that varenicline be explored as a potential treatment for mood disorders. Phillip and colleagues[6] demonstrated the usefulness of varenicline as augmentation treatment for depression. They studied 18 nicotine dependent patients aged 18 to 65 who had a primary Axis I depressive disorder diagnosis (major depression, bipolar depression, depression not otherwise specified, dysthymic disorder, adjustment disorder with depression, or substance-induced mood disorder) in an 8-week open-label trial. The patients were all taking an antidepressant or mood stabilizing medication but continued to experience persistent depressive symptoms. The patients continued their usual antidepressant regimen, and varenicline was added for augmentation treatment. Of the 14 patients who completed the study, the majority improved, and a third reached remission. The overall effect size was large. Improvement in mood significantly correlated with decrease in smoking, although significant mood changes observed during the first 4 weeks of the study did not correlate with smoking status.

Why might targeting nAChRs mediate potential antidepressant effects? A number of hypotheses have been proposed, most notably relationships with other neurotransmitter systems. The alpha4beta2 nicotinic actetylcholine receptors are widely distributed in neuroanatomic regions implicated in depression, and through their actions in these areas, they are thought to regulate the release of dopamine, which is strongly implicated in affect regulation and reward processing reinforcement.[4] In considering this possibility, it is interesting to note that in the above case report the patient had a history of multiple addictions in addition to his nicotine addiction. He had a past history of addiction to gambling, cocaine, and alcohol. During the time that he was without varenicline, he found himself craving alcohol again and had started to drink excessively. He stopped drinking after he started taking the varenicline again. This brings up the issue of the relatively new theory of addiction transfer, or "switching of addictions."[7,8] The theory states that many patients who have one type of addiction may switch to another addiction under certain circumstances, based upon an underlying abnormality of the brain's reward system. It appears that different addictions have in common similar abnormalities in the reward centers of the brain,[8] and the mechanism is thought to involve a deficiency of the dopamine D2 receptor. The theory was spurred on by the clinical observation that following bariatric surgery, a number of patients who were previously thought to have had a "food addiction" developed new addictions to substances such as opioids or alcohol following their bariatric surgery. The abnormality is thought to stem from a genetic variant form of the gene for the dopamine D2 receptor.[9] Since nAChR modulators are thought to regulate the release of dopamine, modulators such as varenicline may act to alter the brain's reward system, leading to an antidepressant effect. Such modulators may also decrease the likelihood of addiction transfer if this tendency is present.

Although one would need to be cautious, clinicians may wish to consider trying varenicline "off label" either as augmentation treatment along with another antidepressant, or occasionally alone when other treatment methods for depression have failed, particularly in those with nicotine and perhaps other addictions. As noted by the study by Philip and colleagues,[6] patients with several different types of depression (major depression, bipolar depression, depression not otherwise specified, dysthymic disorder, adjustment disorder with depression, or

substance-induced mood disorder) might potentially benefit from varenicline treatment.

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