**Case Report**

A Case Report on Varenicline Induced Delirium in an Alcohol and Nicotine Dependent Patient

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**ABSTRACT**

Varenicline is a smoking cessation agent. Varenicline acts as a partial agonist of $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptor and prevents nicotine binding to the same. It also causes dopamine (DA) stimulation that decreases craving and symptoms of dependence. A 40-year-old male diagnosed with alcohol and nicotine dependence syndrome was treated with 1 mg of varenicline for 3 days. Patient developed episodes of transient delirium within 15-30 min after administration of varenicline. Patient was disoriented and did not respond relevantly. Patient would have disorientation and would respond irrelevantly and was unable to recall the event completely. There were no features suggestive of seizures. The episodes resolved after the medication was stopped. Varenicline, with its partial agonistic effect on nicotinergic receptors, stimulates the release of multiple neurotransmitters including DA. DA dysregulation is probably responsible for the development of neuropsychiatric adverse reactions due to varenicline. This is the first case report to the best of our knowledge reporting varenicline induced delirium. In this case, the adverse event was found in an alcohol and nicotine dependent patient undergoing treatment. It is essential to monitor uncommon adverse effects as this can cause significant morbidity.

**Key words:** Delirium, tobacco cessation, varenicline

**INTRODUCTION**

Varenicline is an anti-craving drug used for smoking cessation. The addiction toward smoking is mediated by nicotine, which stimulates $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs) in brain. Varenicline is a novel $\alpha_4\beta_2$ nAChR partial agonist and has been found to be more effective than nicotine replacement therapy or bupropion in relieving craving and withdrawal symptoms after abstinence. It functions by preventing nicotine binding to the above mentioned receptors. It also provides low to moderate level of dopamine (DA) stimulation that helps to alleviate craving and symptoms of dependence.

In tobacco smokers, a partial agonist would mostly work as an antagonist during smoking (i.e., high nicotine occupancy), but as an agonist during abstinence or withdrawal (i.e., low nicotine occupancy). Thus, the rewarding effects of smoking would decrease substantially, but not disappear completely, whereas withdrawal symptoms and craving episodes would occur less frequently during abstinence due to the release of a low-to-moderate level of DA produced by a partial agonist itself. Thus, varenicline has been recently Food and Drug Administration approved to be a first-line medication for smoking cessation.

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in the United States and European countries. The most commonly reported adverse effects include nausea, insomnia, and headache. On the other hand, postmarketing data has linked varenicline to various neuropsychiatric symptoms such as seizures, suicidal attempts, depression, and psychosis. Other serious injuries potentially related to unconsciousness, dizziness or visual disturbances due to varenicline have also been reported.\cite{2}

**CASE REPORT**

A 40-year-old male patient was admitted and treated for alcohol and nicotine dependence syndrome. After discharge, as he had significant craving for nicotine he was started on 0.5 mg tablet varenicline for 3 days, 0.5 mg twice daily for 4 days and then increased to 1 mg twice a day. Patient developed episodes of transient delirium 15-30 min after taking varenicline 1 mg twice a day. Patient was observed to be disoriented to time and place and at times, disoriented to person and would not respond relevantly. These episodes (total of three) were reported to last for around 30 min and resolved spontaneously after 30-40 min. Patient reported a sense of confusion and could not recall the event completely. There were no features suggestive of seizures. The episodes resolved after the medication was stopped. On general physical examination, there were no abnormalities and his investigations looking at electrolytes, liver function and renal function and were normal. Other parameters which could lead to delirium were absent. Patient did not have episodes of delirium after the reduction of the dose. There were no additional drugs prescribed during this period.

**DISCUSSION**

To the best of our knowledge, this is the first report of varenicline induced delirium. There is one case report of varenicline withdrawal delirium.\cite{3} In this case report, the symptoms were noted after abrupt stoppage of varenicline and clear association could not be determined.

In our case, there was temporal relationship between the increase of the dose and delirium, which resolved after reduction in the dose to 0.5 mg twice daily. The prime site of nicotine action in the brain is the mesolimbic system. Nicotine stimulates dopaminergic neurons located in the ventral tegmental area, increasing DA release in the nucleus accumbens. Nicotine interacts with nAChRs, which are pentameric ion channels located in the mesolimbic system. The highest-affinity nAChRs consist of two $\alpha_4$ subunits and three $\beta_2$ subunits. Nicotine binds to and causes a conformational change in the $\alpha_4\beta_2$ nAChR, increasing sodium ($Na^+$) influx, resulting in release of DA. Varenicline causes partial stimulation and competitively inhibits nicotine binding. It helps chronic smokers to stop smoking by maintaining moderate levels of DA to counteract withdrawal symptoms of nicotine abstinence.\cite{4} It mimics the action of nicotine and causes a moderate and sustained release of mesolimbic DA [Figure 1]. Because it is a partial agonist at these receptors, it elicits DA overflow, but not equivalent to the substantial increases evoked by nicotine.

Responses mediated by the $\alpha_4$ subunit are thought to be responsible for sensitization to nicotinic effects, reinforcement, and tolerance, whereas involvement of the $\beta_2$ subunit is thought to be associated with the development of dependence. Stimulation of DA release by nicotine also appears to be related to activation of glutamatergic and GABAergic neurons that contain nAChRs, which may mediate reinforcing behaviors in smokers.\cite{5}

Neural pathways that include prefrontal cortices, anterior and right thalamus, and right basilar mesial temporoparietal cortex, may be a final common pathway for delirium. This pathway may be responsible for symptoms such as disorientation, cognitive deficits, sleep-wake cycle disturbance, disorganized thinking, delusions, and affective lability. An imbalance in the cholinergic (acetylcholine [Ach] deficiency) and dopaminergic (DA excess) neurotransmitter systems appears to be critical in the final common pathway, which is commonly implicated in causing delirium. Varenicline, being a partial agonist of $\alpha_4\beta_2$ nAChR receptors can explain the delirium symptoms and also it is consistent with the neuroanatomical pathways being implicated.\cite{6,7}

Nicotine receptors within the brain bind Ach to modulate cognitive functioning, arousal, learning, and memory. Muscarinic Ach receptors, more widely distributed throughout the brain, may play a larger

![Figure 1: Mechanism of delirium by varenicline](image-url)
role in delirium. Anticholinergic compounds induce delirium through competitive antagonism of post synaptic muscarinic receptors. The cholinergic system is balanced by monoamine activity where dysfunction has also been associated with delirium. DA, NE, and 5HT have roles in arousal and the sleep-wake cycle, mediating physiological responses to stimuli. These responses are mediated by the cholinergic pathway. Thus, delirium development might involve interaction between the cholinergic pathway and these monoamines.

Varenicline has been found to be a full agonist at the alpha 7-homomeric receptors. Several experimental studies have found that alpha 7-homomeric nicotinic receptors in the ventro tegmental area are involved in DA release in the nucleus accumbens.[4]

Dopamine excess may contribute to hyperactive delirium, linked to simultaneous Ach decreases. Thus, Ach and DA may be inversely related in delirium pathogenesis; pharmacological and neuroanatomical evidence support this model. Anatomically dopaminergic and cholinergic pathways overlap significantly in the brain. DA receptors impact Ach levels differently, which may explain the diverse clinical manifestations of delirium.[8]

Varenicline binds with moderate affinity to the 5HT3 receptors it is possible that endogenous 5HT in stratum or nucleus accumbens acts as a local regulator of DA release acting via a transport-dependent mechanism.[6] A micro-analysis study in rats provided in vivo evidence of 5HT3 receptor agonist induced DA transporter mediated increase in DA release.[9] Moreover, stimulation of 5HT3 receptors inhibits Ach release.[10]

Reduced cholinergic function, excess release of DA, norepinephrine, glutamate, alterations in levels of serotonergic, gamma-aminobutyric acid activity may underlie the different symptoms and clinical presentations of delirium.[11]

CONCLUSION

Varenicline is associated with a higher risk of neuropsychiatric events. In this case, delirium was noted in an alcohol dependent patient undergoing treatment of the same. It is essential to monitor uncommon side effects especially delirium as this can cause significant morbidity and also possibility of mortality as a consequence.

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