



Varenicline and Involuntary Intoxication: Forensic Implications

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Abstract

The use of varenicline as an aid to smoking cessation is ordinarily safe and effective. Its mechanism of action includes blockade and partial agonism of central nicotine receptors, thus relieving the user of nicotine withdrawal while providing release of dopamine in the nucleus accumbens. A small fraction of users develop neuropsychiatric effects, which can include changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. When the toxicity includes aggression toward others or dangerous acts that run afoul of the law, the patient may have a defense of involuntary (pathological) intoxication. This article reviews reported cases and scenarios that have utilized a causal relationship between use of varenicline and otherwise unaccountable behaviors. Unlike voluntary intoxication, involuntary intoxication can be used as a defense against criminal charges. The criminal defendant must prove that the drug was used for ordinary medical reasons (not to become intoxicated), that there was a causal relationship between ingestion of the drug and the behavioral effect, and that, at the time of the criminal act, the defendant did not know that his/her actions were wrong. In essence, it is an insanity defense without risk of subsequent civil commitment. Since some physicians and patients with existing mental disorders are afraid of behavioral effects of varenicline, there could be a chilling effect on prescribing. Ethical concerns are addressed.

Keywords: Varenicline; Intoxication; Involuntary intoxication; Pathological intoxication; Criminal responsibility; Behavioral toxicity

Abbreviations

FDA (Food and Drug Administration)

Introduction

Tobacco use is a serious health problem among persons with serious mental illness, significantly reducing life expectancy [1,2]. It has long been known that smoking among individuals with schizophrenia is greatly increased over both the general population and those with other psychiatric diagnoses [3]. The association has persisted over time and smoking cessation has been regarded as a priority among patients with schizophrenia [4,5]. After much study, however, the dynamics of the association remain obscure. There is no solid evidence that nicotine improves cognition or core symptoms of schizophrenia (self-medication theory) [3], but the negative effect of tobacco on health is a robust finding, with patients at risk for at least twice the mortality risk if they smoked [6,7]. Meanwhile, since smoking induces the metabolic enzyme CYP1A2, blood levels of at least olanzapine and clozapine are reduced [3]. Whether this effect can be mitigated by use of vaping devices (e-cigarettes) remains to be seen [4].

It is apparent that the psychoeducational approach to smoking cessation, by itself, has not been effective among persons with serious mental illness. Indeed, cigarette use is entrenched in the culture, both among persons with schizophrenia and in recovery programs. Within the culture of some programs, there is a philosophy that patients' smoking is better than other addictions and therefore not treating it is a form of harm reduction; this is a dangerous rationalization [8,9]. There are several medication-assisted approaches to cessation that are both effective and not known to create relapse risk. These include nicotine replacement, antidepressants (for example, bupropion), varenicline, and clonidine [5].

This article focuses on the use of varenicline in smoking cessation, warnings about its use in persons with psychiatric disorders, and behavioral toxicity leading to criminal charges. Varenicline is derived from the plant *Cytisus laburnum*. An agonist at $\alpha_4\beta_2$ nicotinic acetylcholine receptors, it was used in World War II to reduce tobacco craving in soldiers [10,11]. First marketed in 2006, its proposed mechanism of action is premised on the effect of nicotine increasing production of dopamine in the terminal synapses of the nucleus accumbens [12]. Because of its partial-agonist quality, varenicline blocks withdrawal from nicotine while replacing some of the behaviorally reinforcing dopamine. Safety and efficacy of varenicline have been studied extensively, including the recent EAGLES clinical trial [13-15]. For the purpose of this mini review, the results indicated efficacy for varenicline, bupropion, and transdermal nicotine and safety in relation to use in patients with psychotic, anxiety, and mood disorders versus placebo [8]. Even so, the EAGLES authors reported serious neuropsychiatric effects in 5.9% of the 4050 subjects in the safety cohort [8].

Varenicline and behavioral toxicity

Postmarketing surveillance prompted the Food and Drug Administration (FDA) in America to report the potential for neu-

Submitted: 14 January 2020 | **Accepted:** 19 February, 2020 | **Published:** 21 February, 2020

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Citation: Weiss KJ (2020) Varenicline and Involuntary Intoxication: Forensic Implications. SM J Forensic Res Criminol 4: 5. doi: <https://dx.doi.org/10.36876/smjfr945423>



neuropsychiatric adverse effects of varenicline in 2007 [6], prompting a “boxed warning” to prescribers in 2008 [8,16,17]. Dutch authorities reported treatment-emergent psychiatric events: depressed mood, insomnia, suicidal ideation, depression, abnormal dreams, and aggression [6]. Ahmed and colleagues [6] summarized the known adverse events associated with varenicline: mania, psychosis, delirium, suicidal ideation, depression, sleep disturbances, and anxiety; aggression by itself was not mentioned. The authors concluded that while varenicline was a more effective aid to smoking cessation, there was increased risk of “serious neuropsychiatric adverse events, especially in patients with a psychiatric illness” [6, p 60]. A meta-analysis from the United Kingdom [18] examined 39 randomized trials with over 10,000 subjects. There was no increased risk found for depression, suicide or aggression among varenicline-treated participants, including those with pre-existing psychiatric illness; sleep disturbances were at increased risk.

Since serious neurotoxicity from varenicline is rare, Pfizer objected to the characterization of the drug as meriting a “boxed warning.” In 2016, the FDA demoted the labeling to “warnings and precautions” [19,20], largely on the strength of the EAGLES Trial. European regulators had rescinded the warning in May 2016 [10]. The listed potential neuropsychiatric effects, based on postmarketing reports, include: “changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide” [12].

Postmarketing surveillance was repeated more recently, examining the efficacy and safety of varenicline in subjects with schizophrenia [21]. It confirmed efficacy in reducing cigarette use among the 191 mostly male subjects, with no significant risk for neuropsychiatric adverse effects. The authors cautioned that placebo-controlled studies were lacking. A placebo-controlled study had been done with nonpsychiatric subjects [22]. The results included no significant difference in neuropsychiatric adverse events between varenicline and placebo. In a 2015 survey of the entire population of Sweden (about 8 million), nearly 70,000 were identified as having been treated with varenicline [23]. During the study period, 2006–2009, there were over 300,000 new psychiatric conditions recorded. The use of varenicline was not associated with suicidal behavior, criminal offending, traffic offenses or psychosis; the risk of anxiety was slightly increased.

Application of defenses of intoxication and insanity: A Micro-Primer

In most jurisdictions, an individual on trial for a crime may claim insanity at the time of the offense. There is no constitutional requirement in American jurisdictions for such a defense. There are variations on the details, but invariably the defendant must prove the existence of mental disease at the time in question [24]. In a successful insanity defense, the defendant will be found not guilty and subject to civil commitment. The mental disease states required are usually not specified by law, but would not include self-induced intoxication, impulse disorders, or conditions characterized by criminality. Jurisdictions, at their discretion, can

permit evidence of intoxication to lessen the severity of a crime, but they can also exclude it by law [25]. Finally, a defendant may claim involuntary or pathological intoxication. In involuntary intoxication, the defendant would claim that he or she was dosed without awareness or that a substance had an unexpected and unwanted effect on behavior. In pathological intoxication, a small amount of a substance would have caused a disproportionately large effect on behavior. In each case, since the intoxication was not brought about intentionally and the defendant can establish that the effect was that he or she did not know the act was wrong, there can be an acquittal [26].

There is rarely a “smoking gun” level of causality in criminal and civil cases. Since the arrival of fluoxetine and other SSRIs, there have been many attempts at both product liability civil lawsuits and criminal defenses suggesting that a prescription drug was causally related to violence. The evidence has been both anecdotal [27] and statistical [28], but has implicated varenicline and, to a lesser degree, SSRIs. Because each case is different, and there may have been multiple dynamics in the criminal cases, it is unusual for these matters to proceed to court, since defendants risk conviction.

Tragedy in the army

In 2008, U.S. Army Private George MacDonald, 19, visited the Army hospital and received a varenicline prescription on April 18. After a few uneventful weeks, he began to experience odd thoughts and feeling as if he was being told to kill someone, which he reported to his girlfriend on May 17 [29,30]. Then on May 18, he attacked 23-year-old Private Rick Bulmer, fatally stabbing him 50 times. The victim was initially asleep and then tried to fight off the assailant. The incident was witnessed from a distance and, while Private MacDonald tried to flee in civilian clothing, he was apprehended by another soldier and turned over to Military Police. Two days before the incident, the FDA had issued its third warning in six months about varenicline. Private MacDonald voluntarily agreed to speak with police, handwriting a statement that included (edited lightly for readability): “[I] was someone else, something was wrong...[I] didn’t even know the guy...I guess I thought I was supposed to kill this man...I want help” [21, p 10].

The defense sought reliance on involuntary intoxication, citing expert testimony “that involuntary intoxication occurs when an individual takes a prescription drug without correct warnings and is thereby not responsible for his behavior” [21, p 20]. The military judge, however, denied the motion. In a colloquy between the judge and defense counsel, it was apparent that the judge declined to stray from the military rules authored by Congress, instead relying on a misunderstanding of the difference between involuntary intoxication and the insanity defense.

Private MacDonald was convicted and sentenced, among other things, to life imprisonment without parole and loss of rank. He appealed, but the appellate court, while finding that the trial judge erred in not instructing on involuntary intoxication, considered the error harmless and affirmed the conviction and sentence. A second court in 2014 ruled that a specific defense need not be listed, but the court would still have to consider it. The court also found precedent for involuntary intoxication and,



more important, that there was reasonable doubt as to whether the absence of the proper instruction contributed to the verdict. The findings of the military court, and the sentence, were reversed and a rehearing authorized. On September 11, 2015, the press announced that Mr. MacDonald had accepted a plea offer of 45 years' imprisonment in exchange for a guilty plea to unpremeditated murder with parole eligibility [22].

Reported and decided cases

In 2011, England's *Daily Mail* [23] reported varenicline-associated violence, homicide and suicide. In America, murder-suicide in Pennsylvania eventuated in a lawsuit against Pfizer for inadequate research and notification [24]. A husband, who had been using varenicline for a week or two, went into a rage and killed his wife before killing himself. Since there was no criminal case, it is unknown whether the perpetrator would have been regarded as involuntarily intoxicated. In 2012, a federal court ruled that the manufacturer's warnings in 2009 were adequate, but that individual claims could go forward [25]. The cases, called "Chantix (Varenicline) Products Liability Litigation," were resolved without trial in North America in 2017, after the release of the EAGLES Trial data [26].

The incidence of involuntary intoxication claims made is not known. In a California matter that, like *MacDonald*, began in 2008 [27], the defendant/appellant, Mr. Motta, was found guilty of attempted murder and related offenses and sentenced to 95 years' imprisonment under a three-strikes law. His appeal issue in 2013 was about being denied a new trial and self-representation. Mr. Motta started taking varenicline in August 2008; the incident occurred in November. According to the victim, his "conduct changed and he displayed agitation, homicidal ideation, aggression, anger, paranoia, trouble sleeping, and vivid or unusual dreaming" [27]. Defense counsel wanted to argue, among other things, voluntary and/or involuntary intoxication. Mr. Motta testified that his doctor did not warn him about side effects and that he did not volunteer effects such as nightmares, irritability, aggression, and ideas of jealousy. Mr. Motta presented evidence about varenicline, but the jury also heard evidence that suggested Mr. Motta had acted voluntarily. He was convicted and then appealed. The appellate decision found that, while the evidence on varenicline was well presented, the jury simply did not accept it. Mr. Motta's appeal failed.

A Florida federal court in 2015 ruled on a homicide matter that involved varenicline; the issue on appeal, however was ineffective assistance of counsel for alleged failure to raise mental competency at trial [28]. The defendant, Mr. Prendergast, started using varenicline in late December 2006 and fatally stabbed his father, following an argument over money, in March 2007. According to Mr. Prendergast, his doctor permitted him to take two benzodiazepines, chlorthalidopoxide and lorazepam, alongside varenicline. In October 2008, he entered a plea of no contest in exchange for a 15-year prison sentence. After doing research on his own, in December 2008, Mr. Prendergast appealed, but his motion was denied because he had negotiated his own plea agreement.

In another postconviction case [29], a Texas man, Mr. Gillam, had been convicted for murder in 2010. At trial, he testified about shooting under conditions of feeling that his wife and child were threatened by the victim and that he had feelings of being a robot. He wanted a psychologist, Dr. McClung, to testify about family dynamics affecting the defendant's state of mind at the time of the shooting, but the court ruled against including the testimony in the guilt phase; he could use it as mitigation. He was convicted of murder and subjected to a sentencing trial, in which the psychologist spoke about varenicline. Mr. Gillam received a 65-year prison sentence. Further appeals were denied.

Discussion

Although the literature overall suggests that varenicline is a safe and effective agent in an approach to smoking cessation, it also includes reports of abnormal behavior that have been incorporated into the product's package insert. No immediate inferences should be made about causality in such cases, especially where there is pre-existing mental illness, since the medication is not always to blame. At minimum, clinicians and expert witnesses need to be open-minded about all permutations: that the drug in question is implicated, that an underlying mental disorder is behind the behavior, some combination, or neither [30]. Thus, the difficulty of mounting a defense of involuntary intoxication may be a deterrent to proceeding to trial, where the stakes are high. During the pretrial period of plea negotiation, it is essential that relevant and competent expert testimony be secured. That is, the connection between any substance and proffered behavioral effect must be based on science and clinical data, expressed by someone with requisite ability, typically a psychiatrist, pharmacologist/toxicologist, or both.

Involuntary intoxication defenses are complex and, at times, difficult to navigate. Several elements are involved: validating that the ingestion took place in the relevant time frame; distinguishing the person's behavior post-ingestion from what had been the norm; having a scientific explanation for the drug's effect on humans, with literature citations; verifying that the defendant was intoxicated at the time of the incident (generally via eyewitness accounts, since many defendants will have amnesia); ruling out other dynamics/causes of the mental state; concluding that the defendant was unaware of the effects and did not intend intoxication; and concluding that the defendant, due to the intoxicating effects of the drug, did not know that the behavior was wrong (wording may differ among jurisdictions).

Involuntary intoxication implies no culpability. It differs from insanity, in that future dangerousness is not implied, and from a *mens rea* approach (diminished capacity), in that it attacks *actus reus* (whether there was a voluntary act). It is technically difficult for attorneys and expert witnesses. The evidence must link the substance in question to the defendant, rule out voluntary intoxication, document the clinical sequelae, find that the defendant was intoxicated, and opine that the defendant did not know the act was wrong. Thus, it is twice as complex as an ordinary insanity defense. Clinicians must also rule out a variety of alternate causes for the behavior. The defense is difficult when the behavior is similar to past acts, when it appears the defendant is ma-



lingering, or when a mental disorder may better explain the act. In some of the cases cited above, the presence of psychotropic or recreational substances tends to cloud the picture, making the involuntary intoxication approach less likely to succeed. For these reasons, many defendants avoid raising involuntary intoxication which, like the insanity defense, by implication imputes wrongdoing to the defendant.

Finally, there is an ethical question for physicians: Given even the low risk of behavioral toxicity from varenicline, should the drug be reserved for treatment-resistant patients? In this author's opinion, no. The reason is that it is likely that continued smoking will shorten life expectancy, whereas the likelihood of extreme behavioral toxicity from varenicline (or other psychotropics) is quite small. It would be wrong for clinicians not to discuss options with the patient by taking the position that varenicline is dangerous for persons with serious mental illness. In the case of persons with schizophrenia, those with highest rates of smoking [1], the ethical consideration should shift away from potential drug side effects toward sparing the patient the serious health hazards associated with chronic tobacco use.

Conclusions

While varenicline has been associated with disastrous neuropsychiatric sequelae, instances of acute behavioral toxicity are unusual. This small possibility should not deter prescribers from using varenicline in smoking cessation, even among psychiatric patients, since the health hazards of smoking are greater. Criminal defenses of involuntary intoxication are difficult to mount, and the distinction from voluntary intoxication often misunderstood. However, forensic psychiatrists must be prepared to include this condition when assessing otherwise unaccountable violence to self or others. Defense attorneys must be sure that the trial judge instructs the jury on involuntary (pathological) intoxication, a complete defense, and that it is distinguished from voluntary intoxication and from an insanity defense based on mental illness.

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