

## Substance Abuse

## Thoughts and Acts of Aggression/Violence Toward Others Reported in Association with Varenicline

Thomas J Moore, Joseph Glenmullen, and Curt D Furberg

Varenicline was approved by the Food and Drug Administration (FDA) in May 2006 as an aid to smoking cessation treatment.<sup>1</sup> The drug binds as a partial agonist to the  $\alpha 4\beta 2$  subtype of nicotinic acetylcholine receptors on neurons.<sup>2</sup> This is posited to have 2 effects: to reduce the craving for nicotine through causing the release of dopamine and to reduce the rewards of nicotine stimulation because the drug already occupies many nicotinic receptors.<sup>2</sup> Treatment is initiated through a 7-day program of dose titration that begins at 0.5 mg/day and escalates to 1 mg twice daily. On day 8 the patient is advised to quit smoking and take varenicline 1 mg twice daily for a total of 12 weeks; an additional 12 weeks of treatment may be considered for successful quitters.<sup>1</sup>

Public concern about possible psychiatric adverse effects of varenicline began with a highly publicized episode in which a Dallas musician taking varenicline exhibited bizarre and aggressive behavior after an evening of drinking and was shot dead while trying to kick in the door of a girlfriend's neighbor.<sup>3</sup> An increasing number of adverse drug event reports about serious psychiatric adverse effects led to an escalating series of FDA regulatory actions that included an "Early Communication" of a possible risk, 2 public health advisories, a requirement for a Risk Evaluation and Management Strategy, a

**BACKGROUND:** Thoughts and acts of aggression/violence toward others have been reported in postmarketing surveillance of varenicline, an aid to smoking cessation.

**OBJECTIVE:** To identify the common characteristics of these thoughts and acts of aggression/violence toward others and assess the likely relationship to varenicline treatment.

**METHODS:** We obtained 78 adverse event reports from the Food and Drug Administration MedWatch database containing medical terms describing possible acts or thoughts of aggression/violence; 4 additional cases were reported in clinical trials, and 3 others came from the published literature. We used psychiatric diagnostic criteria and an adverse event causality assessment tool to identify 26 case reports for study.

**RESULTS:** The selected cases described 10 events with assault, 9 cases of homicidal ideation, and 7 cases of other thoughts or acts of aggression/violence. The most frequent common characteristics were (1) inexplicable and unprovoked event, (2) the victim was anyone nearby, (3) no indication of a prior history of similar behavior in the patient, and (4) early onset of psychiatric adverse effects, often before stopping smoking. Where dechallenge/rechallenge information was available, psychiatric adverse effects resolved in 13/14 (93%) cases after discontinuation.

**CONCLUSIONS:** The clear temporal relationship, lack of prior history of this behavior, and unusual nature of these events strengthens the accumulating scientific evidence that varenicline is associated with thoughts and acts of aggression/violence. We recommend that physicians and pharmacists ensure that all patients are informed of possible psychiatric symptoms of varenicline, including violent and aggressive thoughts. All patients should be advised to contact a health-care provider immediately if these symptoms occur and varenicline should be discontinued without delay.

**KEY WORDS:** adverse drug effects, nicotonic agonists, varenicline.

*Ann Pharmacother* 2010;44:xxxx.

Published Online, 20 Jul 2010, *theannals.com*, DOI 10.1345/aph.1P172

mandatory Medication Guide to be given to every patient, and a boxed warning on the product package insert.<sup>4-9</sup> While the boxed warning focuses primarily on suicidal behaviors, the warnings section of the varenicline prescribing information also indicates that postmarketing reports have included

Author information provided at end of text.

“psychosis, hallucinations, paranoia, delusions, homicidal ideation, anxiety and panic...”<sup>1</sup>

Given that little is known about the characteristics of aggression/violence events associated with prescription drugs, the varenicline reports from postmarketing surveillance provided an opportunity to study this poorly understood adverse drug event. In this study we examined a series of case reports to identify the common characteristics of these events and assess the likely relationship to varenicline treatment.

## Methods

From the FDA we obtained 78 full-text MedWatch reports of adverse drug events that identified varenicline as the principal suspect drug, and which contained standardized medical terms suggesting possible acts and thoughts of aggression or violence. We also collected 3 case reports from the published scientific literature using a MEDLINE search with the MeSH terms varenicline and case reports, and identified 4 additional case reports of serious psychiatric adverse effects reported during the pre-approval clinical trials.<sup>10</sup>

Two of us reviewed the 85 case reports according to the following selection criteria: each case report had to qualify for a clinical diagnosis of substance intoxication.<sup>11</sup> The diagnosis had to describe reversible behavioral or psychological changes associated with recent ingestion of a substance—in our case, specifically the drug varenicline. Furthermore, each report had to meet the criteria for possible, likely, or certain association with the drug according to the World Health Organization (WHO) causality criteria for assessing the weight of adverse drug event case reports.<sup>12</sup> In addition, we eliminated cases that indicated an act of aggression/violence (for example, gunshot wound) only directed toward self but not others. Reports of suicides and attempts were allowed if there were also indications of aggression, anger, or violence directed toward others. Finally, the case reports had to include sufficient detail to make a determination according to these criteria. One reviewer (JG) examined the cases primarily from the perspective of the *Diagnostic and Statistical Manual of Mental Disorders* psychiatric criteria,<sup>11</sup> while the other (TJM) focused on the WHO causality criteria. The reviewers had to agree on all cases.

We measured 2 different forms of event onset. Each report was evaluated for the number of days from the initiation of therapy to initial onset of any reported psychiatric adverse effects, including nightmares, sleep disturbances, anger, or irritability. Cases were also evaluated for the number of days until the index event of aggression/violence toward others. Each case was examined for information about medication status—whether disturbing psychiatric symptoms resolved on discontinuation (dechallenge) or if they reappeared when medication was restarted (rechallenge).

From the reports available 2 of us agreed that 26 cases met all the criteria. The most common reasons for exclusion were violence limited to suicidal behaviors, alternative causation, consumption of large quantities of alcohol, and insufficient detail.

## Results

The case series included 20 females (77%) and 6 males (23%) with a mean  $\pm$  SD age of  $41.1 \pm 11.5$  years. The events reported included 10 assaults, 9 cases of homicidal ideation without a physical act of aggression, and 7 cases of violent or aggressive thoughts that were not specifically homicidal. In addition, 3 cases ended in suicide and 4 cases included a suicide attempt. Under the causality criteria 18 of 26 cases were classified as probable association and 8 cases as possible association. In 7 of 8 cases of possible association the reason for the lesser classification was missing information about what happened after discontinuation. Essential features of each case are listed in Table 1. The common characteristics identified are summarized in Table 2.

### INEXPLICABLE AND UNPROVOKED ACTS

In all 26 cases, the acts or thoughts of violence appeared to be inexplicable and unprovoked. A woman struck her 17-year-old daughter in the mouth while the daughter was driving a car, with a young granddaughter also present (case 19). A 42-year-old man punched a stranger at a bowling alley (case 3). The stranger and 2 friends responded and knocked out the subject's front teeth. A 24-year-old female started beating her boyfriend in bed because he “looked so peaceful” and she later attempted suicide (case 1). A 29-year-old female struck an acquaintance twice in the face, and then started smashing doors in her own home and beating on her truck (case 21).

The actual or intended victims of aggression/violence were anyone who happened to be nearby. Frequently this included a boyfriend, fiancée, daughter, or husband, but also included neighbors, a policeman, an acquaintance, coworkers, and strangers who happened to be in the same place.

### NO PRIOR HISTORY OF AGGRESSION/VIOLENCE

In 24 of 26 cases there was no indication of any prior history of a similar event and many explicitly indicated the behavior was out of character. In the 2 exceptions both patients had a previous stable history of bipolar illness. In 12 cases the report contained language specifically stating this behavior was unusual: “Meltdown at work—which is totally not me” (case 5), “Completely out of character” (case 12), “He never acted this way before” (case 2), “It wasn't me at all during the time I was taking the drug” (case 11).

Uncontrollable rage was explicitly described in 16 of 26 cases: “I was completely out of control” (case 1), “I have no control over my emotions” (case 3), “She tried to stop her behavior but had no control” (case 17), “She called me at 3 AM in the morning screaming at me and cursing” (case 12), “She couldn’t control the rage” (case 21).

#### EARLY ONSET OF PSYCHIATRIC ADVERSE EFFECTS

Initial symptom onset data were available for 18/26 cases. Initial onset occurred in a median of 2 days (range 1–14). In 9 of 18 (50%) cases where information was available the onset began with or soon after the first 0.5-mg dose. The most common initial adverse effects were nightmare, abnormal dreams, or other sleep disruption.

Nightmares and sleep disturbances were reported in 17 of 26 (65.4%) cases. In 2 cases (cases 1, 23) an assault occurred immediately as a person awakened; another case involved sleepwalking (case 7). Others reported “kicking

and screaming in sleep” (case 16) or “itching and crawling as if feet would not stop moving” that resolved by morning (case 20). A mental health professional reported a vivid dream in which a close relative suddenly appeared in a cooking pan. “I saw her side that was in the pan as brown and crispy, leg dragging, while the other side was bright pink and functioning” (case 4).

Index event onset had greater variation, and ranged from a minimum of 3 days to a maximum of 42 days, a mean of  $15 \pm 12$  days. In 3 cases the patient continued to take the drug for 4–9 weeks, with no specific event date being identified.

#### MEDICATION STATUS

Dechallenge information was available for 11 cases; in 10 of 11 (91%) the symptoms resolved within a few days after discontinuation. In 1 case the symptoms had improved but not fully resolved at the time of the report (case 21).

**Table 1.** Features of Reported Adverse Events Associated with Varenicline

Case No.	Sex/ Age (y)	Medication Status	Symptom Onset (days)	Event Onset (days)	Event Summary
1	F/24	Dechallenge	3	10	Woke up boyfriend, started beating him, attempted suicide
2	M/45	Died	Not stated	30	Agitated, angry acts that pt. could not control; hung self in closet
3	M/42	Still taking	Not stated	42	Punched a stranger at a bowling alley
4	F/Not stated	Rechallenge	1	8	Bizarre nightmares, suicidal, homicidal thoughts, state of rage
5	F/48	Dechallenge	1	30	Irrational and aggressive thoughts, meltdown at work, crying in closet
6	F/28	Dechallenge	Not stated	14	Uncontrollable rage, beat boyfriend, suicide attempt; alcohol consumption earlier
7	F/Not stated	Not stated	14	42	Nightmares, mood swings, attacked fiancé with knife
8	F/67	Dechallenge	Not stated	(during 30 days)	Very aggressive, irritable, mood swings, very nervous
9	F/21	Dechallenge	1	14	Threatened mother with shotgun, locked self in bathroom
10	M/27	Dechallenge	1	4	Became aggressive and odd; attempted to kill self with shotgun but survived
11	F/55	Rechallenge	1	(took 8– 9 wks)	Nightmares, anger and depression; felt would kill someone
12	F/Not stated	Not stated	7	7	Punched policeman, threatened others
13	F/47	Died	7	30	Started hitting daughters, came out of room, yelled at them, and shot self
14	F/40	Dechallenge	1	5	Depression, anger, suicidal thoughts, violent thoughts
15	F/43	Dechallenge	1	12	Wanted to get key to gun cabinet to shoot husband
16	F/44	Not stated	2	6	Screaming and kicking in sleep; suicidal, feared might attack boyfriend with axe
17	F/54	Not stated	Not stated	7	Became violent and wanted to kill someone
18	F/Not stated	Dechallenge	Not stated	(took for 60 days)	Wanted to run off porch and hit neighbors in the face and start killing them
19	F/Not stated	Not stated	7	13	Gave fat lip to 17-year-old daughter while driving her car; rage uncontrollable
20	F/43	Still taking	1	7	Uncontrolled extreme irritation, felt could kill someone and have no remorse
21	F/29	Not resolved	14	21	Beat her friend, broke doors in own home, beat on side of truck
22	M/46	Dechallenge	1	3	Had crazy thoughts of killing himself and his parents
23	M/31	Not stated	Not stated	7	Got up from dead sleep, assaulted someone, had mood changes, went “ballistic”
24	M/Not stated	Died	4	8	Choked his wife in fit of rage and hung himself
25	F/41	Rechallenge	3	21 (after restart)	Irritable, angry, 2 hours’ sleep, fight with husband, suicidal gesture
26	F/46	Not stated	Not stated	7	Confronting colleagues at work, turning over furniture

Rechallenge was reported in 3 cases (cases 4, 11, 25). In all 3, symptoms reappeared when the drug was restarted, and resolved again after discontinuation. For cases without dechallenge/rechallenge information, 3 ended in suicide, 2 patients continued to take the drug, and in 7 cases discontinuation information was unavailable.

#### ADDITIONAL CHARACTERISTICS

Two additional characteristics of aggression/violence events appeared in a minority of cases, but were of interest. In 4 cases it appeared the patients understood a significant loss of control had occurred, and they took precautions. A woman experiencing repeated thoughts of homicide sent her young daughter to live with her sister for a month because “she was afraid she was going to do something wrong to the little girl she loves so much” (case 18). The woman who had struck her 17-year-old daughter in the face with the granddaughter present (case 19) sent the granddaughter the next day “to live with the father because she was afraid she would hurt her.” In a third case, a mental health professional who managed a clinic remained at home and did not talk to her employees because of her personality change (case 4), and in the fourth case a 42-year-old-male simply remained at home because he feared he would strike another stranger (case 3). Suicidal thoughts and acts frequently accompanied violent thoughts and acts involving others. The case series included 3 completed suicides (cases 2, 13, 24), 3 attempts or gestures (cases 1, 10, 25), and 5 cases of suicidal and homicidal or violent thoughts occurring together (cases 4, 14, 16, 21, 22).

Four of 26 cases involved some indication of previous or newly developing psychiatric illness. One patient had been taking sertraline for depression (case 7), another reported ongoing treatment for posttraumatic stress syndrome (case 10), 1 case mentioned a patient with bipolar illness whose condition was stable for 22 years (case 12), and 1 was in active treatment for bipolar disorder II of unspecified duration (case 25). In addition, in 1 case the pa-

tient had no history or treatment of any previous mental disorder, but after the violent episode was thought to have had auditory hallucinations prior to treatment (case 26).

#### Discussion

These data contain several characteristics that add scientific weight to the accumulating evidence that varenicline is associated with unprovoked acts and thoughts of aggression/violence toward others. The temporal relationship evidence was strong, with an early and often immediate onset of abnormal dreams and thoughts, and the adverse effects usually resolved with discontinuation of treatment. In the 3 rechallenge cases, the adverse effects reappeared (often in more severe form) when the drug was restarted and disappeared when the drug was stopped again. The patient population of predominantly middle-aged women was typical of those who are trying to quit smoking with varenicline but is an unlikely age group and sex for assault and acts of violence toward others.

This study also has limitations that should be considered in interpreting these findings. A case series is always vulnerable to both conscious and subconscious bias. We sought to minimize this potential through the use of formal published diagnostic and selection criteria. These cases were uncomplicated by prior behavior and most patients were taking no concomitant medication. While the lack of complications made them suitable for analysis, these cases may not be typical of the larger population of adverse events involving thoughts and acts of aggression/violence. For example, the FDA concluded that in 2007 nearly 40% of patients taking varenicline were also taking antidepressants, antipsychotics, or tranquilizers.<sup>13</sup> Varenicline could be more or less likely to be associated with an adverse event in patients on concomitant medication. Finally, this study provides no information into how frequently such events may occur.

An additional question is whether these acts might be part of a withdrawal syndrome from stopping smoking rather than an effect of varenicline. We believe this is unlikely for 2 reasons. In this study the initial onset of adverse effects in 16/18 (89%) patients occurred in the first week of treatment before the patients reached a target quit date. Also, in our quantitative studies of MedWatch reports, these events were rarely seen in the similar quit-smoking population using nicotine replacement products.<sup>14,15</sup>

It appears likely that these events occur typically in a relatively small and susceptible population that is affected early. Many of these patients reported initial psychiatric adverse effects prior to reaching the full prescribed dose, often before stopping smoking. In addition, there was a suggestion of a cumulative dose effect over time, with the psychiatric symptoms worsening. However, insufficient data are available to support a hypothesis about what underly-

**Table 2.** Common Characteristics of Reported Adverse Events

Characteristic	Cases/ Observed, n (%)
Inexplicable and unprovoked act	26/26 (100)
Victim anyone nearby	26/26 (100)
Symptoms within first week of treatment	16/18 (89)
No prior history	24/26 (92)
Resolved on discontinuation	13/14 (93)
Nightmares, sleep disturbances	17/26 (65)
Uncontrollable rage explicitly stated	16/26 (62)
Aggression/violence to both self and others	11/26 (42)

ing characteristics might render patients vulnerable to this syndrome.

It will be difficult to study this phenomenon using more systematic data. While serious psychiatric adverse effects did occur during the clinical trials of varenicline, we agree with the FDA's conclusion that the design limitations of completed clinical trials rendered them incapable of either ruling in or ruling out such an effect.<sup>13,16</sup> Insurance claims and medical record databases are unlikely to include systematic information about violent thoughts and acts toward others that would permit a useful estimate of incidence. Therefore, a well-designed case-control study appears to be the most feasible approach.

We recommend that physicians and pharmacists ensure that all patients are informed of possible psychiatric symptoms of varenicline—including violent and aggressive thoughts—as described in the mandatory patient medication guide.<sup>4</sup> All patients should be advised to contact a health-care provider immediately if these symptoms occur and varenicline should be discontinued without delay.

**Thomas J Moore** AB, Senior Scientist, Institute for Safe Medication Practices, Horsham, PA

**Joseph Glenmullen** MD, Clinical Instructor in Psychiatry, Department of Psychiatry, Cambridge Hospital, Harvard Medical School, Cambridge, MA

**Curt D Furberg** MD PhD, Professor, Division of Public Health Sciences, School of Medicine, Wake Forest University, Winston-Salem, NC

**Correspondence:** Mr. Moore, [tmoores@ismp.org](mailto:tmoores@ismp.org)

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**Conflict of interest:** A portion of the research for this study was performed under consulting contracts by Mr. Moore and Dr. Glenmullen with the US Army Trial Defense Service in connection with expert testimony in a criminal case. The Army had no involvement in the conduct, design, or conclusions reached in this study. Dr. Glenmullen has been retained as a potential consultant in legal cases involving varenicline.

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