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Extinction Burst after Varenicline Titration: A Case Report

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Background: The mechanism of action of varenicline as a partial agonist may make it useful for cigarette reduction as smokers experience reduced craving and withdrawal at the same time their cigarettes provide reduced reinforcement value.

Case Description: The current case report describes a 51-year-old African American woman using varenicline to reduce her cigarette use. After making a substantial reduction in cigarettes per day (from 25 to 8), the patient unexpectedly began smoking considerably more (from 8 to 20) after 11 days treatment with varenicline.

Conclusions: The temporary increase in smoking while taking varenicline was likely the result of an 'extinction burst' where the extinction of a reward (e.g., nicotine's rewarding effects after smoking a cigarette) was temporarily associated with an increase in the behaviour usually associated with the reward (e.g., smoking a cigarette). Once explaining to her that no amount of cigarettes would overcome the feeling of reduced reward she likely felt while taking varenicline, she was able to reduce her smoking again.

Keywords: varenicline, tobacco, cigarette, cessation, extinction burst

Varenicline is the newest of the federally approved medications for smoking cessation, after being approved by the US Federal Drug Administration (FDA) and the UK National Institute for Health and Clinical Excellence (NICE) in 2006. Varenicline's partial agonist effects at $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors (nAChRs) facilitate withdrawal and craving relief by activating the receptor and causing the release of some dopamine in the nucleus accumbens, although less than from nicotine. With a strong affinity for the receptor, varenicline also acts like an antagonist and therefore is able to block nicotine's effect on dopamine release and reward (Coe et al., 2005). These mechanisms of action may make varenicline especially useful for not only quitting smoking, but for cigarette reduction as smokers experience reduced craving and withdrawal at the same time their cigarettes provide reduced reinforcement value. In fact, some very preliminary evidence indicates that individuals taking varenicline may reduce cigarettes per day even without instructions to do so (Ashare et al., 2012).

Because varenicline can partially block nicotine's reinforcing effects on dopamine release in the nucleus accumbens, smoking behaviour may be reduced or eliminated as the smoking behaviour no longer results in the desired reward. Operant conditioning paradigms (Skinner, 1933, 1934, 1938) refer to this reduction or elimination of a behaviour as 'extinction.' Extinction occurs when the reinforcement (e.g., nicotine's pleasurable effects) is removed from a previously reinforced behaviour (e.g., cigarette smoking). Paradoxically, when the reinforcement (e.g., nicotine's pleasurable effect) is first removed, it may result in a temporary increase in the frequency or intensity of the behaviour in question (e.g., cigarette puffing). This temporary increase is called an 'extinction burst' (Cooper, Heron, & Heward, 1987; Skinner, 1983). An extinction burst effect for nicotine self-administration has been observed under certain conditions in rodents (e.g., Harris, Pentel, & Lesage, 2007) and in humans (MacQueen, Heckman, Blank, Van Rensburg, Evans, & Drobes, 2012). A review of studies in which extinction was used as a treatment for behaviour disorders in humans found that an extinction burst only occurred in 12% of the cases in which extinction procedures were implemented in conjunction with other procedures (Lerman & Iwata, 1995).

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Case Description

We report the case of a 51-year-old, divorced African American woman (Ms. F) seeking treatment as part of a research study recruiting smokers who were 'not yet ready to quit, but willing to cut down.' The study was a double-blind, placebo controlled trial of varenicline for smoking reduction which included four weekly therapy sessions. As part of the IRB approved study, Ms. F provided written informed consent for participation. Ms. F had been smoking daily since the age of 15 and had made multiple quit attempts in her life using several different approaches, including behavioural therapy, the nicotine patch, nicotine nasal spray, nicotine lozenge, and hypnosis. She also tried quitting unassisted but had not previously used varenicline. Her longest ever quit attempt lasted for six months. At intake, Ms. F reported smoking 25 cigarettes per day and was highly nicotine dependent (Fagerstrom, Heatherton, & Kozlowski, 1990) based on a score of 6 on the Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). While she recognised the importance of quitting smoking, she had fairly poor self-efficacy for quitting as evidenced by a score of 38 (indicating being very tempted to smoke in a variety of situations) on the Self-Efficacy/Temptation Scale Short Form (Velicer, DiClemente, Rossi, & Prochaska, 1990). She was confident, however, that she could reduce the number of cigarettes she smoked per day. Ms. F denied current use of alcohol or illicit drugs and did not present with depressive or other psychiatric symptoms. Her scores on empirically supported self-report measures of depression and recent substance use were consistent with her verbal reports (Beck Depression Inventory-II = 6; Alcohol Use Disorders Identification Test = 0; Drug Abuse Screening Test = 0).

The research study in which Ms. F was enrolled included four therapy sessions conducted within the spirit of Motivational Interviewing (Miller & Rollnick, 2002) and included empirically supported behavioural strategies (Fiore, Jaen, Baker, et al., 2008). As part of the trial, Ms. F was told that she would be randomised to receive a 28-day regiment of varenicline or placebo. At the conclusion of each session, Ms. F was encouraged to pick a goal for the following week with respect to number of cigarettes per day. Mrs. F. was encouraged to try to reach a 50% reduction by end-of-treatment, but her only weekly instructions were for her to choose a goal that felt achievable, but challenging. She was also asked to monitor and record her cigarette intake daily.

Ms. F. began taking varenicline according to the package insert instructions (0.5 mg QD on days 1–3, 0.5 mg BID on days 4–7, and 1 mg BID after day 8) on the day after intake and continued at 1mg BID until day 28 at which time varenicline was discontinued. By day 8, Ms. F reported being able to reduce her smoking to eight cigarettes per day (compared to 25 cigarettes per day at intake). Ironically, she reported that she was 'very sure' that she was assigned to the placebo condition and attributed her ability to reduce her smoking to high motivation. She denied medication side effects or significant nicotine withdrawal symptoms at this time. By her next counselling session (day 14 of varenicline treatment), Ms. F reported returning to near baseline levels of smoking, having 20 cigarettes per day on days 11 through 14. She described the cigarettes as feeling 'light' and explained that the cigarettes didn't have their usual 'kick.' Upon further discussion, her therapist (MLS) hypothesised that if she were, indeed, taking varenicline rather than placebo, that the increase in smoking corresponded to when she received the full dose of varenicline which perhaps was blocking her usual feeling of reward associated with smoking. Her increase in smoking behaviour at that time may have represented an attempt to compensate for the reduced reward she may have experienced from smoking while taking varenicline, a partial agonist. Ms. F accepted this hypothesis as a reasonable explanation and was willing to try to reduce her smoking again.

At the following appointment on Day 21, she was able to reduce her smoking to 8 cigarettes per day. By the end of the 28 days of varenicline, Ms. F was smoking only two cigarettes per day and maintained this level until day 35. Ms. F's score of 0 on the FTND indicated very low (Fagerstrom et al., 1990) nicotine dependence from end-of-treatment and for the following five months although she continued to smoke very low amounts (< 2 cpd). Her motivation to eventually quit was high at the 6-month assessment point, and perhaps more importantly, Ms. F's demonstrated a substantial increase in self-efficacy for quitting which was maintained for the following five months. Ms. F's depression and negative affect scores remained low during the 6-month follow-up period. In conclusion, Ms. F exceeded her goal of reducing her cigarette intake by at least 50% and remained motivated and confident that she would be able to go beyond this reduction and actually quit, thus greatly improving her chances of avoiding substantial tobacco related harm. After the study was unblinded, it was revealed that Ms. F had, in fact, been randomised to receive varenicline (though neither she nor her therapist (MLS) was aware of this fact during the trial or therapy sessions.

Conclusions

Our report describes a rare case of increased smoking in response to varenicline treatment. Clinicians should note the possibility that varenicline's partial agonist properties could produce a situation in which patients seek the reward from their cigarettes despite reduced reinforcement from nicotine. In the case presented here, Ms. F seemed to be trying harder to obtain reinforcement from her cigarettes by smoking additional cigarettes when she didn't get the level of reinforcement to which she was accustomed. This phenomenon can be described by an

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'extinction burst' (Cooper et al., 1987; Skinner, 1938) in which humans and animals actually increase their rate of responding to a once reinforcing stimulus. In an operant conditioning framework, Ms. F can be said to have engaged in the behaviour of puffing on a cigarette to get the reinforcing effects of nicotine. Once on varenicline treatment for 11 days, Ms. F no longer felt reinforced by puffing on a cigarette because varenicline partially blocked nicotine's reinforcing effects. Because Ms. F was accustomed to being reinforced with nicotine every time she puffed on a cigarette, she began puffing on additional cigarettes in an attempt to receive the reward she was accustomed to receiving. While an extinction burst is certainly the most parsimonious explanation for Ms. F's increased smoking on day 11, it is also possible that she simply had an unrelated slip.

The fact that Ms. F did not experience the extinction burst until day 11 is consistent with data suggesting that varenicline's effect may take longer to emerge than suggested by the current varenicline labelling (Hajek, McRobbie, Myers, Stapleton, & Dhanji, 2011; Hawk et al., 2012). While steady-state conditions are reached within four days of titrating up to 1mg bid (Pfizer Laboratories, 2011) (i.e., day 8), the full effect on reinforcement may not occur until later.

While rare, it is important for clinicians to be aware of the possibility of extinction burst in their patients taking varenicline. In the case described above, a simple reminder regarding varenicline's properties and the phenomenon of extinction burst worked as a cognitive 'reframe' of the patient's experience. She recognised that smoking additional cigarettes and smoking more intensely was unlikely to produce the desired effects and this realisation made it easier for her to resist smoking additional cigarettes.

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Conflict of interest

Both authors (MLS and JMW) have received unrestricted educational grants and research grant support from Pfizer. MLS received funding for a Global Research Award for Nicotine Dependence, an independent, competitive grants programme sponsored by Pfizer.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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