t is illegal to post this copyrighted PDF on any website. Varenicline Use for Cocaine Dependence

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Cocaine addiction is an important public health issue worldwide and has severe costs for both the individual and society at large. Cocaine is a psychoactive substance that causes its so-called high by the buildup of dopamine in the brain centers, especially the limbic system, which is the center for regulating pleasure and motivation.¹ Although the effects of cocaine make it an addictive substance, half of a person's risk of addiction has been found to be genetic,^{2,3} but the genes responsible have yet to be determined. To date, most medications for cocaine addiction have focused more on suppressing its effects, including the cocaine "vaccines."¹

Varenicline was approved by the US Food and Drug Administration (FDA) in 2006 for the treatment of nicotine dependence. It has shown efficacy as a treatment for smoking cessation^{4,5} and prevention of relapse.^{6,7} Varenicline is a partial agonist at the $\alpha 4\beta 2$ nicotinic acetylcholine (ACh) receptors⁸ and a full agonist at the α7 nicotinic receptor.^{4,5} The α4β2 nicotinic ACh receptors facilitate the dopaminereleasing effects of nicotine in the nucleus accumbens, a key component of the reward circuit⁴ in the limbic area of the brain. These outcomes led researchers to postulate that the drug might be helpful in the treatment of cocaine addiction.¹ Varenicline, as suggested by evidence, also acts as a partial agonist at a6b2* nicotinic ACh receptors in both rat and monkey striatal synaptosomes.⁹ The importance of a6b2* nicotinic ACh receptors in regulating dopamine release is increasingly acknowledged.¹⁰

To date, a few trials have been conducted to assess the efficacy of varenicline in cocaine dependence with mixed results. These studies had limitations, which the authors highlighted, but none were large-scale studies with hundreds of participants; hence, the evidence should be taken with a grain of salt.

A pilot study conducted in 2010 by Poling et al¹¹ found no significant differences in the efficacy of varenicline in reducing cocaine use compared to placebo in patients on methadone maintenance and at the time smoking nicotine. The study had a small sample size of 31 participants, which the authors¹¹ mentioned as a limitation. In contrast, Plebani and colleagues¹² in 2012 demonstrated opposite findings, as

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they suggested a small to moderate efficacy of varenicline in cocaine dependence. They also measured cocaine reinforcement with the use of varenicline, which showed a significant improvement compared to placebo. However, their study¹² also had a major limitation of a small sample size of only 37 participants.

An animal study¹⁰ conducted in 2014 with 6 rhesus monkeys assessed the effects of chronic varenicline treatment on self-administered nicotine, cocaine, and nicotine and cocaine combined. The results showed that varenicline had no effect on cocaine alone self-administration, but the nicotine alone group and high-dose nicotine with cocaine group showed a statistically significant decrease in selfadministration. The finding that varenicline did not decrease cocaine use was in accordance with that of Poling et al¹¹ in human participants and in an animal study¹³ conducted in 2011.

A recently published 12-week, double-blind, placebocontrolled study¹⁴ of 156 subjects with cocaine dependence receiving varenicline showed little difference in cocaine craving and abstinence in the participants, which indicates that varenicline might not be as effective for treating cocaine dependence as it is in the treatment of nicotine dependence. None of the studies referenced here reported any side effects of varenicline, and all stated it was well tolerated.

Varenicline is an FDA-approved drug for the treatment of nicotine dependence. It has been shown to be well tolerated and efficacious in nicotine-dependent patients. But the results of clinical trials and preclinical trials to date on cocaine dependence are mixed. Most of the studies show a nonsignificant difference in the efficacy of varenicline, with few demonstrating that it can be a viable option. Studies in rhesus monkeys suggest that it might be useful for smokers with low-dose cocaine dependence, but none outright prove its efficacy. No large, controlled trial exists to date, and until one is conducted, varenicline should be used with caution in cocaine-dependent patients.

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