

Review article

Varenicline for smoking cessation: a review

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Abstract

Tobacco use is the leading cause of preventable death and disability in the world. Although gradually declining in most developed countries, the prevalence of tobacco use has increased among developing countries. Nicotine is an addictive chemical that is inhaled from the tobacco present in the cigarettes. It acts on neuronal nicotinic acetylcholine receptors within the ventral tegmental area of the brain, causing dopamine release in the nucleus accumbens which reinforces nicotine-seeking behavior. Reward through the dopaminergic system is a common thread among many drugs of addiction. According to the National Anti-Tobacco Communication Campaign Strategy for Nepal smoking prevalence in Nepal is higher (38.4%) than the smoking prevalence in the world (29%). Smoking attributable annual deaths in Nepal is estimated at nearly 14,000 (9,000 male deaths and 5,000 female deaths) for population aged 35 and over. First-line pharmacotherapies for smoking cessation are varenicline, sustained-release bupropion and various forms of nicotine replacement therapy (i.e., patch, gum, lozenge, inhaler, nasal spray). These drugs can be used as monotherapy or combination therapy for the treatment of smoking cessation. After studying the outcome of many clinical trials and meta-analysis, it is concluded that cigarette smokers taking varenicline have the most success quitting smoking as compared with those taking other first-line pharmacotherapies for treating smoking cessation.

Keywords: nicotine replacement therapy, varenicline

Introduction

Cigarette smoking is one of the leading causes of preventable death and disability in the world. It is the single most important modifiable risk factor for cardiovascular, respiratory and cerebrovascular diseases, and cancer. Globally there are 1.3 billion smokers, and the majority of these are from developing countries.¹ The use of tobacco kills nearly six million people a year. More than five million of those deaths are the result of direct tobacco use while more than 600000 are the result of non-smokers being exposed to second-hand smoke. Unchecked,

tobacco-related deaths will increase to more than eight million per year by 2030.²

Although gradually declining in most developed countries, the prevalence of tobacco use has increased among developing countries.³ The smoking prevalence in Nepal is 31.6% which is higher than that of the world.⁴ Smoking attributable annual deaths for Nepal is estimated at nearly 14,000 (9,000 male deaths and 5,000 female deaths) for population aged 35 and over.⁵

Addictive nature of nicotine

Nicotine is an addictive chemical that is inhaled from the tobacco in cigarettes, bidi, hukka and chilim or kankad. It gets into the bloodstream, readily penetrates the blood-brain barrier and reaches the brain. It subsequently acts on

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neuronal nicotinic acetylcholine receptors within the ventral tegmental area of the brain, causing dopamine release in the nucleus accumbens which reinforces nicotine-seeking behavior.⁶ Reward through the dopaminergic system is a common thread among many drugs of addiction.⁷ Nicotine is the primary factor in continued and compulsive smoking. The important factors that both reinforce continued smoking and prevent smokers from achieving sustained abstinence from smoking are its pleasurable effects (e.g., arousal and relief of anxiety), its association with the pleasurable effects with environmental triggers (e.g., after meals, with morning coffee, and during periods of stress), and the presence of craving and other uncomfortable symptoms of nicotine withdrawal with the cessation of tobacco use. Most regular smokers are addicted to nicotine; when its blood level falls, the smokers usually develop withdrawal symptoms such as restlessness, increased appetite, inability to concentrate, irritability, dizziness, insomnia, constipation and craving for nicotine. These symptoms begin within a few hours after having the last cigarette. If they are not relieved by the next cigarette, withdrawal symptoms get worse.^{8,9} Therefore most smokers smoke regularly to prevent withdrawal symptoms. The main reason why so few smokers succeed, even though they want to stop smoking, is that nicotine addiction pathway in the brain is very strong and difficult to break.

Pharmacotherapy of smoking cessation

Intervention for smoking cessation has become an urgent need because of increasing tobacco use and health hazards, especially in developing countries. The first line pharmacologic management for smoking cessation is nicotine replacement therapy (NRT), bupropion and varenicline and second-line are clonidine and nortriptyline. Currently there are five forms of NRT and they are nicotine patch, gum, lozenge, inhaler and nasal spray. These first-line drugs are approved by the US Food and Drug

Administration (FDA) for smoking cessation.^{3,10} However, the second-line treatments have not been approved for smoking cessation by the FDA.¹¹

NRT is the best-documented and oldest drugs used for smoking cessation.^{12,13} Lower nicotine levels are reached in blood with NRT compared to smoking. Therefore, the high peak plasma levels of nicotine reached during smoking are not achieved with NRT and this is the main reason why these products are not as effective as "cigarettes" regarding effects on craving and urge.^{14,15} Bupropion is another first-line drug approved for smoking cessation. It is an atypical antidepressant and it inhibits the reuptake of both dopamine and norepinephrine in the central nervous system.¹⁶ Its dopaminergic activity on the pleasure and reward pathways in the mesolimbic system and the nucleus accumbens could explain its success in reducing nicotine craving and the symptoms of withdrawal. It may also function as a nicotine acetylcholine receptor antagonist, which may be critical for smoking cessation.¹⁷

Pharmacodynamic effects of varenicline

Varenicline is a partial agonist at $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype.^{18,19} After binding to its receptor, it stimulates the release of small amounts of dopamine. The released dopamine reduces nicotine withdrawal symptoms. In addition, varenicline has an antagonistic effect. By blocking the nicotine from binding to its receptor, it also reduces the rewarding aspects of nicotine.

Clinical studies

Many clinical trials indicate that varenicline is an effective aid to smoking cessation. During the last four weeks of treatment, carbon monoxide-confirmed continuous abstinence rates were generally significantly higher with varenicline than with placebo, bupropion sustained release or NRT. Varenicline also reduced cravings, the reinforcing effects of smoking and some

withdrawal symptoms.⁶ Varenicline also appears to be more efficacious than nicotine replacement therapy. In an open-label study, the participants randomly received varenicline (1 mg twice daily) for 12 weeks or transdermal NRT (21 mg/day, tapered to 7 mg/day) for 10 weeks. Prolonged smoking abstinence for the last four weeks of treatment was higher for varenicline-treated participants than patients receiving the nicotine patch (56% versus 43.2%, OR 1.70, 95% CI: 1.26–2.28). At one year, a trend was observed toward increased efficacy with varenicline compared with the nicotine patch for prolonged smoking abstinence (26% versus 20% prolonged abstinence, OR 1.40, 95% CI: 0.99–1.99).²⁰ Another meta-analysis reported that compared to sustained-release bupropion, varenicline was observed to be superior (RR 1.52, 95% CI: 1.22–1.88) for continuous abstinence at week 52.²¹

Another study reported that varenicline has superior efficacy compared with placebo and bupropion. The pooled odd ratio (OR) for validated continuous abstinence at 12 months for varenicline versus placebo was 3.22 (95% CI 2.43–4.27) and 1.66 (95% CI 1.28–2.16) for varenicline versus bupropion.^{22,23} The relapse prevention trial concluded that varenicline offers significant benefit versus placebo with an OR for validated continuous abstinence of 1.34 (95% CI 1.06–1.69).²⁴ A recent study has also suggested that varenicline is more effective than NRT in short-term routine treatment of tobacco dependence, with a benefit similar to that seen for varenicline over bupropion in the previous RCTs. The study also demonstrated that the efficacy of varenicline was similar in both patients with and without mental illness.²⁵ Multiple trials of combination therapy for smoking cessation have also been published, and such studies show improved smoking abstinence rates compared with monotherapy. In one such study, varenicline (standard treatment regimen) co-administered with sustained-release bupropion (150 mg twice daily after a three-day dose escalation) in smokers for 12 weeks. The

seven-day point prevalence smoking abstinence rate among the smokers was 71% (95% CI: 54–85) at the end of treatment. At six months, combination therapy continued to appear more effective than monotherapy.²⁶

Combination therapy with varenicline and NRT has also been evaluated. Heavier smokers might benefit from this combination because varenicline might not fully saturate nicotinic receptors during dose escalation. Incompletely saturated receptors may lead to partial attenuation of nicotine cravings. If supplemental nicotine replacement therapy can lead to more complete receptor saturation, then urges to smoke could be more completely attenuated. This possible effect was evaluated and confirmed in an eight-day residential treatment program.²⁷

Adverse effects profile of varenicline

The most commonly reported adverse events experienced by subjects on varenicline in clinical trials were nausea (28.1%), headache (15.5%), insomnia (14.0%), and abnormal dreams (10.3%).²³ The most common adverse events from bupropion are insomnia and dry mouth. The most serious adverse event is major motor seizures, which have been reported in 0.1% of patients treated with bupropion, and allergic reactions (1–2%), with 0.1% of serious cases of hypersensitivity. Compared with NRT and varenicline, bupropion has more serious side-effects and more contraindications.^{12, 28, 29}

Varenicline is an FDA pregnancy category C drug. Studies on rats and rabbits observed decreased fetal weight and decreased offspring fertility after administration of high doses of varenicline. Its effects on pregnant humans and their offspring have not been adequately investigated, nor is it known whether varenicline is excreted in the milk of nursing mothers. For this reason, varenicline is not recommended for pregnant or nursing mothers unless the drug's benefit justifies the potential risk posed to the fetus. Its dose should be decreased in dose of varenicline.³⁰

Some clinical studies have shown that varenicline may increase suicidal thoughts in some patients. Data from a large treatment database from UK which included 80,660 males and females (aged 18–95 years), were prescribed a new course of a smoking cessation product between September 1, 2006 and May 31, 2008: NRT (n=63,265), varenicline (n=10,973) and bupropion (n=6,422). There was no clear evidence that varenicline was associated with an increased risk of fatal (n=2) or non-fatal (n=166) self-harm, although a 2-fold increased risk cannot be ruled out on the basis of the upper limit of the 95% confidence interval. Compared with NRT, the hazard ratio for self-harm among people prescribed varenicline was 1. 12 (95% CI 0.67–1.88), and 1.17 (0.59–2.32) for people prescribed bupropion. There was no evidence that varenicline was associated with an increased risk of depression (n=2,244) [HR 0.88 (0.77–1.00] or suicidal thoughts (n=37) [HR 1.43 (0.53–3.85)]. In conclusion, although a 2-fold increased risk of self-harm with varenicline cannot be ruled out, these findings provide some reassurance concerning varenicline's association with suicidal behaviour.²²

Another new meta-analysis, which included all trials published to date, focused on events occurring during drug exposure and analyzed findings using four summary estimates, and found no significant increase in cardiovascular serious adverse events associated with varenicline use.³¹ A detailed analysis of adverse events of varenicline can be found on the US Food and Drug Administration website.³²

In an attempt to conduct a more rigorous assessment of the safety profile of varenicline, a pooled analysis of psychiatric adverse events from 10 randomized controlled trials treating a total of 3091 participants with varenicline was performed. The analysis reported no significant increase in overall psychiatric disorders due to varenicline other than sleep disorders and disturbances (RR 1.70, 95% CI: 1.50–1.93).³³ Presently available data have not proven that varenicline causes significant neuropsychiatric

adverse events.³⁴ In the absence of a proven causal link between varenicline and a serious risk of neuropsychiatric adverse effects, the immense health benefits of smoking cessation warrant its continued use as a pharmacologic aid for treating tobacco dependence.

Conclusion

Cigarette smoking continues to be an important cause of morbidity and mortality worldwide. Varenicline exhibit a dual action by sufficiently stimulating $\alpha 4\beta 2$ -nAChR-mediated dopamine release to reduce craving when quitting and by inhibiting nicotine reinforcement when smoking. Its clinical efficacy has been demonstrated in various clinical trials. It has significantly better quit rates than do other treatments and offers a new option for smoking cessation pharmacotherapy. Taking into account that varenicline is very effective and that there is no evidence of a causal relationship between the above severe adverse events and varenicline, it is recommended as a first line agent in smoking cessation. Smokers taking varenicline have the most success quitting smoking as compared with those taking other first-line pharmacotherapies for treating tobacco dependence.

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