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Review Article

RECENT ADVANCED NICOTINE DRUG DELIVERY SYSTEM AND NICOTINE ABUSE

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ABSTRACT

While the proportion of the adult population that smokes has declined steadily in several westernized societies, the rate of successful quit attempts is still low. This is because smokers develop nicotine dependence, a powerful addiction that may require multiple attempts and long-term treatment to achieve enduring abstinence. Currently available first-line agents for smoking cessation therapy include nicotine replacement therapy (available in several formulations, including transdermal patch, gum, nasal spray, inhaler, and lozenge), bupropion (an atypical antidepressant), and varenicline (a partial agonist of the α4β2 nicotinic acetylcholine receptor that was recently developed and approved specifically for smoking cessation therapy). Second-line agents are nortriptyline (a tricyclic antidepressant agent) and the antihypertensive agent clonidine. With the exception of varenicline, which has been shown to offer significant improvement in abstinence rates over bupropion, all of the available treatments appear similarly effective. The adverse event profiles of nortriptyline and clonidine make them more appropriate for second-line therapy, when first-line treatments have failed or are not tolerated. However, the currently marketed smoking cessation drugs reportedly lack high levels of efficacy, particularly in real-life settings. New medications and vaccines with significant clinical advantage are now in the advanced stage of development and offer promise. These include nicotine vaccines and monoamine type B inhibitors. In this review article we discuss current and emerging pharmacotherapies for tobacco dependence focusing on their mechanisms of action, efficacy and adverse event profiles.

KEYWORDS: *Bupropion, Clonidine, Monoamine Oxidase Inhibitors, Nicotine Replacement Therapy, Nicotine Vaccines, Nortriptyline, Smoking Cessation, Varenicline.*

INTRODUCTION

Tobacco use is a global pandemic, affecting an estimated 1.2 billion people, which poses substantial health burden and costs. With approximately 5 million tobacco-related deathsannually, cigarette smoking is the leading cause of preventable premature mortality in the world [World Health Organization, 1997]. Death is mainly caused by lung cancer, coronary heart disease, chronic obstructive pulmonary disease, and stroke [Doll *et al.* 2004; US Department of Health and Human Services, 2004]. The risk of serious disease diminishes rapidly after quitting and permanent abstinence is known to reduce the risk of lung cancer, heart disease, chronic lung disease, stroke, and other cancers [Lightwood and Glantz, 1997; US Department of Health and Human Services, 1990]. 'Offer help to quit tobacco use' in people addicted to nicotine is one of the six proven policies identified by the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) to expand the fight against the tobacco epidemic [World Health Organization, 2009]. In keeping with these recommendations, state governments (the FCTC has been endorsed by over 160 countries) have the obligation to address and treat tobacco dependence in their primary healthcare services. Treatment for smoking cessation includes various methods, from simple medical advice to pharmacotherapy. Evidence-based recommendations indicate that although counselling and medication on their own are helpful for treating tobacco dependence when used in combination, however, they are more effective than either alone [Fiore *et al.* 2008]. Moreover, treatments aimed at smoking cessation are among the most cost-effective interventions in health care [West, 2007; Parrott *et al.*1998].Unfortunately, the powerful addictive qualities of nicotine create a huge hurdle, even for those with a sincere desire to quit. Once established, smoking is a very difficult addiction to break. It has been shown that approximately 80% of smokers who attempt to quit on their own relapse within the first month of abstinence and only about 3–5% remain abstinent at 6 months [Hughes *et al.* 2004]. The pharmacologic effect of nicotine plays a crucial role in tobacco addiction [Benowitz, 2008] and therefore pharmacotherapy is important to address this component of tobacco dependence in order to improve success rates.In this article, we review all available and potentially usable pharmacological treatments for

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tobacco dependence. According to the current guidelines, these drugs have been classified in first-line and second-line medications. New smoking cessation products in clinical development are also discussed.

Current Pharmacological Smoking Cessation Drug:

All medications have potential adverse effects, and those used for smoking cessation are no exception. The primary rationale for using these drugs is that they are clearly safer than continuing to smoke cigarettes. The United States Department of Health and Human Services Public Health Service 2008 update of the *Treating Tobacco Use and Dependence* clinical practice guidelines categorizes pharmacotherapy for treatment of tobacco dependence into first-line (nicotine replacement therapy [NRT], bupropion, and varenicline) and second-line medications (include nortriptyline and clonidine), and also discusses combination medications [Fiore *et al.* 2008]. Although second-line therapies do not have US Federal Drug Administration (FDA) approval for smoking cessation, they are recommended by current guidelines for patients unresponsive to or unable to tolerate first-line agents.

Compared with placebo alone, first-line medications are modestly effective, but counselling and psychological therapies can substantially enhance the effectiveness of smoking cessation products [Fiore *et al.*2008]. This is because these approaches help smokers in coping with psychological aspects (cognitive and behavioural) associated with tobacco dependence and improve their adherence to medication. With the exception of varenicline, which has been shown to offer significant improvement in abstinence rates over bupropion, all first-line medications appear to be of similar effectiveness, but there have been few direct comparisons. There is evidence of efficacy even for second-line medications but the FDA has not approved them for a tobacco dependence treatment indication and there are more concerns about potential side effects. In addition to decreasing withdrawal symptoms and craving, pharmacotherapy decreases the short-term reinforcing effects of tobacco. This form of relief can help ease the process of a patient learning new coping skills. The addition of a pharmacologic agent to a quit plan can have a positive psychological impact on those making quit attempts.

Nicotine replacement therapy:

NRT is the most common medication used to assist in quit attempts [George, 2007]. Its main mechanism of action is to partially replace the nicotine formerly obtained from tobacco smoking, which aids smoking cessation by reducing the severity of withdrawal symptoms and cravings [Gross and Stitzer, 1989] and also reduces the reinforcing effects of nicotine delivered *via* tobacco while providing an alternative source of some reinforcing and cognitive effects [Foulds *et al.* 2004].

NRT does not completely eliminate all symptoms of withdrawal because the available delivery systems do not reproduce the rapid and high levels of nicotine achieved through inhalation of cigarette smoke [Benowitz, 1993; Johansson *et al.* 1991; Benowitz *et al.* 1988]. Differences in formulations may have an impact on the efficacy for some of these effects, but there is little direct evidence that one nicotine product is more effective than another. A Cochrane review article recently found that all forms of NRT approximately double the chance of long-term abstinence from smoking [Stead *et al.* 2008]. Likewise, a study enrolling 504 patients found that all forms of NRT tested (gum, patch, nasal spray and inhaler) produced similar quit rates and were equally effective at reducing the frequency, duration and severity of urges to smoke [Hajek *et al.* 1999].

In general, NRT is considered safe for most patients, with a relatively low rate of discontinuation due to adverse events [Stead *et al.* 2008; Hajek *et al.* 1999]. Adverse events are generally formulation specific, depending on the delivery system used [Henningfield *et al.* 2005]. Some of the contraindications and warnings for NRT include history of myocardial infarction within the past 6 weeks, uncontrolled hypertension (or hypertension that emerges during treatment), severe dysrhythmia, or unstable angina. Severe chronic obstructive pulmonary disease (COPD), uncontrolled diabetes mellitus (nicotine can impair insulin sensitivity in type II diabetes mellitus), and other forms of cardiovascular disease (CVD) may be contraindications, although the risks have to be weighed against a continued smoking habit [Eliasson, 2003; Joseph *et al.* 1996]. Owing to the slower delivery of nicotine and in part because NRT only partially addresses the reinforcing behavioural and social effects of smoking, these products have been shown to have low liability for abuse and low dependence potential [West *et al.* 2000]. In addition, there is no evidence of withdrawal discomfort when patients discontinue NRT use [West *et al.* 2000].

Bupropion:

Initially, bupropion was initially researched and marketed as an antidepressant. Bupropion was subsequently found to be effective as a smoking cessation aid, sustained-release formulations being preferred over the immediate release; bupropion SR (Zyban, GlaxoSmithKline) is taken twice daily and bupropion XL (Wellbutrin, GlaxoSmithKline) is taken once daily. Patent protection for bupropion has expired and generic versions of the drug are marketed for smoking cessation. Furthermore, some healthcare practitioners prescribe Wellbutrin offlabel as a smoking cessation aid. Its mode of action in smoking cessation is not completely understood, but dopamine and norepinephrine reuptake inhibition together with a weak nicotinic antagonist activity may contribute to the reported reduction in the severity of nicotine cravings and withdrawal symptoms [Cryan *et al.*2003; Slemmer *et al.* 2000; Fryer and Lukas, 1999].

A Cochrane review article found that bupropion doubles the chances of quitting smoking compared with placebo [Hughes *et al.* 2007]. Also, it has been shown to decrease nicotine withdrawal symptoms and cravings [Jorenby, 2002]. Pooled analyses of studies with bupropion generally show quit rates similar to NRT [Stead *et al.* 2008; Hughes *et al.*2007]. Bupropion has also been found to be equally effective in smokers with and without a history of depression [Hughes *et al.* 2007].

The most common adverse events with bupropion are insomnia, which occurs in 30–40% of patients, and dry mouth, which occurs in approximately 10% of patients [Hughes *et al.* 2007]. In a comparative trial, the incidence of nausea was similar with bupropion, NRT, and the combination of both, and approximately doubles that observed with placebo. Rates of discontinuation from clinical trials due to adverse events generally range from 7% to 12% [Hughes *et al.* 2007]. A small risk of seizures has been observed with two large studies reporting seizure incidences of approximately 1 per 1000 [Boshier *et al.* 2003; Dunner *et al.* 1998]. Therefore, prescription is contraindicated in patients with a history of seizures. Bupropion is safe for use in patients with CVD [Tonstad *et*

al. 2003]. The prescribing information for bupropion carries a 'black-box' warning based on observations that antidepressants have increased the risk for suicidal ideation and behaviour in children and adolescents with certain psychiatric disorders.

Varenicline:

Varenicline (Chantix/Champix, Pfizer), launched in 2006, is the first new prescription drug for smoking cessation for around 10 years. It is a partial agonist selective for α4β2 nicotinic acetylcholine receptor subtypes in the ventral tegmental area of the brain, which has dual effects: partial stimulation of the receptors, without creating the full effect of nicotine (agonist action), and blocking the receptors thus preventing nicotine from reaching them (antagonist action) [Rollema et al. 2007; Coe et al. 2005]. These effects provide relief from the cravings and withdrawal symptoms experienced by smokers during an attempt to stop smoking [Rollema et al. 2007; Coe et al. 2005]. Furthermore, the drug may reduce smoking satisfaction, thereby potentially reducing the risk of relapse.

In two identically designed randomized, double-blind, multicentre trials, which were placebo-controlled and active-controlled with bupropion-SR 150 mg twice daily, investigators demonstrated that in healthy smokers the odds of quitting with varenicline 1 mg twice daily were approximately 2.5 times that of placebo, and approximately 1.7 times better than with bupropion after 1 year [Gonzales et al. 2006; Jorenby et al. 2006]. When evaluated for long-term maintenance treatment in patients who quit smoking during 12-week open-label treatment with varenicline, this agent was shown to offer significant advantages over placebo after 6 months of treatment (odds ratio [OR], 2.48; 95% confidence interval [CI], 1.95–3.16) and at 1-year follow up (OR, 1.34; 95% CI, 1.06–1.69) [Tonstad et al. 2006]. Varenicline works well in smokers with COPD and with established CVD as it does in the general population. In a recent multicentre, double-blind, placebo-controlled trial of 499 patients with mild-to-moderate COPD who had smoked for an average of 41 years, a cessation efficacy OR of 3.1 (95% CI, 2.5–3.8) has been reported with varenicline 6 months after cessation, compared with placebo [Tashkin et al. 2009]. In 714 smokers with stable CVD enrolled in a multicentre, randomized double-blind study conducted in 15 countries, the continuous abstinence rate for weeks 9–52 was higher with varenicline compared with placebo (19.2% versus 7.2%; OR 3.14) [Rigotti et al. 2010].

Varenicline is generally well tolerated, with the most commonly reported adverse effects being nausea (in about 30%, with the majority rating it as mild), insomnia, gastrointestinal upsets and headache [Gonzales et al. 2006; Jorenby et al. 2006]. It is recommended that varenicline is taken after eating with a full glass of water to reduce the incidence or severity of nausea. The overall incidence of adverse events leading to discontinuation is similar to that observed with placebo [Gonzales et al. 2006; Jorenby et al. 2006]. The prescribing information for varenicline carries a 'black-box' warning highlighting an increased risk of psychiatric symptoms and suicidal ideation in patients using varenicline. Patients should be asked to report any history of psychiatric illness prior to starting varenicline and advised to stop varenicline if they experience agitation, depressed mood, or any changes in behaviour that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behaviour.

Nortriptyline:

Nortriptyline is a second-generation tricyclic antidepressant used in the treatment of major depression. Nortriptyline has been administered as a second-line agent in smoking cessation studies at dosages of 75–100 mg/day [Pamelor, 2006; Hughes et al. 2005]. Several plausible theories for the nortriptyline's therapeutic effect on tobacco dependence have been proposed, including its antidepressant action, its noradrenergic effects replacing those of nicotine, and its nicotine receptor antagonist activity; however, there are no preclinical or clinical studies available to support any of these potential mechanisms [Hughes et al. 2005].

A Cochrane review meta-analysis of six randomized clinical trials indicated that nortriptyline treatment doubles the odds of smoking cessation, with an OR for abstinence of 2.14 (95% CI, 1.49–3.06) [Hughes et al. 2005]. Thus, nortriptyline appears to be as effective as NRT or bupropion. However, nortriptyline has been evaluated in a much smaller number of smokers than either bupropion or NRT [Hughes et al.2005].

As is typical with antidepressants, there are a number of potential adverse effects, including sedation, dizziness, insomnia, blurred vision, constipation, and nausea. Whereas these adverse events occur frequently in patients being treated for depression, they have been less common at the doses used for smoking cessation [Hughes et al. 2005]. Despite this, the prescribing information for nortriptyline carries a 'black-box' warning similar to that for bupropion regarding an increased risk of suicidal ideation and behaviour among children and adolescents taking antidepressants. Caution should be exercised when considering nortriptyline for patients with cardiovascular disorders, since it can increase the risk of dysrhythmia, hypertension, orthostatic hypotension and tachycardia [American Psychiatric Association, 2000]. In addition, the safety of nortriptyline has not been evaluated in special populations, such as pregnant women, patients with CVD, or individuals who continue to smoke. Owing to the limited number and range of patients in whom nortriptyline has been evaluated for smoking cessation, the complete safety profile in these patients is unclear [American Psychiatric Association, 2000].

Clonidine:

Clonidine is approved by the FDA only for the treatment of hypertension. However, it has been also shown to be effective in reducing symptoms of nicotine withdrawal, and for this reason is listed as a second-line tobacco-cessation drug [Fiore et al. 2008]. Consistent with its α2-adrenergic agonist activity [Gowing et al. 2003], clonidine's central effects include sedation and anxiolysis, while its systemic effects include hypotension, bradycardia, dry mouth and dizziness [Gourlay and Benowitz, 1995]. It is believed that clonidine's efficacy for smoking cessation is based on its ability to counteract CNS features of nicotine withdrawal, including craving and anxiety [Gourlay and Benowitz, 1995]. A specific dosing regimen for tobacco cessation has not been established.

Clonidine, either the oral tablet at dosages of 0.15–0.45 mg/day or the transdermal patch at dosages of 0.1–0.3 mg/day, has been shown to be an effective aid for smoking cessation [Gourlay et al. 2004]. Pooled results from six randomized controlled trials demonstrated an approximate doubling of the rate of abstinence after at least 12 weeks of follow up compared with placebo (OR, 1.89; 95% CI, 1.30–2.74) [Gourlay et al. 2004].

The Cochrane review noted a high incidence of dose-dependent adverse events with clonidine, including significant

sedation and postural hypotension [Gourlay *et al.* 2004]. Other dose-related adverse events with clonidine include dry mouth and constipation. Caution should also be used when coadministering clonidine with β-blockers, calcium channel blockers, and digitalis.

The 'nicotine effect':

When a body is exposed to nicotine, the individual experiences a "kick." This is partly caused by nicotine stimulating the adrenal glands, which results in the release of adrenaline. This surge of adrenaline stimulates the body. There is an immediate release of glucose, as well as an increase in heart rate, breathing activity, and blood pressure. Nicotine also makes the pancreas produce less insulin, causing a slight increase in blood sugar or glucose.

Dopamine is a brain chemical that affects emotions, movements, and sensations of pleasure and pain. If your brain dopamine levels rise, the feeling of contentment is higher.Depending on the dose of nicotine taken and the individual's nervous system arousal, nicotine can also act as a sedative.

Pharmacologic effects:

When humans, mammals, and most other types of animals are exposed to nicotine, it increases their heart rate, heart muscle oxygen consumption rate, and heart stroke volume. These are known as pharmacologic effects.

Psychodynamic effects:

Consuming nicotine is also linked to raised alertness, euphoria, and a sensation of being relaxed.

Concentration and memory:

Studies have shown that nicotine appears to improve memory and concentration. It is thought that this is due to an increase in acetylcholine and norepinephrine. Norepinephrine also increases the sensation of wakefulness, or arousal.

Reduced anxiety:

Results in increased levels of beta-endorphin, which reduces anxiety.

How the body processes nicotine:

After inhaling tobacco smoke, nicotine rapidly enters the bloodstream, crosses the blood-brain barrier, and reaches the brain within 8 to 20 seconds. Within approximately 2 hours after entering the body, half of the nicotine has gone.

How much nicotine may enter a smoker's body depends on: the type of tobacco being used.

Whether or not the smoker inhales the smok whether a filter is used, and what type of filter it is Tobacco products that are chewed, placed inside the mouth, or snorted tend to release considerably larger amounts of nicotine into the body than smoking. Nicotine is broken down in the liver.

Addiction:

People who regularly consume nicotine and then suddenly stop experience withdrawal symptoms, which may include:

1. Cravings
2. A sense of emptiness
3. Anxiety

4. Depression
5. Moodiness
6. Irritability

Ifficulty focusing or paying attention. The American Heart Association says that nicotine consumed from smoking tobacco is one of the hardest substances to quit. It is considered to be at least as hard as quitting heroin. A 2013 study showed that reducing the amount of nicotine in cigarettes also brings down their level of addictiveness.A study carried out at the National Institute on Drug Abuse found that nicotine consumption makes cocaine more addictive.

Side effects:

Nicotine causes a wide range of side effects in most organs and systems.

The circulation of the blood can be affected in the following ways:

- An increased clotting tendency, leading to a risk of harmful blood clots
- Atherosclerosis, in which plaque forms on the artery wall
- Enlargement of the aorta Side effects in the brain include:
- Dizziness and lightheadedness
- Irregular and disturbed sleep
- Bad dreams and nightmares
- Possible blood restriction In the gastrointestinal system, nicotine can have the following effects:
- Nausea and vomiting
- Dry mouth, or xerostomia
- Indigestion
- Peptic ulcers
- Diarrhea
- Heartburn The heart can experience the following after taking in nicotine:
- Changes in heart rate and rhythm
- An increase in blood pressure
- Constrictions and diseases of the coronary artery
- An increased risk of stroke If a woman smokes while pregnant, the following risks are likely in the development of the child:
- Obesity
- High blood pressure
- Type 2 diabetes
- Respiratory difficulties
- Infertility
- Problems with brain development
- Behavioral issues Other effects include:
- Spasms in the lungs
- Pneumonia
- Tremors and pain in the muscles
- Increase levels of insulin and insulin resistance, contributing to the risk of diabetes
- Joint pain

Are e-cigarettes and vaporizers safe?

In recent years, liquid nicotine has been touted as a less risky replacement for smoking cigarettes. This can be delivered to the system in an electronic cigarette or vaporizer. These are known as electronic nicotine delivery systems (ENDS).

These battery-operated 'e-cigs' and 'vapes' atomize the liquid nicotine by applying heat but without the harmful, oxidative effects of burning. Liquids are available in a range of strengths and flavors.

Current evidence suggests that using liquid nicotine is a safer alternative to inhaling tobacco smoke, as nicotine in itself is not classified as carcinogenic, or cancer-causing, by the International Agency for Research on Cancer.

It may also help people that are trying to quit smoking mimic some of the addictive behaviors of cigarette use, such as raising the hand to the mouth or seeing smoke inhaled, that other types of nicotine replacement therapy (NRT) cannot imitate. Liquid nicotine can help replicate these behaviors without the harmful effects of tobacco use.

Any form of nicotine is highly addictive, so e-cigarettes and vaporizers remain unsuitable for young people and those who do not already smoke. Liquid nicotine can act as a gateway to cigarettes for those not already regularly taking in nicotine.

The use of e-cigarettes rose from 1.5 percent to 16 percent among high-school students and from 0.6 percent to 5.3 percent in middle-school students between 2011 and 2015, with 81 percent of young e-cigarette users putting their use of the products down to the wide availability of flavors.

There are also other chemicals present in e-cigarette and vaporizer liquid that could be harmful, and these chemicals will be different in various brands, products, devices, and uses. Some products that are available online may also contain dangerous concentrations of nicotine.

While nicotine does not itself cause cancer, some of the other substances in liquid nicotine may well contribute to it. For example, a flavoring called diacetyl, used in some e-liquids, is also associated with severe respiratory problems seen in workers at a factory that produces microwaveable popcorn, known as "popcorn lung."

These products have been regulated by the FDA since 2016 and, as of 2018, must bear the nicotine addictiveness warning on packaging and marketing materials. However, as a relatively new technology, the full effects of liquid nicotine are not known, and caution is advised.

CONCLUSION

Once established, cigarette smoking is a very difficult addiction to break. Smokers trying to quit have to simultaneously cope with psychological and pharmacologic aspect of tobacco dependence. The pharmacologic effect of nicotine plays a crucial role in tobacco addiction and therefore pharmacotherapy is important to address this component of tobacco dependence in order to improve success rates. There is little doubt that currently marketed smoking cessation products (such as NRT, buproprion and varenicline) increase the chance that committed smokers will stop smoking, particularly when combined with counselling programmes. This is because psychological therapies and counselling help smokers in coping with psychological aspects (cognitive and behavioural) associated with tobacco dependence.

Unfortunately, these programmes reportedly lack high levels of efficacy with many smokers eventually relapsing while receiving treatment for tobacco dependence, particularly in real-life settings. We acknowledge that this reflects the chronic relapsing nature of tobacco dependence and not a failure by physicians or their patients, but more effective smoking cessation interventions are clearly needed.

The increase in our understanding of the mechanisms involved in nicotine dependence has recently been translated into new treatments. The success of varenicline as the first partial agonist selective for α4β2 nicotinic acetylcholine receptor subtypes opens new opportunities for using partial agonist agents to target other important specific receptor subtypes that are involved in nicotine signalling. Moreover, vaccine approaches to prevention and treatment of nicotine dependence are developing rapidly and nicotine vaccines could change the way healthcare practitioners will provide smoking cessation. Lastly, the programmed launch of the novel MAO-B inhibitors also has the potential to satisfy the need for more effective smoking cessation interventions. Extensive research about new pharmacological approaches is ongoing and in the not-too-distant future it will be possible that personalized pharmacological stimulation of nicotinic receptors could be achieved through use of medical devices, such as the electronic cigarette [Bullen *et al.* 2010; Eissenberg, 2010], that can also simultaneously address the challenge of reinforcing psychological and social effects of smoking.

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