Smoking and Vaping
Health Needs Assessment

Appendix 7: Evidence base for stop smoking interventions & products

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June 2024

Contents

Stop smoking interventions

The National Centre for Smoking Cessation and Trading (NCSCT) outline an array of interventions, rating each to show the extent to which it is evidence-based[1]. This is based upon an adapted version of the Scottish Intercollegiate Guidelines Network (SIGN) rating system, an internationally-recognised scale used to rate research evidence[2]. These ratings are as follows:

- A: The intervention is supported by strong evidence
- B: The intervention is supported by reasonable evidence but there may be minimal inconsistency or uncertainty
- C: The intervention is supported by expert opinion only
- I: There is insufficient evidence
- ✓ : Good practice point (in the opinion of the guidance development group

Table 4 provides a summary of the evidence ratings awarded by NCSCT for each form of smoking support.

Table 1: Summary of interventions and their evidence rating

Intervention	Evidence rating
Behaviour support	A
Very brief advice	A
Intervention types	
Digital support	
Digital applications (apps)	B-C
Hybrid support (digital + person)	B-C
Online support (not live)	B
Text messages	B
Drop-in support	I
Group support	
Closed group support	A
Open (rolling group support	B
One-to-one support	A
Couple/family support	I
Multi-session support (Standard treatment programme)	A
Single-session support	B
Tailored specialist, multi-session support	A-B
Telephone or video support	
Proactive telephone	A
Reactive telephone	B
Real time video-link (live)	C
Assessing nicotine dependency and smoking status	
Carbon monoxide testing	A
Cotinine testing	A
Quantitative approach to assessing nicotine dependency	A
Stop smoking aids	
First Choice	
Combination nicotine replacement therapy (patch plus faster-acting product)	A
Cystisine	A
Nicotine vapes	A
Varenicline	A
Second choice	

Bupropion (Zyban)	A
Non-nicotine vapes	I
Single form NRT	A
Method of use	
Cut Down to Stop without stop smoking aid	I
Cut Down to Stop with NRT	B
Cut Down to Stop with varenicline	B
Extended use of NRT	A
Extended use of vapes	A
Extended use of varenicline	A
Preloading NRT	B
Population	
Black and minority ethnic groups	B
Children and young people Prevention and tobacco control Stop smoking intervention	 B I
LGBTQ+ communities	B-C
People experiencing homelessness	B
People in prison	C
People in routine and manual occupations	B
People who use cannabis	I
People with mental health conditions	B
People with severe mental illness (SMI)	B
People with substance misuse disorders and co-addictions	B
Pregnant women Behavioural support NRT NRT in teenage pregnancy Vapes	 A B ✓ B
Treated in secondary care with follow-up for at least 1 month	A
Treated in secondary care with follow-up for less than 1 month	B
Incentives	
General population	B
Incentives among pregnant women	A
Relapse prevention	
Extended behavioural support	A-B
Extended use of stop smoking medication/ vape	A-B
Other strategies	I

Source: NCSCT

NRT products

Nicotine gum

The first NRT product that was readily available was nicotine gum. It is offered in doses of 2 and 4 mg. According to studies, 4 mg of chewable gum has a higher success rate than 2 mg in helping smokers quit smoking. There was no distinction between starting the nicotine gum medicine four weeks earlier or starting it on the designated quit date. However, different people consume different amounts of nicotine gum, depending on their daily intake limits in addition to other variables such as age, body mass index, gene expression, peak concentration, and age may influence effectiveness[3].

Rapid-release gum

The gum base used in rapid-release gum has been shown to enable both biphasic nicotine delivery (sustained long-term release of nicotine) and speedy initial nicotine release (rapid short-term release of nicotine). Furthermore, it elevates the pH to accelerate time of absorption through the oral mucosa. Compared to regular nicotine gum, rapid-release nicotine gum offers an advantage because it is quick and completely relieves nicotine cravings[3].

Nicotine lozenges

Nicotine lozenges can be used in place of nicotine gum by patients who need sporadic and periodic nicotine dosages but are not able to chew gum for an extended amount of time. They are available in doses of 1,2, and 4mg. Although there was a noticeable decrease in desire to use tobacco (i.e. cravings) compared to baseline during the first two weeks of quitting, users of smokeless tobacco, who took nicotine lozenges did not notice any differences in their overall tobacco withdrawal symptoms. Although, smokeless tobacco users tolerated and approved of the nicotine lozenge overall[3].

Transdermal Patch

Nicotine is progressively absorbed through the skin once nicotine patches are applied. Smokers with a greater dependence level can use the strongest patches, while those with a lower dependence level can use a lesser dosage. Thanks to the range of dosages, users can progressively reduce their nicotine intake over a few weeks or longer, letting their bodies adjust to reduced nicotine doses and eventually reach a nicotine-free state. The key advantage of nicotine patches over acute NRT formulations is the simplicity of compliance; rather than actively using a medicine throughout the day, the patient only needs to apply the patch to their skin in the morning. Localised skin responses are the side effects that are most frequently reported. Skin responses can be minimised by changing the patch application site, as directed, each day[3].

High-dose nicotine patches

Standard 22mg patches can only restore around half of smoker's baseline blood nicotine and cotinine levels. As a result, 42mg of greater transdermal nicotine dosages were investigated. In terms of efficiency high-dose transdermal NRT achieved a statistically greater abstinence rate. According to the medical literature, high-dose transdermal NRT has not been demonstrated to be safe or helpful for smoking cessation[3].

Nicotine sublingual tablet

Because the pill is taken sublingually, there is no need to chew it. It is recommended that it should be used for at least 8 to 12 weeks before progressively reducing the number of tablets. For people who are very dependent on nicotine, 16 to 24 sublingual tablets per day (i.e., a maximum of 302 mg tablets dispersed throughout the day) are recommended, whereas 8 to 12 tablets per day are recommended for those who have a low reliance. It should be taken with caution in persons who are addicted to nicotine. The two most common side effects are mouth soreness and sleeplessness[3].

Nicotine oral inhaler

A brand-new inhaler that mimics many of the smoking rituals while administering nicotine aerosol has been developed. The device is similar to a regular cigarette in size and form, and it features a tiny

breath-operated valve that allows the user to control how much air they inhale. Because of this, the number of puffs in one charge (or dose) of the inhaler device that is regulated by the user's depth of inhalation determines the speed at which nicotine is administered from that charge. A nicotine inhaler typically resembles a cigarette or cigar and is composed of a mouthpiece and a plastic cartridge filled with nicotine. Ten milligrams of nicotine are contained in each cartridge. The mouth, oesophagus, and stomach deliver about 36% of the nicotine, while the lungs only receive 4% of it. Because the inhaler absorbs nicotine at the exact pace as nicotine gum, caution is required to avoid placing it on the lip[3].

Nicotine nasal spray

When compared to a placebo, nasal spray nearly doubles the quit rate. Nicotine patches and nasal sprays reduce foetal nicotine exposure when compared to smoking. The fastest mode of delivery, nasal spray, most closely resembles the rise in nicotine levels observed when smoking. Because it quickly reduces appetite, the nasal spray is most beneficial to highly dependent smokers[3].

Nicotine analogue medications

Varenicline [Champix]

Varenicline is a prescription-only medicine that has been available in the UK since 2007 and it is a classified as a first choice stop smoking medication. However, licensed varenicline is currently not available in the UK due to an impurity found in the medicine. It may be unavailable long-term. It's not yet known whether it will be available again in future[4].

Varenicline, also referred to as Champix, is a nicotinic acetylcholine receptor partial agonist (a drug that mimics the action of nicotine). Similarly to nicotine, varenicline can support the release of dopamine (the principle ‘pleasure/satisfaction’ neurotransmitter associated with nicotine addiction). Although, due to its partial agonistic characteristics it does not produce a maximal response; therefore, it can alleviate withdrawal symptoms without further exaggerating addiction. Titration starts with 0.5 mg administered orally once daily for three days and then increased to 1 mg given orally twice daily for the final three days of the course of treatment. In patients who have unfavourable side effects, lower dosages of varenicline (such as 0.5 mg twice daily) may be used. Varenicline may be used for up to six months of nonstop abstinence if well tolerated. Frequent adverse effects of using varenicline include nausea, sleeplessness, strange nightmares, headaches, nasopharyngitis, and xerostomia. Patients who have previously experienced significant skin reactions and hypersensitivity responses to varenicline should not use it[3].

Cytisine

Cystine has been approved by the Medicines and Healthcare products Regulatory Agency (MHRA) as a prescription-only medication in the UK and has been available since January 2024. While new to the UK, cystine has been used as a stop smoking aid in Eastern European countries since the 1960s and have been approved for use in Canada since 2017[1].

Like varenicline, cytisine acts to reduce withdrawal symptoms and cravings by simulating nicotine receptors. It also reduces the reward and satisfaction associated with smoking. A cytisine treatment course is 25 days. One of the benefits of cytisine is that it is relatively low cost (around £115).

Studies evaluating cytisine as a stop smoking aid have been promising and data suggests cytisine is significantly more effective than both placebo and single-form NRT in supporting quitting at six months. However, when compared to varenicline data suggests that cytisine may not work quite as well[5].

Second choice stop smoking aids

Second choice stop smoking aids include single-form NRT and bupropion. These medications have good evidence to show they increase the chance of quitting. However, they are less effective when compared to first choice stop smoking aids[6].

Bupropion

Although this medication is an antidepressant, it is unknown how it works to treat nicotine addiction. Whether a smoker is depressed or not, bupropion with continuous release is an aid in helping smokers quit. It is equally effective as the nicotine patch and monotherapy. One to two weeks before the patient's anticipated termination date, a dose of 150 mg of bupropion is typically started. The dosage must be increased after three days to 150 mg twice daily for 7 to 12 weeks. As long as abstinence is kept up, bupropion can be administered for up to 12 months (maintenance dose = 300 mg/day). One of the adverse effects is insomnia, which is less common if the medication is given at least eight hours before going to bed. Other side effects include headaches, dizziness, diaphoresis, weight loss, xerostomia, nausea, and vomiting[3].

Additionally, a contraindication refers to the possibility that particular treatment may cause harm to the person receiving it. For example, people who are affected by seizures should not use bupropion as it has been shown to lower the seizure threshold. Bupropion is contraindicated in several severe diseases such as brain intravascular malformation, major head injuries, stroke, tumours, or infection of the central nervous system. Anorexia or bulimia; sudden alcohol withdrawal; current use of benzodiazepines, barbiturates, or antiepileptic medications; and the use of linezolid or intravenous (IV) methylene blue, both of which contain reversible monoamine oxidase inhibitors, together with recently using monoamine oxidase inhibitors, are also all contraindications[3].

Other stop smoking products

These pharmacotherapies are not recommended due to insufficient evidence or evidence of no effectiveness.

Clonidine

Clonidine, a medicine that acts on the central nervous system, was initially recommended as an antihypertensive to alleviate the withdrawal symptoms from some addictive behaviours. The existing studies suggest that the dose be titrated up to a maximum of roughly 400 g/day, as tolerated, starting with 100 g twice daily (orally or with an equivalent transdermal patch). If clonidine therapy is anticipated before the quit date, it should begin 48 to 72 hours beforehand. In a trial conducted by

Hilleman et al., no more smokers dropped out of the study when clonidine was administered in place of a placebo. At all follow-up visits, women on clonidine had a significantly greater rate of abstinence than men. Therefore, only female smokers may benefit from clonidine[3].

Nortriptyline

Tricyclic antidepressant nortriptyline has often shown promise as a tool for quitting smoking. Tricyclics are a class of drug that include nortriptyline. These drugs are more frequently referred to as tricyclic antidepressants (TCAs). According to widespread consensus, nortriptyline increases the levels of serotonin and norepinephrine in the synapse by preventing their reabsorption by the presynaptic neuronal membrane. Typically, nortriptyline is consumed orally as a pill or oral solution. The strengths of the capsule form are 10, 25, 50, and 75 mg. Typically, the oral solution version contains the following ingredients: 10 mg/5 mL (473 mL). Adults typically take 25 mg three or four times per day; the dosage should start low and be increased as necessary. The total daily dose may also be administered once daily as an alternative regimen. When nortriptyline is used in doses larger than 100 mg/day, plasma levels should be tracked. A dose of more than 150 mg/day is not recommended. A combined sample of smokers who received a variety of dosages exhibited considerable variation in plasma nortriptyline concentrations. It was shown that only nortriptyline levels that also decreased locomotor activity improved somatic withdrawal symptoms[3].

Anxiolytics

As a form of therapy, anxiolytics have also been suggested. Meprobamate, ondansetron, doxepin, buspirone, diazepam, and the beta-blockers metoprolol, oxprenolol, and propranolol are some of the medications that can help with anxiety, a sign of nicotine withdrawal. For students to successfully quit smoking, this study suggests effective anxiety therapy through psychiatric/psychotherapeutic intervention[3].

Bupirone

Buspirone is a medication that helps reduce anxiety or has an anti-anxiety effect. However, it is not a benzodiazepine drug, which is another class of medications commonly used for anxiety (like Xanax, Valium, etc.). Instead of acting on the same brain receptors as benzodiazepines, buspirone targets a different neurotransmitter system in the brain - the serotonin system. Serotonin is a chemical messenger or neurotransmitter that plays a role in regulating mood, anxiety, sleep, and other functions in the brain. In smoking cessation trials, the maximum daily doses have varied from 30 to 60 mg for 9 to 13 weeks, with therapy starting two to three weeks before the quit date[3].

Diazepam

Diazepam (also known as Valium) is primarily used as an anti-anxiety medication and muscle relaxant. However, some doctors may prescribe diazepam in specific situations related to smoking cessation based on the following reasoning:

- Nicotine withdrawal can cause anxiety, irritability, and restlessness when someone tries to quit smoking. Diazepam, being an anti-anxiety medication, may help relieve some of these withdrawal symptoms in the short-term.

- The act of smoking is both a physical and psychological habit/addiction. Diazepam's calming and anxiolytic (anti-anxiety) effects may help reduce the psychological craving or urge to smoke during nicotine withdrawal.
- In some cases, diazepam may be prescribed for a very brief period (few days to a week) along with approved smoking cessation aids like nicotine patches or gums. This is to help the person get through the most difficult initial withdrawal phase.

However, diazepam itself does not treat the nicotine addiction directly. Its role, if used at all for smoking cessation, is to provide temporary relief from withdrawal effects like anxiety, agitation and cravings in the initial quitting phase. Long-term use is not recommended due to the potential for dependence on diazepam itself.

In one long-term tobacco cessation research, diazepam was compared to a placebo and clonidine in a randomized fashion by Hao in 1988 in China. It was recommended to take 7.5 to 15 mg daily for four weeks. Additionally, subjects got three private appointments with a psychiatrist[3].

Ondansetron

Ondansetron is a medication primarily used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, or surgery. It works by blocking the action of serotonin, a natural substance that can trigger vomiting. When someone tries to quit smoking cigarettes after being addicted to nicotine, they can experience numerous withdrawal symptoms like irritability, anxiety, depression, headaches, and nausea. While ondansetron does not directly treat the nicotine cravings or addiction itself, some doctors may prescribe it specifically to help control the nausea and vomiting that can occur during the nicotine withdrawal phase when quitting smoking. By reducing these particular withdrawal symptoms of nausea and vomiting, ondansetron aims to make the overall experience of quitting smoking a bit more manageable for some people[3].

Beta-blockers

Beta-blockers are medications that block the effects of the hormone epinephrine (adrenaline) on the body's beta receptors. This helps reduce blood pressure, heart rate, and anxiety. When someone tries to quit smoking cigarettes after being addicted to nicotine, they can experience withdrawal symptoms like increased heart rate, high blood pressure, shakiness, and anxiety/stress. These physical and psychological withdrawal effects are partly caused by the body being deprived of nicotine, which normally stimulates the release of epinephrine. While beta-blockers don't treat the nicotine addiction itself, some doctors may prescribe them on a temporary basis during the initial withdrawal phase to help reduce some of the associated physical effects like rapid heartbeat, tremors, and spikes in blood pressure. By blocking epinephrine's effects, beta-blockers can help calm some of these physical nicotine withdrawal symptoms down, which may make the quitting process slightly more manageable for some people[3].

Mecamylamine

Mecamylamine is a medication that blocks the effects of nicotine in the brain. Nicotine is the addictive substance in tobacco that reinforces the smoking habit. When a person smokes, nicotine binds to and activates certain receptors in the brain called nicotinic acetylcholine receptors. This triggers the release of dopamine and other neurotransmitters that cause the pleasurable sensations

and reinforce the addiction. Mecamylamine works by blocking these nicotine receptors in the brain. This means that even if a person smokes, the nicotine cannot bind to and activate the receptors in the usual way.

In a dose-dependent manner, mecamylamine pretreatment decreases the ability of both humans and animals to differentiate between nicotine and placebo. Pretreatment with mecamylamine makes people desire more cigarette smoke when persons are tested using a device that combines the smoke from low- and high-nicotine cigarettes (presumably by lowering its nicotine effects). Mecamylamine pretreatment enhances many indices of tobacco consumption and tobacco smoke consumption when individuals are permitted to smoke. Mecamylamine pretreatment decreases the reinforcer effect of IV nicotine delivery in animals and maybe in humans. When combined with counselling, mecamylamine reduces the desire to smoke in heavy cigarette smokers, and after two weeks of treatment, 50% of patients effectively stop smoking. When mecamylamine use was discontinued, the study's average daily dose was 26.7 mg[3]

Naltrexone

Naltrexone is a medication that was originally developed to treat opioid and alcohol addictions. It works by blocking the euphoric and rewarding effects of these substances in the brain. While naltrexone doesn't directly affect nicotine receptors, some research has shown that it may help reduce cravings and the "rewarding effect" of smoking. Additionally, there is evidence that naltrexone may block the effects of smoking cues or triggers. These are the environmental situations that become associated with smoking pleasure through conditioning over time. Naltrexone is available as a 50 mg oral tablet. Naltrexone can be taken orally with or without food. Adverse gastrointestinal (GI) symptoms may be reduced by administration with or after meals. Another kind of naltrexone is a depot injection (380 mg). The top outer quadrant of the gluteal area must be injected using the given needles when administering the Intramuscular version; doctors should avoid injecting into the blood vessel. Drug administration by IV or subcutaneously or into fatty tissue is not advised. Before beginning naltrexone, the patient must undergo an opioid detox. . As nicotine may have opioid-mediated effects on performance enhancement and other positive outcomes, the use of naltrexone to quit tobacco is supported. Research has also indicated that naltrexone does not have any favourable effects on either short- or long-term smoking cessation when used alone or as an adjuvant to NRT[3].

NicVAX

The adaptive immunity against the nicotine molecule that underlies nicotine vaccination can potentially be a new method of treating tobacco dependence and preventing relapse. This is accomplished by stimulating the immune system to make antibodies that attach to nicotine molecules and expand them, preventing them from crossing the blood-brain barrier and connecting to nicotine receptors, so initiating the pleasurable experience that leads to addiction in smokers. When paired with varenicline and psychological assistance, the nicotine vaccination NicVAX does not seem to increase the likelihood of discontinuing tobacco use[3].

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