

THE MEDICAL MANAGEMENT OF INPATIENTS WITH TOBACCO DEPENDENCY

Supplementary material 2: Summary of evidence in the management of tobacco dependency (NRT, vaping, nicotine analogue medications)

This document provides a summary of the sources of evidence that were used to inform the development of the clinical statement. Please note that this evidence did not undergo the systematic analysis and assessment applied during the development of a BTS Guideline, given that this a BTS Clinical Statement based on consensus and knowledge of best practice.

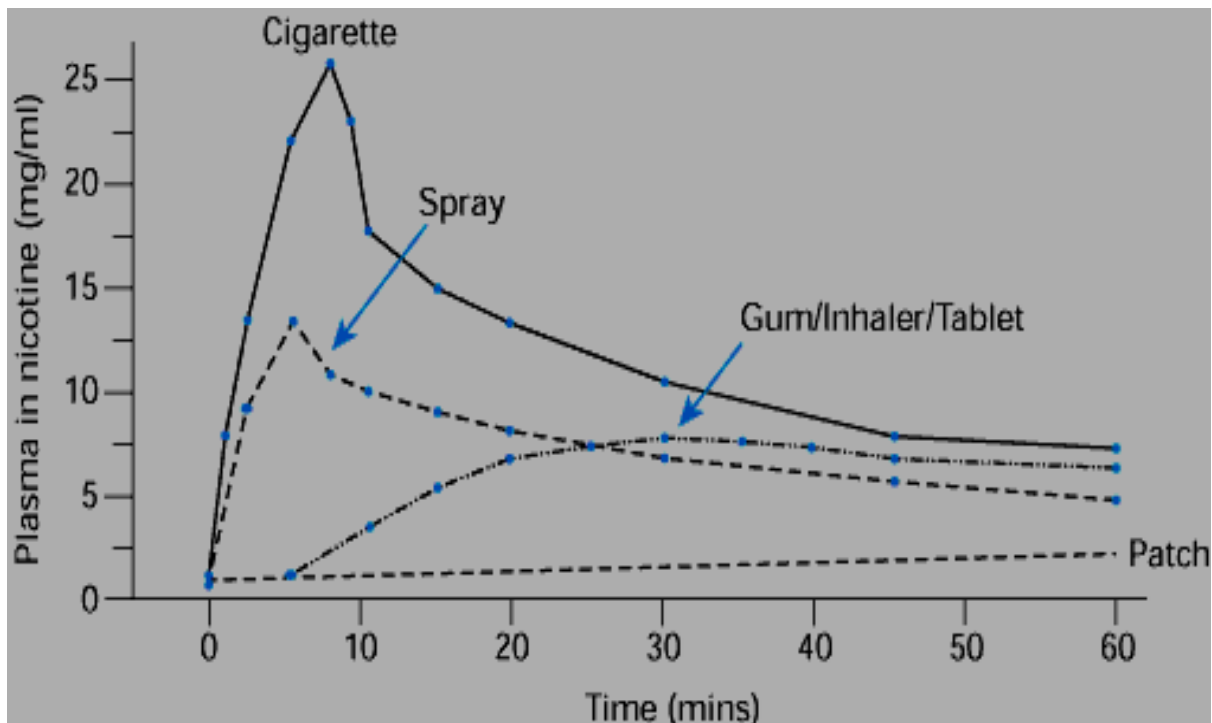
1. Nicotine Replacement Therapy: the evidence base, products and prescribing protocol

Nicotine Replacement Therapy (NRT) is the most widely studied and widely used pharmacotherapy for treating tobacco dependence. NRT aims to reduce motivation to consume tobacco by satisfying the desire for nicotine, dopamine and the pleasurable psychoactive sensations from non-tobacco sources. NRT reduces many of the physiological and psychomotor withdrawal symptoms usually experienced after stopping smoking. A meta-analysis of 136 studies with 64,640 participants has demonstrated high-quality evidence that all the licensed forms of NRT (transdermal patch, gum, nasal spray, inhalator, and sublingual tablets/lozenges) help people who make a quit attempt to increase their chances of successfully stopping smoking by 50-60%.(1). The biggest challenge for delivering effective nicotine replacement therapy is in matching the speed and intensity of nicotine delivery that smoking tobacco delivers (Figure 1).

The most effective NRT treatment regimen is to combine a long-acting transdermal patch with a fast-acting nicotine product. High quality evidence from a Cochrane review of 14 studies and 11,356 participants confirms 'combination NRT' results in higher long-term quit rates than single agent NRT (RR 1.25, 95% CI 1.15 to 1.36) (2). All medically licensed fast-acting nicotine products utilise the oromucosal membranes (none utilise alveolar absorption via inhalation like a smoking tobacco) for absorption into the systemic circulation. There are a range of medically licensed fast-acting nicotine products, all of which can be combined with transdermal nicotine patches. In

the 2021 NICE guidelines on the treatment of tobacco dependency, combination NRT was recommended as one of the most effective treatments and should be offered to all patients who smoke (3). There are no contraindications to the use of NRT and no drug interactions. It is therefore exceptionally easy to prescribe. Some patients may need to be reassured that nicotine is not a hazardous chemical and therefore there is little risk of adverse events or 'over-dosing', and that the biggest risk when using nicotine products is underdosing with break-through cravings leading to risk of relapse back into smoking tobacco.

Figure 1: Speed of nicotine delivery into blood from cigarettes and nicotine replacement (4)



Transdermal nicotine patches

NRT applied onto the skin delivers nicotine at a relatively steady rate to provide slow release, background dose of nicotine to reduce the symptoms of withdrawal. Patches are available in different doses and the strongest deliver between 21mg and 25mg of nicotine over a 24-hour or 16-hour period, resulting in plasma levels similar to the trough levels seen in 'heavy smokers'. Patches allow for escalation and de-escalation according to symptoms facilitating users to gradually decrease their nicotine intake over time. Patches are simple to use and are discreet. There is high quality evidence from the Cochrane review that the highest strength nicotine patches are the most

effective regardless of level of dependency (5). For 16-hour patches, the 25mg nicotine patch is more effective than the 15mg patch (RR 1.19, 95% CI 1.00 to 1.41, three studies, 3,446 participants).and for 24-hour patches, the 21mg nicotine patch is more effective than the 14mg patch (RR 1.48, 95% CI 1.06 to 2.08, two studies, 537 participants). Therefore, when prescribing NRT for a patient, hospital clinicians should first offer a high-dose transdermal nicotine patch (regardless of level of dependency, number of cigarettes smoked per day) to treat withdrawal. It is therefore recommended that acute Trusts make it as easy as possible for clinicians to prescribe the 25 mg/16 hours patch as standard to prevent under-dosing.

For clinicians who want to choose between the 25mg/16-hour patch, and the 21mg/24-hour patch ask the patient how quickly they smoke after waking. If a person smokes within 30 minutes of waking, they can also be offered to use the 21mg/24-hour patch to ensure there is nicotine within the systemic circulation on waking. The most frequently reported side effects of NRT patches are local skin reactions. This is not an allergic reaction and moving the site of patch application daily can reduce the incidence of skin reactions to the patch. Sleep disturbances may be reported with 24-hour patches.

Fast-acting nicotine products

Fast-acting nicotine products empower the user to vary the time and the amount of nicotine according to individual need. Control over the timing of self-dosing enables smokers to use NRT medications as a 'reach for' or 'rescue medication' when they encounter strong cravings or threats to abstinence. It is these acute craving episodes that are problematic for many cigarette smokers and are associated with a high risk of an unsuccessful quit. Fast-acting nicotine products include: gum, lozenges, micro-lozenges, microtabs, inhalator, mouth spray and a nasal spray. There is no evidence that any one fast-acting product is more effective than another, nor that patients should be restricted to one product if different products would be better suited to different scenarios. Like transdermal patches, the highest dose of each product is the recommended starting prescription. It may be helpful to remind a patient that the biggest risk when using nicotine products is underdosing with break-through cravings leading to risk of relapse back into smoking tobacco.

Encourage patients to use fast-acting products 'on the hour every hour' when first trying to stop smoking, as well as whenever cravings occur. All fast-acting nicotine products are absorbed across the oral & nasal membranes. Encourage all patients to try to avoid swallowing the nicotine which can lead to dyspepsia symptoms and impaired absorption into the systemic circulation.

- **Nicotine gum** releases nicotine into the mouth that is then absorbed across the buccal membranes of the oral cavity. It is not meant to be chewed like ordinary confectionary gum. It is most efficacious if it is intermittently chewed (initially chewed until a hot/fiery taste is felt) and then rested between the lip and gum to allow it to release its nicotine. This is called 'chew and park'. A Cochrane review found high quality evidence that 4 mg gum is more effective than 2mg gum (RR 1.43, 95% CI 1.12 to 1.83, five studies, 856 participants, (5)).
- **Nicotine lozenges/ micro-lozenges** should rest on/beneath the tongue or be parked between the lip and gum allowing the nicotine to be released and absorbed through the buccal membrane. They do not require chewing. The amount of nicotine absorbed per lozenge/ micro-lozenges is probably a little higher than that delivered by gum.
- **Nicotine micro-tabs** are placed under the tongue and allowed to dissolve so the nicotine can be absorbed through the buccal membranes.
- **Nicotine mouth spray** is administered to side of mouth and inside the cheek or under the tongue and allowed to rest where the nicotine can be absorbed across the oro-mucosal membranes.
- **Nicotine inhalator** is a popular fast-acting nicotine product. It contains cartridge of liquid nicotine with a mouthpiece. The user sucks on the mouthpiece and lets the liquid rest in the mouth so the nicotine can absorb through the oro-mucosal membranes. It is inappropriately named as an 'inhalator' as there is no inhalation. This product particularly helps with the behavioural aspects of smoking i.e. the hand-to-mouth action, while delivering NRT.
- **Nicotine nasal spray** delivers NRT more rapidly than the other forms of fast-acting nicotine products. Can initially cause eyes to water runny nose or sneezing all of which should reduce and settle after an initial period of usage.

Prescribing protocol for combination NRT incorporating the range of NRT products

Step 1: Prescribe a high dose transdermal nicotine patch

Patient smokes within 30 minutes of waking	21mg/24hrs patch
Patient smokes >30 minutes from waking	25mg/16hrs patch

Step 2: Prescribe a fast-acting nicotine product

Device	Dose	Instructions
Inhalator	15 mg per cartridge	<ul style="list-style-type: none"> • 'Puff' on it: absorbed through the gums • 10 puffs = 1 puff of a cigarette • Use: 'On the hour every hour' plus with cravings
Gum	4 mg per gum	<ul style="list-style-type: none"> • 'Chew and park': chew until fiery taste then park • Use: 'On the hour every hour' plus with cravings
Lozenge	4 mg per lozenge	<ul style="list-style-type: none"> • Suck like a sweet • Chew and park if heartburn, hiccups • Use: 'On the hour every hour' plus with cravings
Microtabs	2 mg	<ul style="list-style-type: none"> • Rest under the tongue – don't chew/swallow • Use: 'On the hour every hour' plus with cravings
Mouth spray	1 mg per spray	<ul style="list-style-type: none"> • Spray under tongue, don't swallow • Use: 'On the hour every hour' plus with cravings
Nose spray	0.5 mg per spray	<ul style="list-style-type: none"> • Spray both nostrils • Watery eyes, runny nose, sneezing should settle • Use: 'On the hour every hour' plus with cravings

2. Vaping

A Cochrane Living Systematic Review (6) has concluded there is high certainty evidence that vaping is an effective treatment for tobacco dependence using an outcome measure of long-term abstinence (at least 6 months). Vaping is more effective than NRT (quit rates 50% higher than NRT, RR 1.63, 95% CI 1.30-2.04) and no pharmacotherapy (quit rates 2.5 times higher, RR 2.66, 95% CI 1.52-4.65). No evidence of harm from vaping was detected with a follow-up period of two years. The 2021 NICE Tobacco Dependency Guideline completed a systematic review and network meta-analysis on the effectiveness of vaping to achieve abstinence from smoking tobacco with a pre-defined primary outcome of abstinence at 6 months. The network meta-analysis determined vaping to be more effective at achieving abstinence at 6 months versus non-nicotine vaping (RR 2.02, 95%CI 0.97-4.21, $p=0.06$, two trials, 489 participants) and usual care (RR 4.92, 95%CI 1.43-16.91, $p=0.01$, two trials, 1239 participants). The NICE meta-analysis also demonstrated a benefit from combining NRT with vaping over NRT alone (RR 1.77, 95%CI 1.07-2.94, two trials, 520 participants). Furthermore, recent publications have identified that people who smoke with no intention to quit smoking are significantly more likely to stop smoking if start using a vape daily than if they do not use a vape at all.

Vaping has consistently been shown to be a popular stop smoking intervention in the UK. In 2017, it was estimated that in the UK 50,700 smokers had quit smoking as a result of using vapes as an alternative method of delivering nicotine (7). In 2020, 27.2% of smokers in the UK used vaping as their chosen quit aid, compared to 15.5% for NRT and 4.4% for varenicline (8). The 2021 Public Health England commissioned report on vaping products found that vaping was the most popular aid used by people trying to quit smoking, and the highest quit rates (74%) were seen when the quit attempt involved using a licensed medicine and a vaping product consecutively (9).

Concerns have been raised about vaping in never smokers, potential harms to health of vaping products, perpetuating the use of nicotine in current and ex-smokers, uptake in children and young people, product regulation and the role and intention of the tobacco industry selling vaping products. The NICE 2021 Tobacco Dependency Guideline concluded that vaping is substantially less harmful than smoking tobacco

(3). The Office for Health Improvement and Disparities (OHID) commissioned a report in 2022 that has examined trends in vaping use and their health effects in detail (10).

Key findings from the report include:

- In the short and medium term, vaping poses a small fraction of the risks of smoking
- Vaping is not risk-free, particularly for people who have never smoked
- Evidence is mostly limited to short- and medium-term effects and studies assessing longer term vaping (for more than 12 months) are necessary
- Significantly lower exposure to harmful substances from vaping compared with smoking, as shown by biomarkers associated with the risk of cancer, respiratory and cardiovascular conditions
- Similar or higher exposure to harmful substances from vaping compared with not using nicotine products
- No significant increase of toxicant biomarkers after short-term secondhand exposure to vaping among people who do not smoke or vape
- Vaping prevalence among adults who have never smoked remained very low, at between 0.6% and 0.7% in 2021
- Most young people who have never smoked are also not currently vaping (98.3%)
- Amongst young people current vaping prevalence (including occasional and regular vaping) is 8.6% in 2022, compared with 4.0% in 2021 and 4.8% in 2020
- Amongst young people use of disposable vaping products has increased substantially, with 52.8% of current vapers using them in 2022, compared with 7.8% in 2021 and 5.3% in 2020
- In stop smoking services in 2020 to 2021, quit attempts involving a vaping product were associated with the highest success rates (64.9% compared with 58.6% for attempts not involving a vaping product)

Public health guidance recommends that never smokers should not vape, current smokers should switch completely to vaping rather than the 'dual use' of e-cigarettes and cigarettes and that vaping should only continue for as long as there is a risk of relapse to smoking. There are many independent vape companies, (not owned by

tobacco companies) that produce devices that NHS hospitals and local government stop smoking services procure. These products are tightly regulated in the UK by tobacco product regulations that were adopted from the European Tobacco Products Directive and consumer product regulations. The responsibility for enforcing the legal framework that prohibits the sale of vaping devices and liquids to any person under the age of 18 and the prevention of uptake in non-smokers falls within legislation, regulation and enforcement which sits outside the remit of this medical guideline for the treatment of tobacco dependency.

3. Nicotine analogue medications

Varenicline

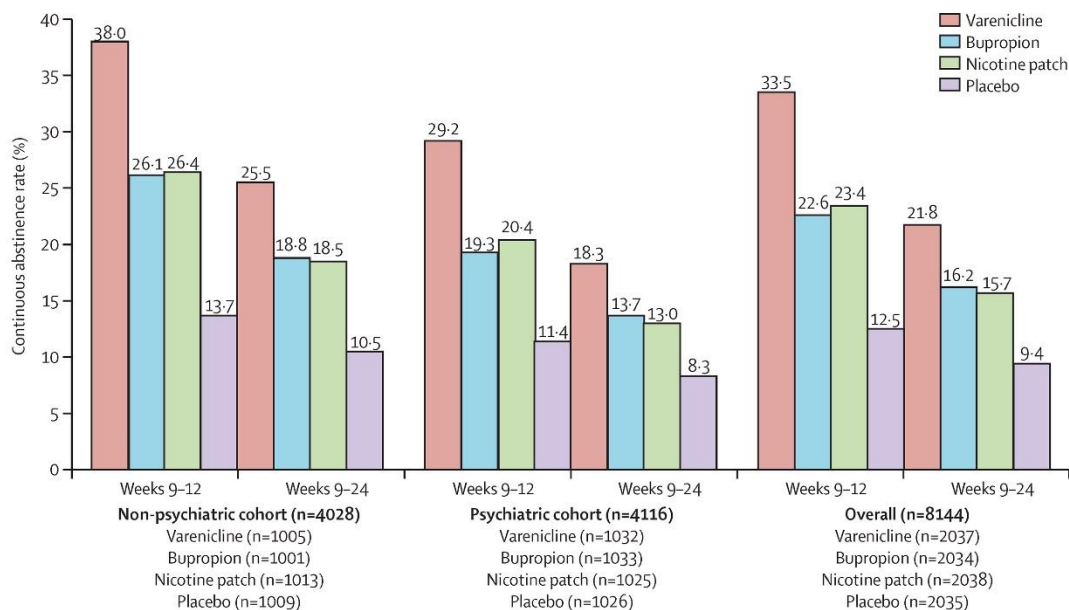
Varenicline is an oral medication that rather than being an alternative source of nicotine, instead it works in the same way as nicotine within the brain. Varenicline is a high affinity partial agonist at the $\alpha 4\beta 2$ nicotinic cholinergic receptors in the brain. Varenicline selectively binds to the nicotine receptor (and therefore creates release of dopamine to help alleviate cravings to smoke tobacco) and its high affinity for the receptor creates an 'antagonist' effect by blocking the ability of nicotine (for example if the person smokes whilst taking varenicline) to stimulate the release of dopamine. Varenicline, therefore, both reduces withdrawal from nicotine and reduces the pleasurable psychoactive effects of smoking by preventing the downstream actions of nicotine at the time of smoking. This separates the reward from the action of smoking and is a very powerful tool to overcome the dependence to tobacco.

In 2007 NICE undertook a meta-analysis as part of a technology appraisal for varenicline concluding that varenicline is superior to NRT and bupropion in achieving continuous abstinence, over a lifetime horizon varenicline dominated NRT and bupropion and was cheaper and more effective in all sensitivity analysis (11). The final technology appraisal publication stated that varenicline should be provided alongside counselling and support but if such support is not available or refused, this should not preclude treatment with varenicline. However, there has been a barrier to varenicline prescription when the recommendation to combine varenicline with specialist support

has been mis-interpreted to mean that varenicline can only be prescribed alongside specialist support and dis-empowering clinicians outside of tobacco dependence treatment services in prescribing this highly effective medication.

Since the 2007 NICE technology appraisal the evidence base for varenicline has continued to strengthen. In 2016, a Cochrane Review synthesised the evidence and confirmed varenicline was a highly effective treatment for tobacco dependence compared to placebo (RR 2.24, 95%CI 2.06-2.43, 27 trials, 12625 patients) and more effective than bupropion (RR 1.39, 95% CI 1.25-1.54, five trials, 5887 patients (12)). This Cochrane Review also calculated a number needed to treat (NNT) to support one person be abstinent from tobacco in the long term (minimum of 6 months). The NNT for NRT, bupropion and varenicline was 23, 22 and 11 respectively. In a very large meta-analysis of 115 trials and 57,000 patients varenicline and specialist behaviour support was the most effective treatment for tobacco dependency compared to all other treatment regimens (13). In the landmark tobacco dependency trial, the EAGLES trial, over 8000 patients that smoke were recruited from around the world. In this double-blind, triple dummy, placebo controlled randomised trial, varenicline, NRT and bupropion were assessed for effectiveness in leading to abstinence from tobacco head-to-head and against placebo. All treatments were effective versus placebo but Varenicline, at all timepoints, was significantly more effective than NRT (OR 1.68, 95%CI 1.46-1.93) and bupropion (OR 1.75, 95% CI 1.52-2.01, Figure 6). The abstinence rates for varenicline, bupropion, NRT and placebo were 33.5%, 22.6%, 23.4% and 12.5% at weeks 9-12 and 21.8%, 16.2%, 15.7% and 9.4% at weeks 9-24 (14). Varenicline has no drug interactions and very few contraindications, so apart from knowing to prescribe according to the recommended escalating dose schedule (days 1-3: 0.5mg once daily, days 4-7: 0.5mg twice daily and day 8 onwards:1mg twice daily), it is very easy to prescribe.

Figure 2: Abstinence rates for varenicline, bupropion, NRT across patients that smoke with and without psychiatric disorders (The EAGLES Study, The Lancet, 2016 (14))



	Weeks 9-12	Weeks 9-24	Weeks 9-12	Weeks 9-24	Weeks 9-12	Weeks 9-24
OR (95% CI) p value						
Primary comparisons						
Varenicline vs placebo	4.00 (3.20-5.00) p<0.0001	2.99 (2.33-3.83) p<0.0001	3.24 (2.56-4.11) p<0.0001	2.50 (1.90-3.29) p<0.0001	3.61 (3.07-4.24) p<0.0001	2.74 (2.28-3.30) p<0.0001
Bupropion vs placebo	2.26 (1.80-2.85) p<0.0001	2.00 (1.54-2.59) p<0.0001	1.87 (1.46-2.39) p<0.0001	1.77 (1.33-2.36) p<0.0001	2.07 (1.75-2.45) p<0.0001	1.89 (1.56-2.29) p<0.0001
Secondary comparisons						
Nicotine patch vs placebo	2.30 (1.83-2.90) p<0.0001	1.96 (1.51-2.54) p<0.0001	2.00 (1.56-2.55) p<0.0001	1.65 (1.24-2.20) p=0.0007	2.15 (1.82-2.54) p<0.0001	1.81 (1.49-2.19) p<0.0001
Varenicline vs nicotine patch	1.74 (1.43-2.10) p<0.0001	1.52 (1.23-1.89) p=0.0001	1.62 (1.32-1.99) p<0.0001	1.51 (1.19-1.93) p=0.0008	1.68 (1.46-1.93) p<0.0001	1.52 (1.29-1.78) p<0.0001
Bupropion vs nicotine patch	0.98 (0.80-1.20) p=0.8701	1.02 (0.81-1.28) p=0.8645	0.94 (0.75-1.16) p=0.5467	1.07 (0.83-1.39) p=0.5824	0.96 (0.83-1.11) p=0.5797	1.04 (0.88-1.24) p=0.6002
Varenicline vs bupropion	1.77 (1.46-2.14) p<0.0001	1.49 (1.20-1.85) p=0.0003	1.74 (1.41-2.14) p<0.0001	1.41 (1.11-1.79) p=0.0047	1.75 (1.52-2.01) p<0.0001	1.45 (1.24-1.70) p<0.0001

The most frequently recorded adverse effects of varenicline are nausea, sleep disturbance and vivid/colourful dreams. Nausea is generally mild to moderate and tends to subside over time. If side effects are intolerable the dose of varenicline can be reduced by half to 0.5mg twice a day, in order to continue treatment whilst simultaneously decreasing the incidence of side effects. A significant barrier to the prescription and usage of varenicline had been concerns over mental health side effects, which have subsequently been disproven by a number of meta-analyses (15) and the EAGLES trial that specifically tested the question of neuropsychiatric complications. In conclusion, varenicline is a highly effective treatment for tobacco dependency.

Cytisine

Cytisine is a naturally occurring chemical derived from the plant *Cytisus laburnum* (golden rain, endemic to the Balkans) and is a nicotine analogue. It is a partial agonist

of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor, similar to varenicline. It was first identified during World War II when soldiers smoked the leaves of Golden Rain when there was a shortage of tobacco. The observation that doing this alleviated the desire to smoke tobacco led to the development of cytisine tablets and they have been used as a tobacco dependence treatment in Eastern Europe since the 1960s. Several randomised controlled trials (12, 16) and a systematic review and meta-analysis in 2013 (17) have concluded that cytisine is an effective tobacco dependence treatment. The meta-analysis synthesised the results of seven RCTs resulting in a RR 1.57, 95% CI 1.42-1.74 in favour of cytisine versus placebo, but when this was restricted to two high-quality RCTs the RR was 3.29, 95%CI 1.84-5.90 (17). Furthermore, trials of cytisine have shown effectiveness for tobacco abstinence at long term follow-up (18-20). In a trial comparing cytisine with NRT in 1310 people there was a benefit of cytisine at six months (RR 1.43, 95% CI 1.13 to 1.80, (21, 22)). A RCT in New Zealand found that cytisine was at least as effective as varenicline at supporting smoking abstinence in indigenous Māori, with significantly fewer adverse events (23). Abstinence rates at 6 months were 12.1% in the cytisine arm versus 7.9% in the varenicline arm (RR 1.55, 95%CI 0.97-2.46).

Cytisine is taken over a 25-day course with the highest dose at the beginning and gradually reducing over the course of 25 days. Cytisine may be marketed as a medicinal product in the UK in the coming years but is currently freely available to be purchased as a consumer product.

Bupropion

Bupropion was initially developed as a non-tricyclic antidepressant and is approved as an antidepressant as well as for tobacco dependence. It is a selective dopamine and noradrenaline reuptake inhibitor and an antagonist at the nicotinic receptor. The exact mechanism of action of bupropion is not fully understood and overall its effect on dopamine is relatively weak. The evidence for bupropion is consistent, it is effective in treating tobacco dependence versus placebo (14) but has a similar efficacy to NRT and is inferior in efficacy to varenicline (11-14).

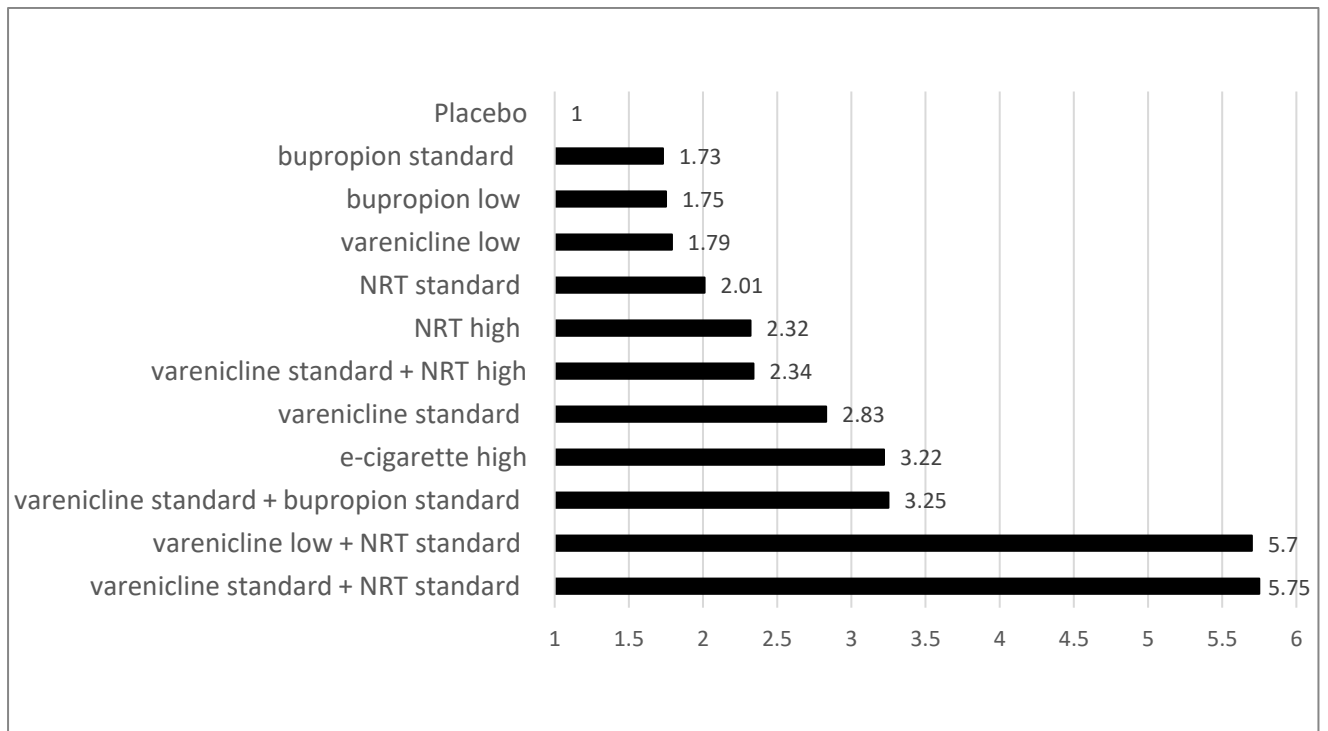
The challenge with bupropion is it has a number of drug interactions that require a dose reduction. It also carries a risk of seizures and therefore requires a careful

medical history to elicit any increased risk of seizures such as falls, alcohol dependency, episodes of hypoglycaemia, epilepsy and medications that reduce the seizure threshold. This makes bupropion a more challenging drug to safely prescribe than NRT or varenicline and should be used with the support of a specialist tobacco dependency practitioner.

4. Tobacco dependency treatments in combination

There is evidence that combining tobacco dependency treatments provides added benefit. Combination therapy of varenicline and NRT is more effective than varenicline alone, especially if pre-cessation treatment of nicotine patch is administered (24). Two studies directly compared varenicline combined with a nicotine patch with varenicline alone and reported on smoking abstinence at 6 months.(25, 26) One found significant increased abstinence in the combination group at 12 weeks and at 6 months (25) and one found that the abstinence rates among smokers who smoked more than 29 cigarettes per day were significantly higher in the combination group at 12 weeks and 24 weeks but not in all smokers as a whole, independent of consumption level (26). The evidence for combination treatments was synthesised in a systematic review and meta-analysis published in 2021 (27). This identified the most effective tobacco dependency treatment regimen was the combination of varenicline and NRT with a RR 5.75 (95%CI 2.27-14.88, Figure 3). The American Thoracic Society clinical practice guideline on tobacco dependency recommends varenicline plus a nicotine patch over varenicline alone.(28). The combination of varenicline and NRT is particularly suited to the inpatient environment where patients who smoke require additional nicotine in the early stages of varenicline treatment but are in the smoke-free environment of a hospital.

Figure 3: Outcomes of a systematic review and network meta-analysis: Effectiveness of treatments for tobacco dependency (27)



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