Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

All Wales Guide:

Pharmacotherapy for smoking cessation

February 2018

(November 2024 – updated after changes to the availability of treatments and AWMSG advice on cytisinicline [cytisine])

This guide has been prepared by Public Health Wales, with support from the All Wales Prescribing Advisory Group (AWPAG), the All Wales Therapeutics and Toxicology Centre (AWTTC) and Help Me Quit advisors, and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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1.0 Introduction

Behavioural support and pharmacotherapies are both effective in helping people to stop smoking. Combining both treatment approaches is recommended where possible[1]. The effectiveness of all smoking cessation pharmacotherapy increases if used in combination with behavioural support.

In April 2017, a new unified brand 'Help Me Quit' (HMQ) was launched in Wales with a single free-phone number and new website making it easier for smokers to access help to quit. Smokers can be referred or signposted by a healthcare professional, or can contact Help Me Quit directly by calling 0800 085 2219, visiting www.helpmequit.wales or texting HMQ to 80818. Healthcare professionals can refer to HMQ by completing the professional referral form on the website, by calling the above number, or through existing referral pathways. By referring smokers to HMQ they will be routed to the most appropriate service and method to quit, following a choice conversation with a trained call handler.

In general, stopping smoking in one step (sometimes called 'abrupt quitting') offers the best chance of lasting success[2]. Pharmacotherapy should normally be supplied as part of an abstinent-contingent treatment, in which the smoker makes a commitment to stop smoking on or before a particular date (target quit date)[3].

This guidance covers the use of licensed pharmacotherapy to support stopping smoking in one step, as well as tobacco harm reduction approaches. Guidance on tobacco harm reduction approaches, including temporary or long-term use of licensed nicotine-containing products, is provided by the National Institute for Health and Care Excellence (NICE)[3].

Our guidance does not cover the use of electronic nicotine delivery systems (ENDS), which include e-cigarettes or vapes, to stop smoking. Some guidance on the use and potential benefits of using ENDS by committed smokers who are unwilling or unable to stop smoking is provided in section 6.0.

1.1 Assessing nicotine dependence

The Fagerström test is widely used to assess nicotine dependence[4]. How soon a person smokes after waking seems to be the most important indicator of dependence[5]. Smoking within 30 minutes of waking is a reliable indicator of nicotine dependence. Smoking within 5 minutes of waking indicates a higher level of dependence.

The number of cigarettes smoked per day is less predictive. Dependence is more likely if more than 10 cigarettes are smoked per day.

The level of nicotine dependence is a predictor of withdrawal symptoms and the intensity of treatment required. Cravings and withdrawal symptoms experienced in previous quit attempts can also be a useful guide.

1.2 Pharmacotherapy forms

The four forms of pharmacotherapy that are licensed for use in the UK to assist with smoking cessation are:

- Nicotine replacement therapy (NRT)
- Varenicline

- Bupropion
- Cytisinicline (cytisine)[6].

A Cochrane meta-analysis concluded that each of these improves the chances of quitting[7]. Combination NRT (the use of an immediate-release formulation plus patches) is more effective than single types of NRT[7].

Clinical suitability, including effectiveness and safety, as well as patient preference are important in guiding the choice of pharmacotherapy[8].

1.3 Cautions

A summary of cautions in the use of pharmacotherapy in special populations is provided in Appendix 1.

Healthcare professionals should refer to the latest edition of the BNF and manufacturers' Summaries of Product Characteristics (SPCs) for further guidance and prescribing information.

1.4 Supply of pharmacotherapy

Clinical responsibility for the supply of pharmacotherapy lies with the healthcare professional authorising the supply. This may be the prescriber (medical or non-medical) or the community pharmacist providing a level 2 or level 3 smoking cessation service; and supply may take place in primary care or in a hospital (inpatient or outpatient) setting. Where the person authorising the supply of non-nicotine-based pharmacotherapy, such as varenicline, cytisinicline (cytisine) or bupropion, is not able to access a patient's medical records, they should ensure a complete medical and medication history has been taken.

People who engage with a smoking cessation service for behavioural support to quit, should receive a supply of NRT, non-nicotine-based pharmacotherapy, such as varenicline or cytisinicline (cytisine) or bupropion, sufficient to last no more than two weeks after the target quit date[3]. Subsequent supplies should be given at regular intervals (phased supply) only to people who have demonstrated, on re-assessment (e.g. by carbon monoxide testing), that their quit attempt is continuing[3]. Phased supply enables ongoing review of the suitability of the formulation and dosage in order to more closely target the person's needs during their quit attempts and reduce the potential for wastage. Because cytisinicline is only a 25-day treatment course, the complete course consisting of a 100-tablet pack should be supplied[6].

A summary dosage and supply guide for smoking cessation pharmacotherapy is provided in Appendix 2.

1.5 Pharmacotherapy and other medicines

Tobacco smoking increases the metabolism of some medicines by stimulating the hepatic enzyme CYP1A2. When a person stops smoking, the dose of these medicines, in particular theophylline, cinacalcet, ropinirole and some antipsychotics (including clozapine, olanzapine, chlorpromazine and haloperidol), may need to be reduced[9]. Regular monitoring for adverse effects is advised.

2.0 Nicotine replacement therapy

Nicotine replacement therapy (NRT) refers to licensed products containing nicotine that are used as a treatment to aid smoking cessation. This guidance covers the use of NRT in place of cigarettes after abrupt cessation of smoking.

The aim of using NRT is to reduce withdrawal symptoms by providing some of the nicotine that would be obtained from cigarettes, without providing the harmful chemicals present in tobacco smoke. NRT delivers nicotine to the body but at a lower dose and slower rate compared with smoking.

2.1 Choice of NRT formulation

The use of a combination of both short- and long-action NRT should be offered as first-line choice[10,11]. There are six different types of short-acting NRT formulations available (gum, lozenges, sublingual tablets, inhalator, oral spray, and nasal spray) and a range of strengths[10,11]. This offers a variety of approaches to best match individual smokers' needs and preferences. Advise people, as appropriate for their age, that stopping smoking is more likely to be successful when combined with behavioural support[3].

Shared decisions made with the person and their healthcare professional should consider the evidence of effectiveness and level of nicotine dependency. The choice of NRT depends largely on:

- patient preference;
- previous patient experience of the type of formulation(s), if any, tried before;
- contraindications, cautions and the potential for adverse effects.

Long-acting patches provide slower, sustained-release delivery of nicotine, while oral and nasal formulations provide faster release of nicotine as intermittent doses used to treat breakthrough cravings. The use of NRT is more effective in achieving abstinence if combined with behavioural support and where combination NRT is used[1].

Table 1. Some advantages and disadvantages of different NRT formulations

Formulation	Advantages	Disadvantages
Patch	• Discreet and easy to use • Long-acting • Doesn't mimic the highs and lows associated with smoking	• Unsuitable for people with certain skin conditions
Gum	• Available in a variety of doses and flavours	• Unsuitable for people who use dentures
Lozenge	• Discreet • Available in a variety of doses and flavours	
Sublingual tablet	• Discreet	• Only one strength available • No flavour
Inhalator	• May be useful for people who miss the hand-to-mouth movements of smoking	

Formulation	Advantages	Disadvantages
Oral spray	• Rapid delivery of nicotine • Available in a variety of flavours	• Only one strength available
Nasal spray	• Rapid delivery of nicotine similar to smoking cigarettes	

Further information about products can be found on the Help Me Quit website.

2.2 Clinical suitability

Most health warnings associated with NRT also apply to continued tobacco smoking, but the risks of continued smoking outweigh any risks of using NRT preparations[9].

NRT should be considered for all people attempting to quit smoking, including pregnant and breast-feeding women. All NRT preparations are licensed for adolescents over 12 years old[12]. All forms of NRT can be used by patients with stable cardiovascular disease but should be used with caution in those in hospital for acute cardiovascular events.

NRT should be considered, alongside behavioural support, at the earliest opportunity in pregnancy and should be continued throughout and after pregnancy if needed to prevent a relapse[3].

A summary table containing more details of cautions in the use of NRT in special populations is provided in Appendix 1.

Specific cautions for individual preparations are usually related to the local effect of nicotine. Examples are provided in Table 2.

2.3 Adverse effects

Minor adverse effects are common with NRT use, particularly in patients using high-strength formulations. They usually improve with time, but treatment may need to be reviewed if they continue or become troublesome.

However, patients may confuse the side effects of NRT with nicotine withdrawal symptoms. Common symptoms of nicotine withdrawal include: malaise, headache, dizziness, sleep disturbance, coughing, influenza-like symptoms, depression, irritability, increased appetite, weight gain, restlessness, anxiety, drowsiness, mouth ulcers, decreased heart rate, and impaired concentration.

Common adverse effects of NRT include: headache, dizziness, coughing, and gastrointestinal disturbances (nausea, vomiting, heartburn, and hiccups). Palpitations may occur, and rarely allergic reactions (including angioedema) and (very rarely) reversible atrial fibrillation.

Mild local reactions are common on initiation of NRT because of the irritant effect of nicotine. Mouth ulcers have also been reported. Examples of cautions and adverse effects which may be related to formulation type are provided in Table 2.

Healthcare professionals and patients are asked to report suspected adverse drug reactions that are serious (i.e. fatal, life-threatening, disabling or incapacitating, result

in or prolong hospitalisation or cause congenital abnormalities), medically significant, or result in harm through the Yellow Card Scheme at https://yellowcard.mhra.gov.uk/.

Table 2. Examples of cautions and adverse effects which may be related to formulation type

NRT formulation	Cautions	Adverse effects
Patch	Nicotine patches should not be placed on broken skin and should be used with caution in patients with skin disorders.	Minor skin irritation at the application site(s). If the skin reaction becomes more severe or more widespread, treatment with patches should be discontinued. Dry mouth, sleep disturbances including abnormal dreams. Chest pain, sweating, myalgia and arthralgia have been reported.
Oral NRT in general	Caution in use with oesophagitis, oral or pharyngeal inflammation, gastritis, or peptic ulcers. Due to the potential for reduced absorption of nicotine through buccal mucosa, patients should generally avoid: • acidic beverages for 15 minutes before using oral NRT; • eating or drinking while using oral NRT.	Gastrointestinal disturbances are common and may be caused by swallowed nicotine; nausea, vomiting, dyspepsia, and hiccupping occur most frequently.
• Gum	The gum may stick to and damage dentures.	Mild local reactions (such as erythema and urticaria), sore mouth or throat, increased salivation, dry mouth, and jaw-muscle ache.
• Lozenge		Mild local reactions (such as erythema and urticaria), sore mouth or throat, dry mouth, increased salivation, mouth ulcers. Less commonly: thirst, taste disturbance, gingival bleeding, halitosis, rash, and hot flushes.
• Sublingual tablet		Dry mouth, sore mouth or throat, burning sensation in the mouth, and cough.

NRT formulation	Cautions	Adverse effects
• Inhalator	Care should be taken with the inhalation cartridges in patients with obstructive lung disease, chronic throat disease, or bronchospastic disease.	Mild local reactions such as cough and irritation to the mouth and throat.
• Oral spray		Mild local reactions such as cough and irritation to the mouth and throat, dry mouth, increased salivation, mouth ulcers, taste disturbance, and toothache. Hiccups can occur if sprayed at the throat instead of cheek lining.
Nasal spray	The nasal spray can cause worsening of bronchial asthma. Use of the spray in patients with hyperreactive airways is not recommended. The nasal spray should not be used whilst the user is driving or operating machinery as sneezing and watering eyes could contribute to accidents.	Nasal irritation (such as rhinorrhoea and sneezing), increased lacrimation, nose bleeds and cough. Both the frequency and severity of nasal irritation and rhinorrhoea has been reported to decline with continued use.

2.4 Supply/prescribing notes for NRT

- The initial supply should be of an appropriate duration to ensure commitment to quit and to minimise waste. Usually a quantity that will last a maximum of 2 weeks after the target quit date is sufficient as an initial supply. Quantity and frequency of supply should be guided by local service specifications and tailored to individual circumstances, e.g. to cover holidays. (Quantity guide in Table 3.)
- Where NRT is added to prescribing systems this should be for short-term use or acute prescription only.
- Emphasise the importance of using NRT regularly at first, and at an adequate dose to reduce the symptoms of nicotine withdrawal sufficiently. (Dosage guide in Table 4.)
- Further supplies should only be issued if the quit attempt is continued.
- Phased supply can help to tailor the NRT formulation and dosage to the individual patient's needs and to avoid potential waste. (Quantity guide in Table 3 and dosage guide in Table 4.)
- Treatment is recommended for 8 to 12 weeks, unless otherwise stated in the product information. Followed by a gradual reduction in dose[3].
- If continued longer and abstinence is not achieved after 6 to 9 months, treatment should be reviewed.

Table 3. Quantity of NRT: first and further supplies

Formulation	First supply	Further supplies
Single NRT (for those unable to use combination NRT)	Usually 1- or 2-week supply at maximum daily dose.	Appropriate quantity at regular intervals based on actual usage and any remaining NRT from previous prescription. Subsequent supplies should only be given to people who on reassessment have demonstrated that they are still engaging with support and treatment.
Combination NRT	Usually 1- or 2-week supply e.g. (7 or 14) patches **plus** up to the maximum daily dose quantity of one immediate-release NRT, to last 2 weeks.	Appropriate quantity of patches plus an appropriate quantity of one immediate-release NRT, at regular intervals based on actual usage and any remaining NRT from previous prescription. Subsequent supplies should only be given to people who on reassessment have demonstrated their quit is continuing.

NB: Quantity and frequency of supply should be guided by local service specifications and tailored to individual circumstances e.g. to cover holidays.

Table 4. Dosage guide for NRT formulations

Patch (transdermal patches)	Strength	More than 10 cigarettes daily	Fewer than 10 cigarettes daily	Relative cost	2-week supply (max dose)
25 mg/16 hours	High	• Specify the patch strength (mg) and duration (16 or 24 hours). • Start with a high-strength patch daily for the first 6 to 8 weeks. • Follow with a medium-strength patch for 2 weeks. • Then a low-strength patch for the final 2 weeks.	• Specify the patch strength (mg) and duration (16 or 24 hours). • Start with a medium-strength patch daily for the first 6 to 8 weeks. • Follow with a low-strength patch for the final 2 to 4 weeks.	£	14 patches
15 mg/16 hours	Medium				
10 mg/16 hours	Low				
21 mg/24 hours	High				
14 mg/24 hours	Medium				
7 mg/24 hours	Low				
Additional information	• 24-hour patches may be more suitable if patients have strong cravings for cigarettes on waking. • Sleep disturbances may be helped by removing the patches before bed (changing from a 24-hour patch to a 16-hour patch). • If abstinence is not achieved, or if withdrawal symptoms are experienced, maintain or increase the strength of the patch until the patient is stabilised. • If patients using a high-strength patch experience excessive side effects that do not resolve within a few days, change to a medium-strength patch for the remainder of the initial period, and then a low-strength patch for 2 to 4 weeks.				
Gum (medicated chewing gum sugar-free)	**Strength**	**More than 20 cigarettes daily**	**Fewer than 20 cigarettes daily**		
4 mg/6 mg	Higher	• Start with higher-strength gum. • Maximum 15 pieces of gum daily. • Consider starting with higher strength if the first cigarette of the day is smoked within 30 minutes of waking up.	• Start with lower-strength gum. • Up to 15 pieces of gum daily. • If patient uses more than 15 pieces of 2 mg gum daily, change to the higher-strength (4 mg or 6 mg) gum. • Consider starting with lower strength if the first cigarette of the day is smoked more than 30 minutes after waking up.	£	210 pieces of gum
2 mg	Lower				

Lozenge (sugar-free)	Strength	More than 20 cigarettes daily	Fewer than 20 cigarettes daily		
4 mg (nicotine resinate) 2 mg (nicotine)	Higher	• Start with higher-strength 2 mg (nicotine) or 4 mg (nicotine resinate) lozenge. • Maximum 15 higher-strength lozenges daily. • Consider starting with a higher strength if the first cigarette of the day is smoked within 30 minutes of waking up.	• Start with lower-strength 1 mg (nicotine) or 2 mg (nicotine resinate) lozenge. • Maximum 30 lower-strength lozenges daily. • Consider changing to higher strength if insufficient effect at 15 or over lower strength lozenges daily. • Consider starting with a lower strength if the first cigarette of the day is smoked more than 30 minutes after waking up.	£	210 lozenges
2 mg (nicotine resinate) 1 mg (nicotine)	Lower				

Sublingual tablets (sugar-free)	More than 20 cigarettes daily	Fewer than 20 cigarettes daily	Relative cost	2-week supply (max dose)
2 mg (cyclodextrin complex)	• Start with higher dosage: 2 tablets each hour. • Maximum 40 tablets daily.	• Start with lower dosage: 1 tablet each hour. • Increase to 2 tablets each hour if necessary. • Maximum 40 tablets daily.	££	280 tablets (lower dose) 560 tablets (higher dose)
Inhalator (inhalation cartridges)	**All dependency levels**			
15 mg	• Maximum 6 cartridges of the 15 mg strength daily.		££	84 cartridges

Oral spray (oromucosal spray sugar-free)	**All dependency levels**		
1 mg per spray (150 sprays per 13.2 ml)	• Maximum 2 sprays per episode (up to 4 sprays every hour). • Maximum of 64 sprays daily.	££	5 packs (150 sprays per 13.2 ml)
Nasal spray	**All dependency levels**		
500 micrograms per dose (200 sprays per 10 ml)	• Use one spray in each nostril, up to twice every hour for 16 hours daily. • Maximum 64 sprays daily.	££	4 packs (200 sprays per 10 ml)

3.0 Varenicline

Varenicline is a selective nicotine-receptor partial agonist. It reduces the severity of cravings and withdrawal symptoms, while simultaneously reducing the rewarding effects of nicotine[13]. It should normally be supplied only as part of a programme of behavioural support[13].

Varenicline is a prescription only medicine (POM) and, in primary care, is usually supplied via a WP10 prescription. However, non-nicotine-based pharmacotherapy can be made available via a community pharmacy enhanced smoking cessation service through a Patient Group Direction (PGD).

3.1 Clinical suitability

Varenicline is licensed for use in adult smokers (18 years old and over), for smoking cessation.

Its use is contraindicated in those with hypersensitivity to varenicline or any of the excipients in the formulation[14]. Due to limited safety data, its use in pregnant women should be avoided. Animal studies suggest that varenicline is excreted in breast milk. However, whether it is excreted in human breast milk is unknown. For this reason, use by breastfeeding women should be avoided. The decision to continue or discontinue breastfeeding or therapy with varenicline should be made taking into account the benefits of breastfeeding to the child and therapy with varenicline to the woman.

Caution is recommended for use in patients with cardiovascular disease. Patients taking varenicline should be instructed to notify their doctor of new or worsening cardiovascular symptoms and seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.

Caution is also recommended in patients with predisposition to seizures (including conditions that lower seizure threshold). Dosage may need to be adjusted in moderate or severe renal impairment. Treatment with varenicline is not recommended for use in patients with end-stage renal disease.

A summary table containing more details of cautions in the use of varenicline in special populations is provided in Appendix 1.

To date, there are no known clinically meaningful drug interactions with varenicline.

3.2 Adverse effects

Gastrointestinal symptoms, including nausea, are the most common adverse effects of varenicline. Other commonly reported adverse effects include: headache, insomnia, abnormal dreams, appetite changes, weight gain, dizziness, cough, back pain and nasopharyngitis.

Varenicline may cause dizziness and drowsiness and therefore influence the ability to drive and use machines. Patients are advised not to drive or operate complex machinery, or take part in potentially hazardous activities until they know how varenicline affects their ability to perform these activities.

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal. Clinicians should be aware of the possible

emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. Despite clinical trial data showing no evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo and independent observational studies reporting no increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed NRT or bupropion, some neuropsychiatric symptoms have been reported in post-marketing experience. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment[14].

Healthcare professionals and patients are asked to report suspected adverse drug reactions that are serious (i.e. fatal, life-threatening, disabling or incapacitating, result in or prolong hospitalisation or cause congenital abnormalities), medically significant or result in harm through the Yellow Card Scheme at https://yellowcard.mhra.gov.uk/.

3.3 Dose and duration of treatment

The recommended duration of treatment with varenicline is 12 weeks. Review every 2 weeks.

The 12-week course can be repeated in abstinent individuals to reduce the risk of relapse.

Table 5. Dosage guide for varenicline

Dose	Relative cost = £
Adults over 18 years	Start 1 to 2 weeks before target quit date (up to maximum of 5 weeks before target quit date). 500 micrograms once daily for 3 days, increase to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks. Reduce dose to 500 micrograms twice daily if not tolerated.
Severe renal impairment (eGFR < 30 ml/min/1.73 m^2). Avoid in end-stage renal disease.	500 micrograms once a day for the first 3 days, then increase to 1 mg once a day.

Stopping varenicline is associated with an increase in irritability, urge to smoke, depression and/or insomnia in up to 3% of patients. Dose tapering should be considered at the end of a 12-week course to prevent symptoms and reduce the risk of relapse.

Table 6. Supply intervals and quantities for varenicline

Varenicline supply	Duration	Quantity
1st	2 weeks (starter pack)	11 x 500 microgram tablets and 14 x 1 mg tablets (starter pack)
2nd, 3rd, 4th, 5th & 6th	Regular intervals usually 2 weeks	Sufficient to cover supply interval e.g. 2 week supply = 1 mg x 28 tablets or 500 microgram x 28 tablets if using lower dose

A gradual approach to quitting smoking with varenicline should be considered for patients who are not able or willing to quit abruptly. Patients should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. Patients should then continue taking varenicline for an additional 12 weeks for a total of 24 weeks of treatment[15].

4.0 Bupropion

Bupropion is a non-nicotine aid to smoking cessation that reduces the urge to smoke and withdrawal symptoms. It has dopaminergic and noradrenergic effects that can aid smoking cessation. Bupropion was originally developed as an antidepressant. As with all other smoking cessation pharmacotherapy, the effectiveness of bupropion increases if used in combination with behavioural support.

4.1 Clinical suitability

Bupropion is licensed for use in adult smokers (18 years old and over). It should be avoided in pregnancy and by breast-feeding women due to a lack of safety data. It is contraindicated in people with hypersensitivity to bupropion or any of the excipients in the formulation[16].

Bupropion is contraindicated in people with: a current seizure disorder or any history of seizures, central nervous system (CNS) tumour, acute alcohol or benzodiazepine withdrawal, eating disorders, severe hepatic cirrhosis, bipolar disorder, or concomitant use of monoamine oxidase inhibitors (MAOIs)[16].

Bupropion is associated with a dose-related risk of seizure. The risk of seizure occurring with the use of bupropion is increased in the presence of predisposing factors including: alcohol misuse, history of head trauma, diabetes, and concomitant use of medicines known to lower seizure threshold. Prescribe only if benefit clearly outweighs risk. In these patients reduced dosage should be considered for the duration of their treatment.

Bupropion may be used with caution in patients with hepatic impairment and in the elderly. Reduced dosage is recommended for these patients.

A summary table containing more details of cautions in the use of bupropion in special populations is provided in Appendix 1.

Bupropion inhibits the CYP2D6 pathway. Medicines predominantly metabolised by CYP2D6, such as certain antidepressants, antipsychotics, beta-blockers, and anti-arrhythmics, should be started at the lower end of the dose range in patients taking bupropion. If bupropion is prescribed to a patient already taking such a medicine, the need to decrease the dose of that medicine should be considered. The expected benefits of treatment with bupropion should be weighed against the potential risks.

Bupropion is metabolised primarily by CYP2B6, and medicines which affect this enzyme such as substrates (e.g. cyclophosphamide) or inhibitors (e.g. orphenadrine or clopidogrel) may alter levels of bupropion and its metabolites. The clinical effect of this is unknown.

Since bupropion is extensively metabolised, medicines that inhibit its metabolism (e.g. valproate) or induce metabolism (e.g. carbamazepine and phenytoin), may affect its clinical effects.

4.2 Adverse effects

Bupropion causes insomnia very commonly. This can be reduced by avoiding bedtime doses, provided there is at least 8 hours between doses. Common adverse effects include: hypersensitivity reactions (e.g. urticaria), dry mouth, gastrointestinal disorders, taste disturbance, agitation, anxiety, tremor, dizziness, depression, headache, impaired concentration, rash, pruritus, sweating, and fever.

Neuropsychiatric reactions have been reported. In particular, psychotic and manic symptomatology have been reported mainly in patients with a known history of psychiatric illness.

Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation and behaviour (including suicide attempt), has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported during bupropion treatment, and generally occurred early during the treatment course.

Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly[16].

Seizures are a rare but clinically important adverse effect of bupropion. Treatment with bupropion should be stopped if a patient has a seizure while taking it.

Hypertension, in some cases severe, has been reported in patients taking bupropion. This has been observed in patients with and without pre-existing hypertension. Blood pressure should be measured at the start of treatment and monitoring undertaken.

The more common adverse effects of bupropion include agitation, anxiety, depression, dry mouth, gastrointestinal disturbances, headache, impaired concentration, insomnia, and skin disturbances.

Patients should exercise caution before driving or using machinery until they are reasonably certain bupropion does not adversely affect their performance.

Healthcare professionals and patients are asked to report suspected adverse drug reactions that are serious (i.e. fatal, life-threatening, disabling or incapacitating, result in or prolong hospitalisation or cause congenital abnormalities), medically significant or result in harm, via the Yellow Card Scheme at https://yellowcard.mhra.gov.uk/.

4.3 Dose and duration of treatment

The recommended duration of treatment with bupropion is 7 to 9 weeks. Review every 2 weeks.

Table 7. Dosage guide for bupropion

Dose	Relative cost = £
Adults over 18 years	Start 1 to 2 weeks before target quit date. Initially 150 mg daily for 6 days, then 150 mg twice daily (maximum per dose 150 mg, maximum daily dose 300 mg; minimum 8 hours between doses). Period of treatment 7–9 weeks; discontinue if abstinence not achieved at 7 weeks.
Elderly	Maximum 150 mg once a day.
Hepatic impairment. (Avoid in severe hepatic cirrhosis.)	Reduce dose to 150 mg once a day.
Renal impairment	Reduce dose to 150 mg once a day.
Predisposition to seizures	Not usually prescribed unless compelling clinical justification outweighs risk of seizure. Consider a maximum dose of 150 mg daily.

Although discontinuation reactions are unlikely on stopping bupropion, a tapering off period may be considered 1 to 2 weeks before stopping if the patient prefers.

Table 8. Supply intervals and quantities for bupropion

Bupropion supply	Duration	Quantity
1st	2 weeks	22 x 150 mg tablets (provides 2-week supply at standard initiation dose)
2nd & 3rd	2 weeks	28 x 150 mg tablets (14 x 150 mg tablets if using lower dose)
4th	Up to 3 weeks (to complete the course of treatment)	Up to 42 x 150 mg tablets (Up to 21 x 150 mg tablets if using lower dose)

5.0 Cytisinicline (cytisine)

Cytisinicline (cytisine) is a plant alkaloid with a chemical structure similar to nicotine[17]. Cytisinicline is a name given to the chemical cytisine, and was coined by Achieve Life Sciences, a US pharmaceutical company. For clarity, this document uses the name cytisinicline, because this is the name used in the SPC, and the recommendations of the All Wales Medicines Strategy Group (AWMSG) and other documentation in Wales[17].

The use of cytisinicline allows for a gradual reduction of nicotine dependence by relieving withdrawal symptoms. Cytisinicline competes with nicotine for the same receptors and gradually displaces nicotine due to its stronger binding[18]. It should normally be supplied only as part of a programme of behavioural support[13].

Cytisinicline is licensed in the UK as a prescription only medicine (POM). Cytisinicline was recommended by the AWMSG in July 2024 as an option for use within NHS Wales for smoking cessation and reduction of nicotine cravings in smokers who are willing to stop smoking[6,19].

5.1 Clinical suitability

Cytisinicline is licensed for use in adult smokers (18–65 years), for smoking cessation[20].

Its use is contraindicated in those with arrhythmias, recent myocardial infarction, recent stroke and unstable angina.

Caution is recommended for use in patients with cardiovascular disease. Patients taking cytisinicline should be instructed to notify their doctor of new or worsening cardiovascular symptoms and seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.

Caution is also recommended in patients with gastric and duodenal ulcer; gastro-oesophageal reflux disease; history of psychiatric illness (may exacerbate underlying illness including depression); hyperthyroidism; peripheral vascular disease; phaeochromocytoma; schizophrenia.

Cytisinicline is contraindicated for use during pregnancy or breastfeeding in the SPC because there no data are currently available[18].

A summary table containing more details of cautions in the use of cytisinicline in special populations is provided in Appendix 1.

Cytisinicline might decrease the efficacy of the combined hormonal contraceptive. The manufacturer advises to use additional contraceptive precautions[20].

5.2 Adverse effects

Gastrointestinal symptoms, including nausea, are the most common adverse effects of cytisinicline. Other commonly reported adverse effects include: headache, appetite changes, weight gain, dizziness, drowsiness, malaise, sleep disorders, fatigue, anxiety, impaired concentration, altered mood, as well as dry mouth, oral disorders, myalgia, tachycardia and skin reactions.

Cytisinicline may cause dizziness and drowsiness and therefore influence the ability to drive and use machines. Patients are advised not to drive or operate complex machinery, or take part in potentially hazardous activities until they know how cytisinicline affects their ability to perform these activities.

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal. Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. There are no direct reports of cytisinicline resulting in suicidal ideation, but if serious neuropsychiatric symptoms occur whilst on cytisinicline treatment, patients should discontinue cytisinicline immediately and contact a healthcare professional for re-evaluation of treatment.

Healthcare professionals and patients are asked to report suspected adverse drug reactions that are serious (i.e. fatal, life-threatening, disabling or incapacitating, result in or prolong hospitalisation or cause congenital abnormalities), medically significant or result in harm through the Yellow Card Scheme at https://yellowcard.mhra.gov.uk/.

5.3 Dose and duration of treatment

The recommended duration of treatment with cytisinicline is 25 days.

Table 9. Dosage guide for cytisinicline

Dose	Relative cost = £
Adults over 18 years	Initially 1.5 mg every 2 hours from day 1 to 3, maximum 9 mg per day. Then reduced to 1.5 mg every 2.5 hours from day 4 to 12, maximum 7.5 mg per day, smoking should be stopped no later than day 5. Then reduced to 1.5 mg every 3 hours from day 13 to 16, maximum 6 mg per day. Then reduced to 1.5 mg every 5 hours from day 17 to 20, maximum 4.5 mg per day. Then reduced to 1.5–3 mg per day from day 21 to 25.
There are no adjustments required in renal impairment[18]	There is no clinical experience of cytisinicline in patients with renal or hepatic impairment; therefore, the medicine is not recommended for use in this patient population.

Table 10. Supply intervals and quantities for cytisinicline

Cytisinicline supply	Duration	Quantity
1st	25 day course pack	100 x 1.5 mg tablets

6.0 E-cigarettes and vapes

Electronic cigarettes, or e-cigarettes, including vapes, e-pens, e-pipes, e-hookah, and e-cigars are known collectively as ENDS – electronic nicotine delivery systems. ENDS deliver nicotine within an inhalable aerosol by heating a solution that typically contains nicotine, propylene glycol and/or glycerol, plus flavours. This aerosol is commonly referred to as vapour and so the use of an ENDS is described as vaping.

For smokers who want to quit, HMQ services, which provide behavioural support and access to licensed smoking cessation pharmacotherapy, currently offer the greatest likelihood of stopping smoking. However, many smokers who make a quit attempt do so without specialist support. For these smokers, ENDS may prove helpful in achieving a successful quit from tobacco although they are not licensed as a medicine for this purpose and are not regulated. The use of ENDS by pregnant women is not recommended[3]. It is essential that advice on smoking cessation is based on evidence and that people who are still smoking should be offered referral to HMQ services, noting that the use of vapes/ENDS will not restrict the options they have and that stopping vapes/ENDS is not a requirement of accessing support. If the person is experiencing problems with nicotine dependency, the healthcare professional should discuss options for referral to HMQ services for Vape/ENDS-only cessation.

If a current smoker decides to use vapes/e-cigarettes and requests advice on using e-cigarettes as part of their quit attempt, all advice given should be in line with the NICE guideline NG209.

6.1 Key points from the NICE guideline NG209

Give clear, consistent and up-to-date information about nicotine-containing e-cigarettes to adults who are interested in using them to stop smoking (for example, see the National Centre for Smoking Cessation and Training (NCSCT) e-cigarette guide https://www.ncsct.co.uk/library/view/pdf/Vaping-a-guide-for-health-and-social-care-professionals.pdf).

This includes:

- E-cigarettes are not licensed medicines but are regulated by the Tobacco and Related Products Regulations (2016).
- There is not enough evidence to know whether there are long-term harms from e-cigarette use.
- Use of e-cigarettes is likely to be substantially less harmful than smoking.
- Any smoking is harmful, so people using e-cigarettes should stop smoking tobacco completely.

Because there are limited data available, healthcare professionals and members of the public can use the Yellow Card Scheme at https://yellowcard.mhra.gov.uk/ to report any suspected side effects or safety concerns with e-cigarettes and the e-liquids used for vaping.

Appendix 1: Summary of cautions in the use of pharmacotherapy in special populations. Sourced from the Summary of Product Characteristics for each medicine and the British National Formulary, October 2024.

Special population	NRT	Varenicline	Bupropion	Cytisinicline
Pregnant women	NRT should be considered, alongside behavioural support, at the earliest opportunity in pregnancy and should be continued throughout and after pregnancy if needed to prevent a relapse.	Avoid – limited safety data.	Avoid – lack of safety data.	Contraindicated.
Breast-feeding women	Nicotine from NRT is present in breast milk; however, the amount to which the infant is exposed is small and less hazardous than second-hand smoke. Intermittent therapy is preferred.	Avoid – lack of safety data.	Avoid – lack of safety data. Present in breast milk.	Contraindicated.
Conception and contraception				It is currently unknown whether cytisinicline may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a second barrier method. Females of childbearing potential should use highly effective contraception during treatment;

Special population	NRT	Varenicline	Bupropion	Cytisinicline
				additional barrier method recommended in females using hormonal contraceptives – effect on hormonal contraception unknown.
Cardiovascular disease	Caution in use with haemodynamically unstable patients hospitalised with severe arrhythmias, myocardial infarction, or cerebrovascular accident. Initiation should only be under medical supervision. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the dose should be reduced or discontinued.	Caution in use with history of cardiovascular disease. Patients taking varenicline should be instructed to notify their doctor of new or worsening cardiovascular symptoms and seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.	Measure blood pressure before and during treatment, especially with pre-existing hypertension.	Caution is advised in patients with history of cardiovascular disease. Patients taking cytisinicline should be instructed to notify their doctor of new or worsening cardiovascular symptoms and seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.
Diabetes mellitus	Care in use in patients with diabetes mellitus. Blood glucose concentration should be monitored closely while using NRT.		Use with caution. Blood glucose concentrations may be more variable when stopping smoking and should be monitored closely.	
Hepatic impairment	Caution in use with moderate to severe hepatic impairment.	N/A	Reduce dose to 150 mg daily. Avoid in severe hepatic cirrhosis.	Not recommended.
Renal impairment	Caution in use with severe renal impairment.	If eGFR less than 30 ml/minute/1.73 m^2, initial dose 500 micrograms once daily, increased after 3 days to 1 mg once daily.	Caution in use with renal insufficiency. Reduce dose to 150 mg daily.	Not recommended.

Special population	NRT	Varenicline	Bupropion	Cytisinicline
		Avoid in end-stage renal disease.		
Psychiatric illness	N/A	Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.	Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly.	Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on cytisinicline treatment, patients should discontinue cytisinicline immediately and contact a healthcare professional for re-evaluation of treatment.
Predisposition to seizures	Potential risks and benefits of NRT should be considered before use in patients taking anti-convulsant therapy or with a history of epilepsy as cases of convulsions have been reported in association with nicotine.	Caution in use, including conditions that may lower seizure threshold.	Prescribe only if benefit clearly outweighs risks. Risks include the concomitant use of medicines and/or presence of other conditions that may lower seizure threshold. Consider a maximum dose of 150 mg daily.	N/A
Phaeochromocytoma	Caution in use.	N/A	N/A	Not recommended.
Uncontrolled hyperthyroidism	Caution in use.	N/A	N/A	Caution in use.
Children and adolescents (12 to 18 years)	All NRT preparations are licensed for adolescents over 12 years old (with the exception of Nicotinell™	Not licensed for use in those under 18 years old.	Not licensed for use in those under 18 years old.	Not licensed for use in those under 18 years old.

Special population	NRT	Varenicline	Bupropion	Cytisinicline
	lozenges which are licensed for those under 18 years old only when recommended by a physician).			
Elderly	N/A	N/A	Maximum dose of 150 mg once a day.	Due to limited clinical experience, cytisinicline is not recommended for use in elderly patients over 65 years of age.

Appendix 2: summary dosage and supply guide for smoking cessation pharmacotherapy

NRT		More than 10 cigarettes daily	Fewer than 10 cigarettes daily	Relative cost	2-week supply (max. dose)
Patch	**Strength**				
25 mg/16 hours	High	• Specify the patch strength (mg) and duration (16 or 24 hours). • Start with a high-strength patch daily for the first 6 to 8 weeks. • Follow with a medium-strength patch for 2 weeks. • Then a low-strength patch for the final 2 weeks.	• Specify the patch strength (mg) and duration (16 or 24 hours). • Start with a medium-strength patch daily for the first 6 to 8 weeks. • Follow with a low-strength patch for the final 2 to 4 weeks.	£	14 patches
15 mg/16 hours	Medium				
10 mg/16 hours	Low				
21 mg/24 hours	High				
14 mg/24 hours	Medium				
7 mg/24 hours	Low				
Gum	**Strength**	**More than 20 cigarettes daily**	**Fewer than 20 cigarettes daily**		
4 mg/6 mg	Higher	• Start with higher-strength gum. • Maximum 15 pieces of gum daily. • *Consider starting with higher strength if the first cigarette of the day smoked within 30 minutes of waking up.*	• Start with lower-strength gum. • Up to 15 pieces of gum daily. • If patient uses more than 15 pieces of 2 mg gum daily, change to the higher strength (4 mg or 6 mg) gum. • *Consider starting with lower strength if the first cigarette of the day smoked more than 30 minutes after waking up.*	£	210 pieces of gum
2 mg	Lower				

Lozenge	Strength	More than 20 cigarettes daily	Fewer than 20 cigarettes daily		
4 mg (nicotine resinate) 2 mg (nicotine)	Higher	• Start with higher-strength 2 mg (nicotine) or 4 mg (nicotine resinate) lozenge. • Maximum 15 higher-strength lozenges daily. • *Consider starting with a higher strength if the first cigarette of the day is smoked within 30 minutes of waking up.*	• Start with lower-strength 1 mg (nicotine) or 2 mg (nicotine resinate) lozenge. • Maximum 30 lower-strength lozenges daily. • *Consider changing to higher strength if insufficient effect at 15 or over lower strength lozenges daily.* • *Consider starting with a lower strength if the first cigarette of the day is smoked more than 30 minutes after waking up.*	£	210 lozenges
2 mg (nicotine resinate) 1 mg (nicotine)	Lower				
Sublingual tablets		**More than 20 cigarettes daily**	**Fewer than 20 cigarettes daily**		
2 mg (cyclodextrin complex)		• Start with higher dosage: 2 tablets each hour. • Maximum 40 tablets daily.	• Start with lower dosage: 1 tablet each hour. • Increase to 2 tablets each hour if necessary. • Maximum 40 tablets daily.	££	280 tablets Lower dose 560 tablets Higher dose
Inhalator		**All dependency levels**			
15 mg		• Maximum 6 cartridges of the 15 mg strength daily.		££	84 cartridges
Oral spray		**All dependency levels**			
1 mg per spray (150 sprays per 13.2 ml)		• Maximum 2 sprays per episode (up to 4 sprays every hour). • Maximum of 64 sprays daily.		££	5 packs
Nasal spray		**All dependency levels**			
500 micrograms per dose (200 sprays per 10 ml)		• Use one spray in each nostril, up to twice every hour for 16 hours daily. • Maximum 64 sprays daily.		££	4 packs

Additional information

NRT

Formulation	First prescription	Further prescription(s)
Single NRT (for those unable to use combination NRT)	Usually 1 or 2-week supply at maximum daily dose.	Appropriate quantity at regular intervals based on actual usage and any remaining NRT from previous prescription. Subsequent supplies should only be given to people who on reassessment have demonstrated that they are still engaging with support and treatment.
Combination NRT	Usually 1 or 2-week supply (7 or 14) patches **plus** up to the maximum daily dose quantity of one immediate-release NRT, to last 2 weeks.	Appropriate quantity of patches **plus** an appropriate quantity of one immediate-release NRT, at regular intervals based on actual usage and any remaining NRT from previous prescription. Subsequent supplies should only be given to people who on reassessment have demonstrated their quit is continuing.

NRT patches

- 24-hour patches may be more suitable if patients have strong cravings for cigarettes on waking.
- Sleep disturbances may be helped by removing the patches before bed (changing from a 24-hour patch to a 16-hour patch).
- If abstinence is not achieved, or if withdrawal symptoms are experienced, maintain or increase the strength of the patch until the patient is stabilised.

If patients using a high-strength patch experience excessive side effects that do not resolve within a few days, change to a medium-strength patch for the remainder of the initial period, then a low-strength patch for 2 to 4 weeks.

Varenicline

Dose		Relative cost = £
Adults over 18 years		Start 1 to 2 weeks before target quit date (up to maximum of 5 weeks before target quit date). 500 micrograms once daily for 3 days, increase to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks. Reduce dose to 500 micrograms twice daily if not tolerated.
Severe renal impairment (eGFR < 30 ml/min /1.73 m^2). Avoid in end-stage renal disease.		500 micrograms once a day for the first 3 days, then increase to 1 mg once a day.
Varenicline supply	**Duration**	**Quantity**
1st	2 weeks (starter pack)	11 x 500 microgram tablets and 14 x 1 mg tablets (starter pack)
2nd, 3rd, 4th, 5th & 6th	Regular intervals usually 2 weeks	Sufficient to cover supply interval e.g. 2 week supply = 1 mg x 28 tablets or 500 microgram x 28 tablets if using lower dose.

Bupropion

Dose	Relative cost = £
Adults over 18 years	Start 1 to 2 weeks before target quit date. Initially 150 mg daily for 6 days, then 150 mg twice daily (maximum per dose 150 mg, maximum daily dose 300 mg; minimum 8 hours between doses). Period of treatment 7–9 weeks; discontinue if abstinence not achieved at 7 weeks.
Elderly	Maximum 150 mg once a day.
Hepatic impairment. (Avoid in severe hepatic cirrhosis.)	Reduce dose to 150 mg once a day.
Renal impairment	Reduce dose to 150 mg once a day.
Predisposition to seizures	Not usually prescribed unless compelling clinical justification outweighs risk of seizure. Consider a maximum dose of 150 mg daily.

Bupropion supply	Duration	Quantity
1st	2 weeks	22 x 150 mg tablets (provides 2-week supply at standard initiation dose)
2nd & 3rd	2 weeks	28 x 150 mg tablets (14 x 150 mg tablets if using lower dose)
4th	Up to 3 weeks (to complete the course of treatment)	Up to 42 x 150 mg tablets (Up to 21 x 150 mg tablets if using lower dose)

Cytisinicline (cytisine)

Dose	Relative cost = £
Adults over 18 years	Initially 1.5 mg every 2 hours from day 1 to 3, maximum 9 mg per day, then reduced to 1.5 mg every 2.5 hours from day 4 to 12, maximum 7.5 mg per day, smoking should be stopped no later than day 5, then reduced to 1.5 mg every 3 hours from day 13 to 16, maximum 6 mg per day, then reduced to 1.5 mg every 5 hours from day 17 to 20, maximum 4.5 mg per day, then reduced to 1.5–3 mg per day from day 21 to 25.

Cytisinicline supply	Duration	Quantity
1st	25 day course pack	100 x 1.5 mg tablets

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