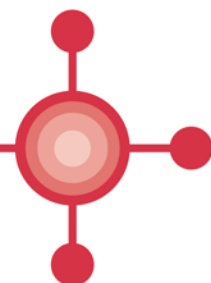


All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan



# **All Wales Guide:**

## **Pharmacotherapy for Smoking Cessation**

February 2018

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## 1.0 INTRODUCTION

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Both behavioural support and pharmacotherapies are effective in helping people to stop smoking. Combining both treatment approaches is recommended where possible<sup>7</sup>. 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* was launched in Wales with 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](http://www.helpmequit.wales) or texting HMQ to 80818. Healthcare Professionals can refer to *Help Me Quit* by completing the professional referral form on the website, by calling the above number or through existing referral pathways. By referring smokers to *Help Me Quit* 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<sup>10</sup>. Pharmacotherapy should normally be supplied as part of an abstinence-contingent treatment, in which the smoker makes a commitment to stop smoking on or before a particular date (target quit date)<sup>5</sup>. This guidance covers the use of licensed pharmacotherapy to support stopping smoking in one step, and does not cover 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)<sup>11</sup>.

This guidance does not cover the use of electronic nicotine delivery systems (ENDS), which include e-cigarettes, 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 5.0.

### 1.1 Assessing nicotine dependence

The Fagerström test is widely used to assess nicotine dependence. How soon a person smokes after waking seems to be the most important indicator of dependence<sup>12</sup>. 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 three forms of pharmacotherapy that are licensed for use in the UK to assist with smoking cessation are:

- Nicotine replacement therapy (NRT),
- Varenicline,
- Bupropion.

A Cochrane network meta-analysis concluded that each of these improves the chances of quitting. Combination NRT (the use of an immediate-release formulation plus patches) is more effective than single types of NRT<sup>13</sup>.

Clinical suitability, including effectiveness and safety, as well as patient preference are important in guiding the choice of pharmacotherapy<sup>14</sup>.

### 1.3 Cautions

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

*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 an enhanced stop smoking service, and supply may take place in primary care or in a hospital (inpatient or outpatient) setting. Where the person authorising the supply of varenicline or bupropion is not able to access the patient's medical records, they should ensure a complete medical and medication history has been taken.

Patients who engage with a smoking cessation service for behavioural support to quit, should receive a supply of NRT, varenicline or bupropion sufficient to last no more than two weeks after the target quit date<sup>5</sup>. 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<sup>5</sup>. Phased supply enables ongoing review of the suitability of the formulation and dosage in order to more closely target the individual's needs during their quit attempts and reduce the potential for wastage.

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

### 1.5 Pharmacotherapy and other medicines

Tobacco smoking increases the metabolism of some medicines by stimulating the hepatic enzyme CYP1A2. When smoking is discontinued, the dose of these medicines, in particular theophylline, cinacalcet, ropinirole, and some antipsychotics (including clozapine, olanzapine, chlorpromazine and haloperidol), may need to be reduced<sup>15</sup>. 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

There are seven different types of NRT formulations available (patches, gum, lozenges, sublingual tablets, inhalator, oral spray, and nasal spray) and a range of strengths. This offers a variety of approaches to best match individual smokers' needs and preferences.

All formulations of NRT have similar effectiveness. Therefore, 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

Patches provide slower, sustained-release delivery of nicotine, while oral and nasal formulations provide faster release of nicotine as intermittent doses. The use of NRT is more effective in achieving abstinence if combined with behavioural support and where combination NRT is used<sup>7</sup>. Combination NRT refers to the use of a patch plus an immediate-release formulation for breakthrough cravings<sup>15</sup>. It is suitable for:

- Those who have used NRT in a previous quit attempt, but relapsed while using it.
- Those who feel they need something more than a patch or other single form NRT.
- Heavier smokers<sup>16</sup>.

**Table 1. Some advantages and disadvantages of different NRT formulations**

Formulation	Advantages/disadvantages
<b>Patch</b>	Discreet and easy to use. Long-acting. Doesn't mimic the highs and lows associated with smoking.
<b>Gum</b>	Allows good control of nicotine dose. Unsuitable for people who use dentures.
<b>Lozenge</b>	Discreet, flexible, good dose control.
<b>Sublingual tablet</b>	Discreet, flexible, good dose control.
<b>Inhalator</b>	May be useful for people who miss the hand-to-mouth movements of smoking.
<b>Oral spray</b>	Rapid delivery of nicotine.
<b>Nasal spray</b>	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<sup>15</sup>.

NRT can 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 (with the exception of Nicotinell™ lozenges which are licensed for those under 18 years old only when recommended by a healthcare professional)<sup>17</sup>. 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.

The use of NRT in pregnancy is considered preferable to the continuation of smoking, but should be used only if smoking cessation without NRT fails<sup>15,18</sup>. Intermittent therapy is preferable to patches, but liquorice-flavoured products should be avoided. Patches may be appropriate e.g. if pregnancy-related nausea and vomiting is a problem. If patches are used they should be removed at night before going to bed<sup>15,18</sup>. Use of a 16-hour patch which is removed at night avoids additional foetal nicotine exposure during maternal sleeping. Intermittent therapy is also preferable for breast-feeding women<sup>15</sup>.

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

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

## 2.3 Adverse effects

Most adverse effects experienced with NRT are not serious and are similar to the effects experienced from nicotine obtained by smoking<sup>19</sup>

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 via 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
<b>Patch</b>	Nicotine patches should not be placed on broken skin and should be used with caution in patients with skin disorders.	<p>Minor skin irritation at the application site(s). If the skin reaction becomes more severe or more widespread, treatment with patches should be discontinued.</p> <p>Dry mouth, sleep disturbances including abnormal dreams.</p> <p>Chest pain, sweating, myalgia and arthralgia have been reported.</p>
<b>Oral NRT in general</b>	<p>Caution in use with oesophagitis, oral or pharyngeal inflammation, gastritis, or peptic ulcers.</p> <p>Due to the potential for reduced absorption of nicotine through buccal mucosa, patients should generally avoid:</p> <ul style="list-style-type: none"> <li>• Acidic beverages for 15 minutes before using oral NRT</li> <li>• Eating or drinking while using oral NRT</li> </ul>	Gastrointestinal disturbances are common and may be caused by swallowed nicotine; nausea, vomiting, dyspepsia, and hiccupping occur most frequently.
<b>Gum</b>	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.
<b>Lozenge</b>		<p>Mild local reactions (such as erythema and urticaria), sore mouth or throat, dry mouth, increased salivation, mouth ulcers.</p> <p>Less commonly: thirst, taste disturbance, gingival bleeding, halitosis, rash, and hot flushes.</p>
<b>Sublingual tablet</b>		Dry mouth, sore mouth or throat, burning sensation in the mouth, and cough.
<b>Inhalator</b>	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.
<b>Oral spray</b>		Mild local reactions such as cough and irritation to the mouth and throat, dry mouth, increased salivation, mouth ulcers, taste disturbance, and toothache.
<b>Nasal spray</b>	<p>The nasal spray can cause worsening of bronchial asthma. Use of the spray in patients with hyperreactive airways is not recommended.</p> <p>The nasal spray should not be used whilst the user is driving or operating machinery as sneezing and watering eyes could contribute to accidents.</p>	<p>Nasal irritation (such as rhinorrhoea and sneezing), increased lacrimation, nose bleeds and cough.</p> <p>Both the frequency and severity of nasal irritation and rhinorrhoea has been reported to decline with continued use.</p>



## 2.4 Supply/prescribing notes for NRT

- Supply of NRT should not commence until the patient has decided on a target quit date.
- 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.
- 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	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 their quit is continuing.
Combination NRT	Usually 1 or 2-week supply e.g. (7 or 14) patches <b>plus</b> 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	<ul style="list-style-type: none"> <li>Specify the patch strength (mg) and duration (16 or 24 hours).</li> <li>Start with a high-strength patch daily for the first 6 to 8 weeks.</li> <li>Follow with a medium-strength patch for 2 weeks.</li> <li>Then a low-strength patch for the final 2 weeks.</li> </ul>	<ul style="list-style-type: none"> <li>Specify the patch strength (mg) and duration (16 or 24 hours).</li> <li>Start with a medium-strength patch daily for the first 6 to 8 weeks.</li> <li>Follow with a low-strength patch for the final 2 to 4 weeks.</li> </ul>	£	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		<ul style="list-style-type: none"> <li>24-hour patches may be more suitable if patients have strong cravings for cigarettes on waking.</li> <li>Sleep disturbances may be helped by removing the patches before bed (changing from a 24-hour patch to a 16-hour patch).</li> <li>If abstinence is not achieved, or if withdrawal symptoms are experienced, maintain or increase the strength of the patch until the patient is stabilised.</li> <li>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.</li> </ul>			
Gum (medicated chewing gum sugar-free)	Strength	More than 20 cigarettes daily	Fewer than 20 cigarettes daily		
4 mg/6 mg	Higher	<ul style="list-style-type: none"> <li>Start with higher-strength gum.</li> <li>Maximum 15 pieces of gum daily.</li> <li>Consider starting with higher strength if the first cigarette of the day is smoked within 30 minutes of waking up.</li> </ul>	<ul style="list-style-type: none"> <li>Start with lower-strength gum.</li> <li>Up to 15 pieces of gum daily.</li> <li>If patient uses more than 15 pieces of 2 mg gum daily, change to the higher-strength (4 mg or 6 mg) gum</li> <li>Consider starting with lower strength if the first cigarette of the day is smoked more than 30 minutes after waking up.</li> </ul>	£	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	<ul style="list-style-type: none"> <li>Start with higher-strength 2 mg (nicotine) or 4 mg (nicotine resinate) lozenge.</li> <li>Maximum 15 higher-strength lozenges daily.</li> <li>Consider starting with a higher strength if the first cigarette of the day is smoked within 30 minutes of waking up.</li> </ul>	<ul style="list-style-type: none"> <li>Start with lower-strength 1 mg (nicotine) or 1.5 mg/2 mg (nicotine resinate) lozenge.</li> <li>Maximum 30 lower-strength lozenges daily.</li> <li>Consider changing to higher strength if insufficient effect at 15 or over lower strength lozenges daily.</li> <li>Consider starting with a lower strength if the first cigarette of the day is smoked more than 30 minutes after waking up.</li> </ul>	£	210 lozenges
1.5 mg (nicotine resinate) 2 mg (nicotine resinate) 1 mg (nicotine)	Lower				

Table 4. Dosage guide for NRT formulations (continued)

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)	<ul style="list-style-type: none"> <li>Start with higher dosage: 2 tablets each hour.</li> <li>Maximum 40 tablets daily.</li> </ul>	<ul style="list-style-type: none"> <li>Start with lower dosage: 1 tablet each hour.</li> <li>Increase to 2 tablets each hour if necessary.</li> <li>Maximum 40 tablets daily.</li> </ul>	££	280 tablets (lower dose)  560 tablets (higher dose)
Inhalator (inhalation cartridges)	All dependency levels			
15 mg	<ul style="list-style-type: none"> <li>Maximum 6 cartridges of the 15 mg strength daily.</li> </ul>		££	84 cartridges
Oral spray (oromucosal spray sugar-free)	All dependency levels			
1 mg per spray (150 sprays per 13.2 ml)	<ul style="list-style-type: none"> <li>Maximum 2 sprays per episode (up to 4 sprays every hour).</li> <li>Maximum of 64 sprays daily.</li> </ul>		££	5 packs (150 sprays per 13.2 ml)
Nasal spray	All dependency levels			
500 micrograms per dose (200 sprays per 10 ml)	<ul style="list-style-type: none"> <li>Use one spray in each nostril, up to twice every hour for 16 hours daily.</li> <li>Maximum 64 sprays daily.</li> </ul>		££	4 packs (200 sprays per 10 ml)

### 3.0 VARENICLINE

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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<sup>20</sup>. It should normally be supplied only as part of a programme of behavioural support<sup>20</sup>.

Varenicline is a prescription only medicine (PoM) and, in primary care, is usually supplied via a WP10 prescription. However, there are a number of local initiatives where varenicline is available via a community pharmacy enhanced smoking cessation service through a Patient Group Direction (PGD) but this is currently not the case throughout Wales.

#### 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<sup>21</sup>. 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 I.

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<sup>21</sup>.

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/>.

### 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 = £
<b>Adults over 18 years</b>	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.	
<b>Severe renal impairment (eGFR &lt; 30 ml/min/1.73 m<sup>2</sup>). Avoid in end-stage renal disease</b>	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
1 <sup>st</sup>	2 weeks (starter pack)	11 x 500 microgram tablets and 14 x 1 mg tablets (starter pack)
2 <sup>nd</sup> , 3 <sup>rd</sup> , 4 <sup>th</sup> , 5 <sup>th</sup> & 6 <sup>th</sup>	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

## 4.0 BUPROPION

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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 (18 years old and over) smokers. It should be avoided in pregnancy and by breast-feeding women due to a lack of safety data. It is contraindicated in those with hypersensitivity to bupropion or any of the excipients in the formulation<sup>22</sup>.

Bupropion is contraindicated in patients 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)<sup>22</sup>.

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 I.

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<sup>22</sup>.

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. 150 mg daily for 6 days then 150 mg twice daily (max. single dose 150 mg, max. daily dose 300 mg; minimum 8 hours between doses). Period of treatment 7–9 weeks; discontinue if abstinence not achieved at 7 weeks.
Elderly	Max. 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
1 <sup>st</sup>	2 weeks	22 x 150 mg tablets (provides 2-week supply at standard initiation dose)
2 <sup>nd</sup> & 3 <sup>rd</sup>	2 weeks	28 x 150 mg tablets (14 x 150 mg tablets if using lower dose)
4 <sup>th</sup>	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 E-CIGARETTES

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Electronic cigarettes, or e-cigarettes, including 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, NHS stop smoking 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 currently licensed as a medicine for this purpose. The use of ENDS by pregnant women is not recommended.

At the time of publication of this guidance (2018) no ENDS products have been brought to market as licensed medicines. Currently available ENDS are not regulated by the MHRA and therefore their effectiveness, safety and quality cannot be assured.

ENDS present both potential benefits and potential harms, so a balance of approaches is needed to help minimise the risks and to maximise the potential benefits of smokers who wish to quit.

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.

The use and potential benefits of using ENDS by committed smokers who are unwilling or unable to quit smoking is not covered in this guidance but further information can be found in the [Public Health Wales ENDS position statement on electronic cigarettes](#) (January 2017).

## APPENDIX I: SUMMARY OF CAUTIONS IN THE USE OF PHARMACOTHERAPY IN SPECIAL POPULATIONS

Special population	NRT	Varenicline	Bupropion
<b>Pregnant women</b>	NRT use in pregnancy is preferable to the continuation of smoking, but should only be used if smoking cessation without NRT fails. Intermittent therapy is preferable to patches. Avoid liquorice-flavoured NRT. Patches are useful, however, if the patient is experiencing pregnancy-related nausea and vomiting. If patches are used, they should be removed before bed.	Avoid – limited safety data.	Avoid – lack of safety data.
<b>Breast-feeding women</b>	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.
<b>Cardiovascular disease</b>	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.
<b>Diabetes mellitus</b>	Care in use in patients with diabetes mellitus. Blood glucose concentration should be monitored closely while using NRT.	No specific cautions. However, blood glucose concentrations may be more variable when stopping smoking and should be monitored closely.	
<b>Hepatic impairment</b>	Caution in use with moderate to severe hepatic impairment.	N/A	Reduce dose to 150 mg daily. Avoid in severe hepatic cirrhosis.
<b>Renal impairment</b>	Caution in use with severe renal impairment.	If eGFR less than 30 ml/minute/1.73 m <sup>2</sup> , initial dose 500 micrograms once daily, increased after 3 days to 1 mg once daily.  Avoid in end-stage renal disease.	Caution in use with renal insufficiency. Reduce dose to 150 mg daily.
<b>Psychiatric illness</b>	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

<b>Predisposition to seizures</b>	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.
<b>Phaeochromocytoma</b>	Caution in use.	N/A	N/A
<b>Uncontrolled hyperthyroidism</b>	Caution in use.	N/A	N/A
<b>Children and adolescents (12 to 18 years)</b>	All NRT preparations are licensed for adolescents over 12 years old (with the exception of Nicotinell™ lozenges which are licensed for those under 18 years old only when recommended by a physician).	Not licensed for use in those under 18 years old.	Not licensed for use in those under 18 years old.
<b>Elderly</b>	N/A	N/A	Maximum dose of 150 mg once a day.

## APPENDIX II: 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	<ul style="list-style-type: none"> <li>Specify the patch strength (mg) and duration (16 or 24 hours).</li> <li>Start with a high-strength patch daily for the first 6 to 8 weeks.</li> <li>Follow with a medium-strength patch for 2 weeks.</li> <li>Then a low-strength patch for the final 2 weeks.</li> </ul>	<ul style="list-style-type: none"> <li>Specify the patch strength (mg) and duration (16 or 24 hours).</li> <li>Start with a medium-strength patch daily for the first 6 to 8 weeks.</li> <li>Follow with a low-strength patch for the final 2 to 4 weeks.</li> </ul>	£	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	<ul style="list-style-type: none"> <li>Start with higher-strength gum.</li> <li>Maximum 15 pieces of gum daily.</li> <li>Consider starting with higher strength if the first cigarette of the day smoked within 30 minutes of waking up.</li> </ul>	<ul style="list-style-type: none"> <li>Start with lower-strength gum.</li> <li>Up to 15 pieces of gum daily.</li> <li>If patient uses more than 15 pieces of 2 mg gum daily, change to the higher-strength (4 mg or 6 mg) gum.</li> <li>Consider starting with lower strength if the first cigarette of the day smoked more than 30 minutes after waking up.</li> </ul>	£	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	<ul style="list-style-type: none"> <li>Start with higher-strength 2 mg (nicotine) or 4 mg (nicotine resinate) lozenge.</li> <li>Maximum 15 higher-strength lozenges daily.</li> <li>Consider starting with a higher strength if the first cigarette of the day is smoked within 30 minutes of waking up.</li> </ul>	<ul style="list-style-type: none"> <li>Start with lower-strength 1 mg (nicotine) or 1.5 mg/2 mg (nicotine resinate) lozenge.</li> <li>Maximum 30 lower-strength lozenges daily.</li> <li>Consider changing to higher strength if insufficient effect at 15 or over lower strength lozenges daily.</li> <li>Consider starting with a lower strength if the first cigarette of the day is smoked more than 30 minutes after waking up.</li> </ul>	£	210 lozenges	
1.5 mg (nicotine resinate) 2 mg (nicotine resinate) 1 mg (nicotine)	Lower					
Sublingual tablets		More than 20 cigarettes daily	Fewer than 20 cigarettes daily			
2 mg (cyclodextrin complex)		<ul style="list-style-type: none"> <li>Start with higher dosage: 2 tablets each hour.</li> <li>Maximum 40 tablets daily.</li> </ul>	<ul style="list-style-type: none"> <li>Start with lower dosage: 1 tablet each hour.</li> <li>Increase to 2 tablets each hour if necessary.</li> <li>Maximum 40 tablets daily.</li> </ul>	££	280 tablets Lower dose 560 tablets Higher dose	
Inhalator		All dependency levels				
15 mg		<ul style="list-style-type: none"> <li>Maximum 6 cartridges of the 15 mg strength daily.</li> </ul>			££	84 cartridges
Oral spray		All dependency levels				
1 mg per spray (150 sprays per 13.2 ml)		<ul style="list-style-type: none"> <li>Maximum 2 sprays per episode (up to 4 sprays every hour).</li> <li>Maximum of 64 sprays daily.</li> </ul>			££	5 packs
Nasal spray		All dependency levels				
500 micrograms per dose (200 sprays per 10 ml)		<ul style="list-style-type: none"> <li>Use one spray in each nostril, up to twice every hour for 16 hours daily.</li> <li>Maximum 64 sprays daily.</li> </ul>			££	4 packs

## ADDITIONAL INFORMATION

### NRT

Formulation	First prescription	Further prescription(s)
Single NRT	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 their quit is continuing.
Combination NRT	1 or 2-week supply (7 or 14) patches <b>plus</b> up to the maximum daily dose quantity of one immediate-release NRT, to last 2 weeks.	Appropriate quantity of patches <b>plus</b> 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 = £
<b>Adults over 18 years</b>		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.	
<b>Severe renal impairment (eGFR &lt; 30 ml/min /1.73 m<sup>2</sup>). Avoid in end-stage renal disease</b>		500 micrograms once a day for the first 3 days, then increase to 1 mg once a day.	
Varenicline supply	Duration	Quantity	
1 <sup>st</sup>	2 weeks (starter pack)	11 x 500 microgram tablets and 14 x 1 mg tablets (starter pack)	
2 <sup>nd</sup> , 3 <sup>rd</sup> , 4 <sup>th</sup> , 5 <sup>th</sup> & 6 <sup>th</sup>	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 = £
<b>Adults over 18 years</b>		Start 1 to 2 weeks before target quit date. 150 mg daily for 6 days then 150 mg twice daily (max. single dose 150 mg, max. daily dose 300 mg; minimum 8 hours between doses). Period of treatment 7–9 weeks; discontinue if abstinence not achieved at 7 weeks.	
<b>Elderly</b>		Max. 150 mg once a day.	
<b>Hepatic impairment. (Avoid in severe hepatic cirrhosis.)</b>		Reduce dose to 150 mg once a day.	
<b>Renal impairment</b>		Reduce dose to 150 mg once a day.	
<b>Predisposition to seizures</b>		Not usually prescribed unless compelling clinical justification outweighs risk of seizure. Consider a maximum dose of 150 mg daily.	
Bupropion supply	Duration	Quantity	
1 <sup>st</sup>	2 weeks	22 x 150 mg tablets (provides 2-week supply at standard initiation dose)	
2 <sup>nd</sup> & 3 <sup>rd</sup>	2 weeks	28 x 150 mg tablets (14 x 150 mg tablets if using lower dose)	
4 <sup>th</sup>	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)	

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