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Nicotine Replacement Therapy (NRT) Guidelines

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Type of document	Guidance
Target audience	All clinical staff
Document purpose	To support the implementation of the Nicotine Management Policy and to ensure NRT is prescribed appropriately. These guidelines concentrate on the practicalities and the protocol of offering NRT to inpatients who wish to set a quit date. They are supplementary to the Trust Nicotine Management Policy. They also cover the effect of smoking cessation on the metabolism of various medicines and necessary dose adjustments.

Approving meeting	Medicines Management Group	21 September 2017
Implementation date	01-Sept-17	

CWP documents to be read in conjunction with	
HR6 CP28 MP6	Mandatory Employee Learning (MEL) policy Nicotine management policy Introduction of new psychotropic medicines and non-formulary named-patient applications
Document change history	
What is different?	3.2 'Exclusions' move to this section to avoid duplication 3.4 Updated information about use of varenicline and bupropion 3.5.1 Changed information about supply of treatment on discharge 4. Updated information on Electronic Cigarettes moved from Appendices to this section **Updated September 2017:** 3.4.1.2 Varenicline formulary status for in-patients across rehabilitation wards. Appendix 3 - Using NRT Products at CWP : use of gum to be risk-assessed on an individual basis
Appendices / electronic forms	Appendix 3 updated varenicline information
What is the impact of change?	Use of varenicline within CWP for mentally stable patients on rehabilitation units. Prescribing responsibility would remain within CWP for the treatment course

Training requirements	No - Training requirements for this policy are in accordance with the CWP Training Needs Analysis (TNA) with Learning and Development (L&D)

Document consultation	
East locality	Nicotine Management Group
Wirral locality	Nicotine Management Group

West locality	Nicotine Management Group
Corporate services	CWP Nicotine Management Group, MMG, Pharmacy team, Fiona Couper Chief Pharmacist, Gill Monteith Records and Information Governance Manager, Avril Devaney-Director of Nursing, Therapies and Patient Partnership
External agencies	Rebecca Mellor, Public Health, Wirral, Mark Dickinson, NHS South Cheshire CCG and NHS Vale Royal CCG,

Financial resource implications	Yes Payment for NRT for all inpatients. Payment will be made from the prescribing budget. Prescribing for outpatients should be via primary care and should not impact on CWP prescribing budget.

External references

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Equality Impact Assessment (EIA) - Initial assessment	**Yes/No**	**Comments**
Does this document affect one group less or more favourably than another on the basis of:		
- Race	No	

Equality Impact Assessment (EIA) - Initial assessment	Yes/No	Comments
- Ethnic origins (including gypsies and travellers)	No	
- Nationality	No	
- Gender	No	
- Culture	No	
- Religion or belief	No	
- Sexual orientation including lesbian, gay and bisexual people	No	
- Age	No	
- Disability - learning disabilities, physical disability, sensory impairment and mental health problems	No	
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Was a full impact assessment required?	No	
What is the level of impact?	Low	

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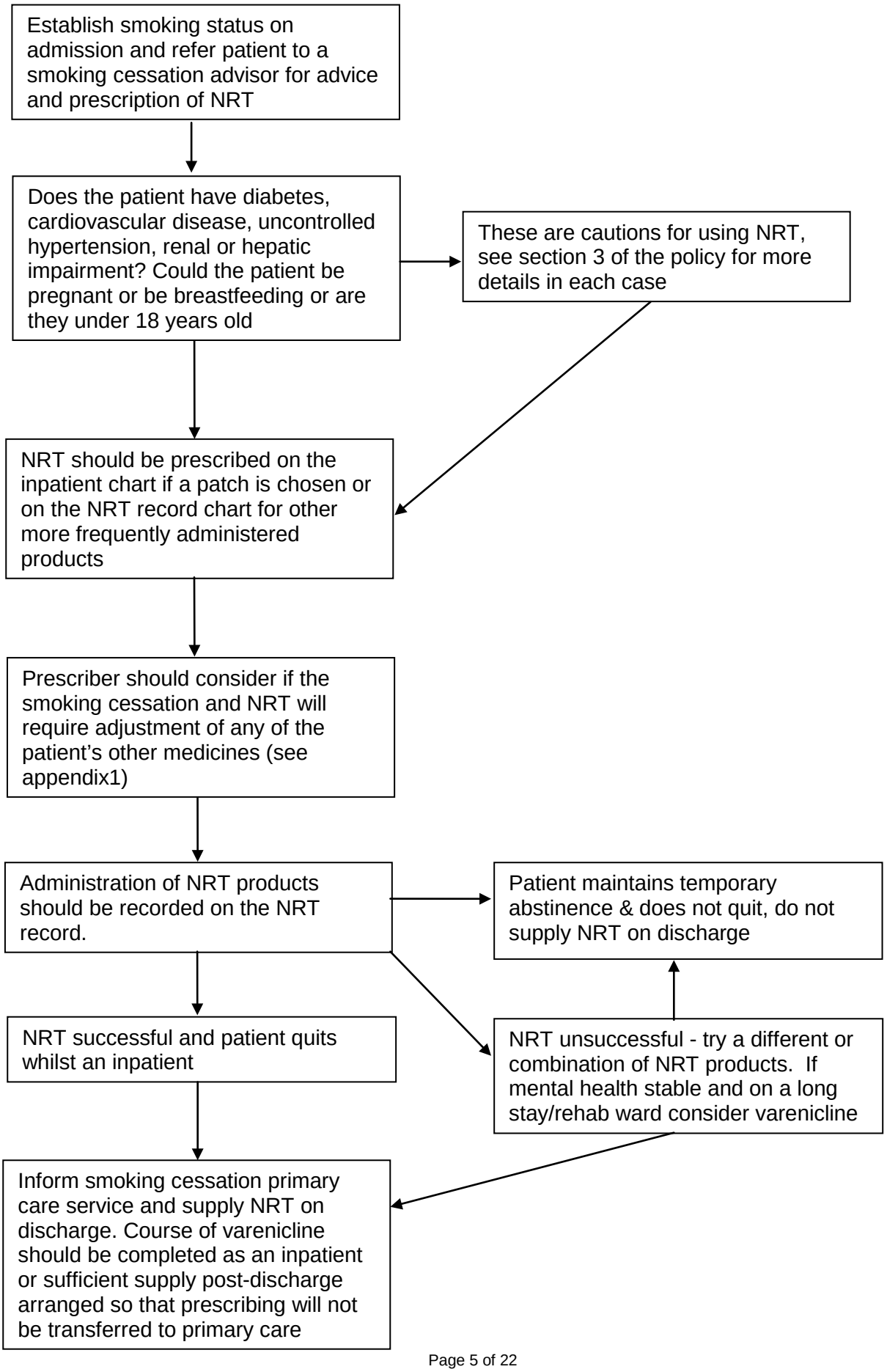
Quick reference flowchart



1. Introduction

The aim of this guideline is to ensure the safe and effective use of Nicotine Replacement Therapy (NRT) by smokers seen by appropriately trained staff in the Cheshire and Wirral Partnership NHS Foundation Trust (CWP).

Sections 1 – 4 of this guideline are aimed at all clinical staff and should be read in conjunction with the Trust nicotine management policy. The appendices are applicable to those staff trained to deliver level 2 smoking interventions as well as medical staff. The following areas are covered within the appendices:

- Record of NRT use chart which is for the prescription and recording of NRT use.
- Smoking and specific drug interactions;
- Summary of NRT products available at CWP.

This guidance document was updated to take into account that the Trust premises and grounds became completely Smoke Free from February 2014 with the formal adoption of the nicotine management policy.

This means that upon admission a patient is unable to smoke and will hence require substitution with a suitable NRT product for the duration of the admission.

This Guideline has been developed to act as a framework under which appropriately trained staff will provide educational support and advice to patients motivated to stop smoking and those who need to stop smoking whilst on Trust premises.

Inpatients wanting to stop smoking can approach or be referred to the service and receive individually tailored smoking advice. This may involve the recommendation of and counselling about the most appropriate forms of NRT by the Smoking Cessation Specialist Advisor (SCSA) or by the trained level 2 advisor (nurse or health / social services care employee).

Smoking remains the leading cause of preventable morbidity and premature death in England. It is estimated that between 1998 and 2002, smoking caused an average 86,500 deaths a year[1]. Smoking rates are much higher amongst people with mental health problems than in the general population. Smokers with mental health problems are heavier and more dependent smokers than those in the general population. Patients with severe mental illness have a higher risk of premature death and the literature shows an elevated risk of death from cardiovascular disease, coronary heart disease, respiratory disease and suicide. It seems likely that smoking would contribute to the elevated risks of cardiovascular and respiratory diseases[1]. For people with schizophrenia, the risk of dying of respiratory disease was found to be almost ten times that for other people[2].

Despite high cigarette consumption, the majority of smokers with severe mental illness want to stop smoking[1]. NHS smoking cessation services across the country are now widely recognised and all smokers who wish to stop smoking should be referred to a trained advisor for specialist support[3]. Government policy now states that health professionals should refer patients who need support to such a service[4]. This guideline has therefore been produced to be read in conjunction with the Trust nicotine management policy and concentrates on the practicalities of issuing appropriate NRT to patients during their inpatient stay.

2. Definitions

Smoking Cessation Advisors

Advisors will be staff members trained by a Specialist Smoking Cessation Advisor to offer level 2 smoking cessation advice. These advisors will have attended the “Stop Smoking Intervention and NRT Prescribing” (Level 2) training. All the advisors will be registered with their local smoking cessation service provider and on their database. Advisors will be expected to attend an annual update after accreditation in order to remain an accredited level 2 advisor.

Complete abstinence
Smokers who are highly motivated to stop smoking and are willing to set a quit date and receive intensive support from a trained smoking cessation advisor for as long as required.

Temporary abstinence (for the duration of their inpatient stay)
Smokers who need NRT to manage the symptoms of nicotine withdrawal for the duration of the admission but who do not wish to set a quit date.

3. Procedure

3.1 Criteria for Inclusion

Since February 2014 the Trust buildings and grounds have become Smoke Free. This means that no-one is permitted to smoke under any circumstances whilst on Trust property.

NRT can be considered for complete abstinence or temporary abstinence.

3.2 Criteria for exclusion

It has become widely accepted that there are no circumstances in which it is safer to smoke than to use NRT[6]. In the following circumstances it is preferable to quit without the aid of NRT:

- People who have had a myocardial infarction or cerebrovascular accident in the last 4 weeks;
- Life-threatening cardiac arrhythmias;
- Severe or worsening angina pectoris.

If the patient meets the exclusion criteria, the advisor should not recommend the use of an NRT product as it is outside the guidelines. The advisor should contact their stop smoking service, as the patient may still be able to use NRT, but will need it prescribed by a ward doctor with advice from the stop smoking service. If NRT is deemed not to be appropriate for the patient after consultation with the stop smoking service and ward doctor, the advisor should provide the behavioural support of the level 2 intervention only.

3.3 Cautions

Risks / benefits must be considered before prescribing NRT in the following circumstances (in line with the Committee on Safety of Medicines Recommendations) [6]

- Those who are under 18 years old;
- Pregnant or breastfeeding women;
- Stable Cardiovascular Disease;
- Uncontrolled hypertension;
- Those with a previous serious reaction to NRT or any ingredients contained in the product, e.g. glue in the patch;
- Those taking medicines which interact with cigarette smoke (appendix 1);
- Diabetes (additional glucose monitoring is required).

Cautions for patches only:

- Those with a chronic generalised skin disease such as psoriasis, chronic dermatitis and urticaria;
- Those who have had a previous reaction to the transdermal patch;
- Occasional smokers.

Cautions for nasal spray only:

- Those with chronic nasal disorders such as polyposis, vasomotor rhinitis and perennial rhinitis.

Adolescents[6,7]
Many young smokers show signs of nicotine dependence. Although there is little published data demonstrating the efficacy of NRT in young smokers, there is no logical reason why it should not help as long as it is used correctly and the smoker is determined to give up. Ultimately the decision to use NRT should be based on the smoker's determination to quit, and on their level of dependence (as opposed to age). Given that NRT is less harmful than smoking, safety concerns should not be a barrier to use and harm reduction principles should be applied when considering NRT for young people (12-17 years). The recommendations are to use NRT for three months in this age group. If it is needed for longer it should be reviewed by a health professional. Young people have the right to confidential medical advice and treatment if the provider assesses that the young person is able to understand what is being proposed and this will apply to the use of NRT products.

Pregnancy[6,7]
Ideally, pregnant women should stop smoking without using NRT but, if this is not possible, NRT may be recommended to assist a quit attempt as it is considered that the risk to the foetus of continued smoking by the mother outweighs any potential adverse effects of NRT

The decision to use NRT should be made following a risk-benefit assessment as early in pregnancy as possible. The aim should be to discontinue NRT use after 2 to 3 months. Intermittent forms of NRT are preferable during pregnancy although a patch may be appropriate if nausea and/or vomiting are a problem. If patches are used, they should be removed before going to bed at night.

Breastfeeding[6,7]
NRT can be used by women who are breastfeeding. The amount of nicotine the infant is exposed to from breast milk is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to if the mother continued to smoke. If possible, patches should be avoided. NRT products taken intermittently are preferred as their use can be adjusted to allow the maximum time between their administration and feeding of the baby, to minimise the amount of nicotine in the milk.

Cardiovascular disease[6,7]
Although nicotine has some acute effects on the cardiovascular system, unlike tobacco smoke it is not a significant risk factor for cardiovascular disease or acute cardiac events. NRT provides less nicotine, less rapidly than cigarette smoking, without substances such as carbon monoxide (which is known to have adverse effects on the cardiovascular system). On this basis, experts agree that smokers with stable cardiovascular disease can safely use all NRT products.

It is recommended that the risks and benefits of using NRT should be assessed for smokers with unstable cardiovascular disease, or who have suffered an acute event in the past four weeks. If the only other option for this group is continued smoking, a risk–benefit assessment invariably leads to recommending NRT. Stopping smoking via non-pharmacological methods should be tried first. When using NRT for smokers with unstable cardiovascular disease, it is advisable to use the shorter-acting oral products, which can be discontinued immediately in the event of any problems. Nicotine patches, even once removed, leave a small reservoir of nicotine under the skin.

Diabetes mellitus
Nicotine releases catecholamines which can affect carbohydrate metabolism. Diabetic patients should be advised to monitor their blood sugar levels more frequently than usual when starting NRT.

Renal or hepatic impairment
NRT should be used with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment, as the clearance of nicotine and/or its metabolites may be decreased, with the potential for increased adverse effects.

Phaeochromocytoma and uncontrolled hyperthyroidism
Use NRT with caution.

3.4 Place in therapy for varenicline and bupropion

Although these two products are not NRT therapy they are included here as people may request information about the use of alternatives to NRT. This request may arise especially if NRT and a quit attempt has not been successful previously. The information below is for guidance and is not a recommendation to prescribe for CWP patients.

3.4.1 Varenicline

Varenicline is cautioned in patients with a history of psychiatric illness in the Champix® Summary of Product Characteristics (SPC). The MHRA has issued advice about suicidal behaviour and varenicline and this is annotated in the BNF as:

‘*’Patients should be advised to discontinue treatment and seek prompt medical advice if they develop agitation, depressed mood or suicidal thoughts. Patients with a history of psychiatric illness should be monitored closely while taking varenicline’*.

The Maudsley Guidelines (2015) state that for patients with a history of depression, they are more likely to experience common side effects of varenicline and/or the symptoms of nicotine withdrawal ie tension/agitation, irritability/anger, confusion and depression. Recent published research has provided some reassuring findings and to date no causal association between varenicline and neuropsychiatric adverse effects has been found.

3.4.1.2 Which group of patients could varenicline be prescribed for?

Any decision to prescribe varenicline for a patient with a history of mental illness needs to be made on a case by case basis and to balance the risks of using varenicline with the benefits of smoking cessation for that individual. Possible exacerbation of mental health symptoms means that varenicline should be used cautiously. Should varenicline be initiated in a patient who has a history of mental illness they should be informed of the risks and monitored for re-emerging symptoms. Prior to initiation the patient’s mental health should be stable. Varenicline should not be initiated whilst a patient is actively suffering from anxiety or other symptoms which would be difficult to differentiate from smoking cessation symptoms and possible adverse effects of varenicline.

Use of varenicline at CWP should take into consideration any updated information in the Summary of Product Characteristics and this can be viewed at www.medicines.org.uk. Varenicline will **not** be initiated on the acute wards but may be considered for mentally stable patients on the rehabilitation wards on a formulary basis when the course of varenicline can be completed prior to discharge. Varenicline prescribing will not be transferred to primary care and responsibility for the treatment course will remain with the CWP prescriber. Primary care prescribing of smoking cessation products is by a variety of providers across Wirral, Central, East and West Cheshire, each service has its own formulary and prescribing process which is not governed by CWP.

3.4.2 Bupropion

Bupropion is contra-indicated in acute alcohol or benzodiazepine withdrawal, severe hepatic cirrhosis, history of seizures, CNS tumours, eating disorders and bipolar affective disorder (may precipitate a manic episode) making it unsuitable for a number of patients of CWP.
It is also cautioned in the elderly, those with a predisposition to seizures or those taking concomitant drugs which lower seizure threshold (this includes most antidepressants and antipsychotics), alcohol abuse, history of head trauma and diabetes.

Concomitant use of bupropion with monoamine oxidase inhibitors (MAOIs) is contraindicated.

The cautions and contra-indications, including interaction with many psychotropic medicines make bupropion unsuitable for the majority of CWP patients and will not be used.

3.5 Inpatient referrals

3.5.1 For those who have agreed a quit date

- Inpatients who have agreed a quit date will be seen by a member of CWP staff who has the relevant level 2 training or by a Specialist Smoking Cessation Advisor. Some patients, particularly those on the rehabilitation units may access smoking cessation advice and products through their GP practice;
- The advisor will provide smoking cessation advice;
- The patient will be assessed for suitability to receive NRT and from their history and preferences, appropriate NRT will be recommended. This may involve using more than one type of NRT product at the same time e.g. patches and gum;
- When NRT is recommended by the advisor the consultation will be documented in the patient's case notes along with the recommended NRT product(s).
- The level 2 smoking cessation advisor or duty doctor will then prescribe the recommended product (s) on the nicotine replacement record chart (appendix 2) and complete the additional chart section on the front of the main prescription chart, checking that there are no contra-indications with current medication. Some medications may require a dose adjustment once smoking has stopped (appendix 1);
- Once the NRT has been prescribed on the chart it can be ordered from the pharmacy in the same way other non-stock medication is ordered (if not already kept as stock on the ward);
- Once the NRT is available on the ward, labelled for that patient, the advisor will counsel the patient on how to use it;
- Patients are entitled to a free supply of NRT for the duration of their inpatient stay. Once discharged, if they are supported by local Stop Smoking Service and normally pay for their medication then they will pay the usual prescription fee;
- When a patient is admitted with NRT already prescribed it is the responsibility of the ward staff to contact the Smoking Cessation Advisor to arrange assessment, counselling and support, as appropriate during their admission. The hospital has a responsibility to continue to provide / pay for NRT until discharge;
- As part of the discharge care plan the ward staff should refer those patients continuing to be abstinent to the primary care smoking cessation advisor for follow-up;
- Upon discharge those patients who continue to be abstinent will receive one week's supply of treatment. After this their ongoing supply will be arranged by the local community smoking cessation advisors. If a patient has been initiated on varenicline CWP will continue to supply the varenicline until the course is complete (usually 12 weeks, maximum 24 weeks). The patient is required to complete the course prior to discharge so that the effect of treatment can be assessed.

3.5.2 Temporary abstinence

- This applies to those patients who are admitted to an inpatient unit who do not wish to set a quit date, but are not permitted to smoke whilst they are an inpatient;
- Following an initial assessment the member of staff will refer the patient to a level 2 specialist advisor on the inpatient unit;
- The advisor will provide smoking cessation advice;
- The patient will be assessed for suitability to receive NRT and from their history and preferences, appropriate NRT will be recommended;
- When NRT is recommended by the advisor the consultation will be documented in the patient's case notes along with the recommended NRT product(s)
- The level 2 smoking cessation advisor or duty doctor will then prescribe the recommended product (s) on the nicotine replacement therapy record chart (appendix 2) and complete the additional chart section on the front of the main prescription chart, checking that there are no contra-indications with current medication. Some medications may require a dose adjustment once smoking has stopped (appendix 1);

- For the purposes of 'temporary abstinence' the wards will have a supply of commonly used NRT products on stock (appendix 3). Alternative nicotine products to this list can be ordered from pharmacy as a non-stock item in the usual way;
- Unless the patient agrees to a 'quit attempt' during their admission, NRT will not be prescribed or supplied on discharge. If a quit attempt is agreed then the level 2 advisor will re-assess and follow Section 3.6.1.

3.5.3 Recording use of NRT by inpatients

- Following assessment of capacity to understand the instructions for use of the NRT product (s), risk assessment regarding safe use of the NRT product(s) and ability to manage safe keeping of the product the patient **may** be given the product to self -administer. The record chart (appendix 2) should be annotated 'self' for the period of time the patient has the product in their possession;
- Where a patient is not able to manage their own NRT product the ward will store the product(s) and a member of ward staff will supervise the patient using the product(s). Staff in this instance includes:
  - qualified nursing staff
  - clinical support workers .
- Staff should sign the record sheet each time they observe the use of NRT and annotate the chart with an 'X' if doses are not required or 'R' if the patient declines the dose.

3.6 Community referrals

People under the care of CWP Community Mental Health Teams (CMHT) needing smoking cessation advice will be referred to a Specialist Advisor and the local primary care smoking cessation services.

3.7 Management and monitoring mechanisms

Advisors will be working under the direction of the specialist smoking cessation service in addition to these guidelines.

The specialist smoking cessation service in each locality will follow a set of nationally agreed guidelines for Nicotine Replacement Therapy. The Trust Level 2 advisors will also work to these guidelines.

3.8 Advice

Advice to those who wish to start NRT should include product specific advice (see current edition of BNF).

The following general advice should also be given:

- Withdrawal symptoms;
- Possible changes in the body on stopping smoking, (e.g. weight gain) and how to manage these;
- The effects of smoking tobacco whilst using NRT – particularly in vulnerable groups, e.g. pregnant women, clients with cardiovascular disease;
- Follow up and obtaining further supplies of NRT;
- Written information on products supplied, self-help leaflets and where to obtain more information, in particular the NHS Helpline numbers for:
  - **NHS Helpline:** 0800 022 4 332
  - **Pregnancy Helpline:** 0800 169 9 169

3.9 Informed consent

Patient information relating to the supply of NRT under these guidelines may be passed to other health service organisations, e.g. a patient's GP or specialist clinics for purposes such as referral, discharge information or audit.

3.10 Staff referrals

CWP Staff can seek smoking cessation advice through Occupational Health or through their GP and their local primary care smoking cessation services.

3.11 Side effects and adverse reactions

These are usually transient but may include the following, some of which are consequences of stopping smoking:

Nausea, dizziness, headache, cold and flu like symptoms, palpitations, dyspepsia and other gastro-intestinal disturbances, hiccups, insomnia, vivid dreams, myalgia, chest pain, blood pressure changes, anxiety and irritability, somnolence and impaired concentration, dysmenorrhoea.

Any serious side effects should be discussed with the patient's advisor in the first instance. In addition a "yellow card" should be completed, informing the Medicines and Healthcare Products Regulatory Agency (MHRA). Guidance on the use of the Yellow Card System and Yellow Cards are available in the current edition of the BNF and they can also be completed via: http://yellowcard.mhra.gov.uk/

Advisors should seek appropriate advice about any suspected adverse drug reactions from the stop smoking services and offer this advice to the patient. The advisor should also record details of the adverse drug reaction and an incident form must be completed

4. Electronic cigarettes

Electronic cigarettes (e-cigarettes) [9] will not be supplied by CWP as they are not currently available as licensed medical products, although British American Tobacco expect to launch a product at the end of the year. The evidence around the safety of e-cigarettes in terms of smoking cessation success and risks to health remains controversial. Physical safety in terms of fire risk, or consumption of the refill liquid for example are also considered by the Nicotine Management Group in relation to maintaining safety for all people on Trust premises. There is a huge variety of products available, some refillable, some with cartridges, some disposable, some rechargeable and it is difficult to differentiate between different products and know which are licensed and which brings difficulties to the safe management of e-cigarettes. Until the safety of E-cigarettes is clearer and differentiation between products can be reasonably assessed they will not to be used inside CWP premises. A range of alternative NRT products are available as is smoking cessation advice from trained staff. The position of e-cigarettes will be reviewed regularly by the Nicotine Management Group and a new product request made to MMG should e-cigarettes become available on prescription and be compatible with the Nicotine Management Policy.

Appendix 1 – Smoking cessation and drug interactions

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Effects on psychotropic drugs

When people stop smoking, enzyme activity reduces over a week or so. Plasma levels of affected drugs will then rise, sometimes substantially. Dose reduction will usually be necessary. If smoking is re-started enzyme activity increases, plasma levels fall and dose increases are then required. The process is complicated and effects are difficult to predict.

Few people manage to give up smoking completely so additional complexity is introduce by intermittent smoking and repeated attempts at stopping completely. Close monitoring of plasma levels (where useful) clinical progress and severity of adverse effects are essential (Maudsley Guidelines 2015).

1. Recommendations for the prescribing of psychotropic drugs during smoking cessation

a. General recommendations:

On admission to non-smoking inpatient unit:

- Ascertain pre-admission smoking status;
- Determine effect on specific psychotropic medication (see table below);
- Adjust dose taking in to consideration age, hepatic function, time delay for onset of changes to metabolising enzymes;
- Monitor for possible emergence of side effects due to raised serum levels (or for lack of efficacy due to reduced serum levels – usually only the case when a patient is smoking without the knowledge of the treating team);
- Monitor for change in smoking status e.g. leaves;
- Ascertain likely smoking status on discharge (i.e. is the patient going to resume smoking?)

b. Specific recommendations:

The MHRA have issued guidance on 'Smoking and smoking cessation: clinically significant interactions with commonly used medicines'. This states that:

Polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke are potent inducers of the hepatic cytochrome P450 (CYP) isoforms 1A1, 1A2, and possibly 2E1. Of these, 1A2 is the most important. Enzyme induction results in increased metabolism of substrates. Thus larger doses of CYP1A2 substrates may be required to ensure efficacy in people who smoke, and a reduction in dose may be needed during smoking cessation to prevent side effects.

Many commonly used medicines are substrates for CYP1A2: theophylline; fluvoxamine; caffeine; coumarins, including warfarin; and the antipsychotics clozapine and olanzapine. However, not all possible drug-smoking interactions are clinically significant. Important factors that determine the clinical significance of an interaction in smokers are:

- The extent to which the medicine is metabolised by CYP1A2—ie, the fractional clearance. The interaction will be most significant when CYP1A2 is the main elimination pathway
- The therapeutic index of the medicine metabolised for CYP1A2. For example, for a narrow therapeutic index drug such as theophylline, small changes in drug concentration may have significant clinical effects

From the NHS evidence website www.evidence.nhs.uk the more significant interactions are considered to be with theophylline, clozapine and olanzapine. More moderate interaction is considered to occur with warfarin, chlorpromazine, methadone and insulin. The table below shows the

interactions predicted to occur on smoking cessation with these medicines and what prescribing changes might need to be made.

BNF category / drug name	Nature of interaction	Clinical relevance	Action to take when stopping smoking
2.8.2 Warfarin	Warfarin is partly metabolised via CYP1A2. An interaction with smoking is not clinically relevant in most patients. The dose of warfarin is adjusted according to a patient's INR (International Normalised Ratio).	Moderate	If a patient taking warfarin stops smoking, their INR might increase so monitor the INR more closely. Advise patients to tell the physician managing their anticoagulant control that they are stopping smoking.
3.1.3 Theophylline	Theophylline is metabolised principally via CYP1A2. Smokers need higher doses of theophylline than non-smokers due to theophylline's shortened half-life and increased elimination. Some reports suggest smokers may need twice the dose of non-smokers.	High	Monitor plasma theophylline concentrations and adjust the dose of theophylline accordingly. The dose of theophylline may need to be reduced by about one quarter to one third one week after withdrawal. However, it may take several weeks for enzyme induction to dissipate. Monitor theophylline concentration periodically. Advise the patient to seek help if they develop signs of theophylline toxicity such as palpitations or nausea.
4.2.1 Chlorpromazine	Chlorpromazine is metabolised principally via CYP1A2. Smokers have lower serum levels of chlorpromazine compared with non-smokers. A case report describes a 25 year old patient with schizophrenia who experienced increased adverse effects of chlorpromazine (sedation and dizziness) and increased plasma chlorpromazine levels after abruptly stopping smoking.	Moderate	Be alert for increased adverse effects of chlorpromazine (e.g. dizziness, sedation, extra-pyramidal symptoms). If adverse effects occur, reduce the dose as necessary.
4.2.1 Clozapine	Clozapine is metabolised principally via CYP1A2 and clearance is increased in smokers. Serum clozapine levels are reduced in smokers compared with non-smokers; smokers may need higher doses. There have been case reports of adverse effects in patients taking clozapine when they have stopped smoking.	High	Monitor serum drug levels before stopping smoking and one or two weeks after stopping smoking. Be alert for increased adverse effects of clozapine. If adverse effects occur, reduce the dose as necessary. Reduce clozapine dose according to plasma levels and adverse effects. One study suggests that in 80% of cases the change in clozapine plasma levels can be predicted by using the formula: Non-smoking

BNF category / drug name	Nature of interaction	Clinical relevance	Action to take when stopping smoking
			clozapine level = 45.3 + (1.474 x smoking clozapine level) (Meyer, 2001 Desai et al) In the only study looking at changes in plasma levels in patients who stopped smoking, there was a mean ↑ in clozapine levels of 71.9% on smoking cessation. (Meyer, 2001) Case report of tonic clonic seizures, stupor and coma 2 weeks after abrupt cessation of smoking (Skogh et al, 1999) Case report of seizure occurring 3 weeks after smoking cessation (McCarthy, 1994) Faber et al, 2004 recommends a stepwise daily dose reduction of ~ 10% until the 4th day post smoking cessation as well as therapeutic monitoring. See below for further information.
4.2.1 Olanzapine	Olanzapine is metabolised principally via CYP1A2 and clearance is increased in smokers. Serum olanzapine levels are reduced in smokers compared with non-smokers; smokers may need higher doses. There have been case reports of adverse effects in patients taking olanzapine when they have stopped smoking.	High	Be alert for increased adverse effects of olanzapine (e.g. dizziness, sedation, hypotension). If adverse effects occur, reduce the dose as necessary.
4.10 Methadone	Methadone is metabolised via isoenzymes including CYP1A2. There has been a case report of respiratory insufficiency and altered mental status when a patient taking methadone for analgesia stopped smoking.	Moderate	Be alert for signs of opioid toxicity and reduce the methadone dose accordingly.
6.1.1 Insulin	Smoking is associated with poor glycaemic control in patients with diabetes. Smokers may require higher doses of insulin but the mechanism of any interaction is unclear.	Moderate	If a patient with insulin-dependent diabetes stops smoking, their dose of insulin may need to be reduced. Advise the patient to be alert for signs of hypoglycaemia and to test their blood glucose more frequently.

2. Clozapine

Smoking reduces plasma levels by up to 50% with plasma level reduction being greater in those receiving valproate. Maudsley Guidelines (2015) recommend that plasma clozapine levels should be taken before stopping smoking. On stopping dose should be gradually reduced (over a week) until around 75% of the original dose is reached (ie reduce by 25%). The guidance also recommends repeating plasma levels one week after stopping, with an anticipation of further dose reductions. Plasma clozapine levels should also be taken before re-starting and dose increased to previous smoking dose over one week, with a further repeat of the plasma clozapine level. Only cigarette smoking induces hepatic enzymes in the manner described above – nicotine replacement and electronic cigarettes (which do not contain polycyclic aromatic compounds) have no effect on enzyme activity.

a. Metabolism/Induction CYP1A2:

Clozapine is metabolised through the CYP1A2 enzyme (cytochrome P450 1A2). In smokers metabolism of clozapine is increased and so serum clozapine levels are reduced. On cessation of smoking, reversal or decay of the induction of CYP1A2 occurs resulting in a 30% reduction in CYP1A2 activity over approximately 4 days (Faber). Serum clozapine levels rise and probably achieve steady state approximately 7-10 days after smoking cessation.

b. Estimated changes in serum clozapine levels:

i. At low to moderate serum levels:

The difference in serum clozapine levels can be represented by a linear equation:

Serum ng/mL $Cloz_{NonSmoker}$ = 1.5(Serum ng/mL $Cloz_{Smoker}$) + 50

(E.g. Clozapine level $_{Smoker}$ of 400ng/ml, therefore: Clozapine level $_{NonSmoker}$ = (1.5 x 400) + 50 = 650**)**

(N.B. For higher initial clozapine level, say above 700ng/ml, serum levels might increase by much more than this formula on smoking cessation e.g. case report 750ng/ml →3000ng/ml).

Set target serum clozapine level and adjust dose

ii. High serum levels

At high levels (e.g. levels of clozapine greater 700ng/ml) the CYP1A2 enzyme may become saturated with the substrate clozapine causing greater reductions in the rate of metabolism. Serum levels may then rise by much more than the above formula (e.g. case report - Serum $Cloz_{Smoker}$ = 850ng/mL; Serum $Cloz_{Nonsmoker}$ = 3300ng/mL).

c. Factors to consider:

- Smoking status: light / moderate / heavy smoker, preadmission / in community, on admission, on leaves from ward, on discharge / return to community;
- Clozapine compliance preadmission;
- Serum clozapine levels: preadmission / outpatient / baseline at admission, at what doses, with what degree of compliance, what amount of smoking;
- History of side effects on clozapine and the approximate serum clozapine levels at which these occurred.

d. Specific recommendations regarding clozapine

On admission to a non-smoking inpatient unit:
Assess preadmission smoking status, and clozapine compliance. Review preadmission (outpatient) serum clozapine levels and obtain baseline admission serum clozapine level. Review history of side effects and the serum clozapine levels at which these occurred.

Assess risk of toxicity (e.g. risk of level >1000ng/mL or levels higher than where previous side effects occurred) by predicting likely serum clozapine level using above formula or graph (N.B. for high initial clozapine levels, >700ng/ml, or clozapine doses (>700mg this formula might not apply).

Set target serum clozapine level taking into consideration the patient's current mental state and the clinical response to the current dose.
Example: Smoker admitted on clozapine dose 600mg with level of 500ng/ml, known to be compliant, clinically unwell on this dose and so requires higher serum level. Estimated serum level if ceases smoking at this dose = 800ng/ml (ie 1.5x(600) + 50).

If clinician determines that target serum level of 800ng/ml is appropriate, then no dose change is necessary. If lower target serum level is desired, say 600ng/ml, then estimate a reduced dose e.g. approximately 500mg

Monitor:

a. Serum clozapine level
   - at 3 to 5 days, 7 to 10 days, weekly and pre-discharge unless level obtained in previous 48 hours

b. clinically for side effects – maybe as late as 2 to 3 weeks

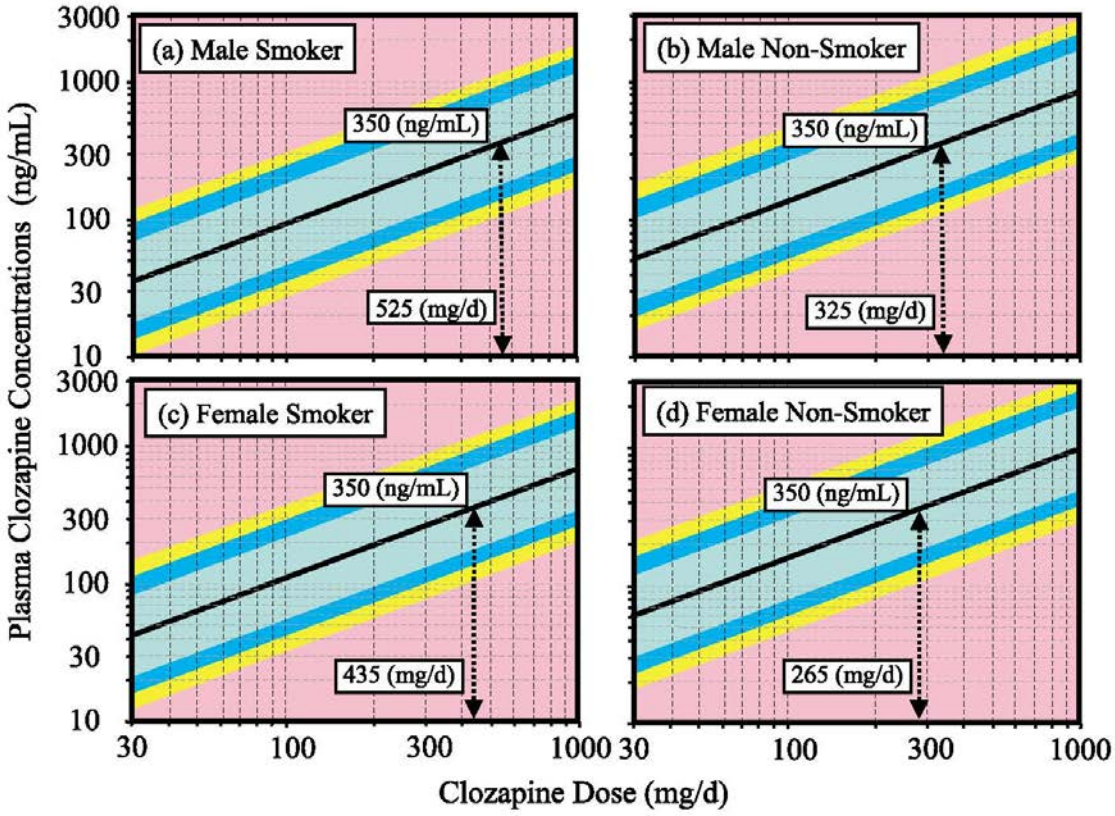
On discharge / leaves:
When a patient is discharged or allowed leave, reassess for potential smoking status and for a potential reduction in serum clozapine if the patient resumes smoking. Clozapine may need to be increased if this is the case.

Post discharge:
Post discharge, repeat serum clozapine weekly until the clinical situation is stable.

e) Effect of gender and smoking status on clozapine levels

The following nomographs are reproduced with kind permission from the paper by Rostami-Hodjegan A, Amin AM, Spencer EP, Lennard MS, Tucker GT, Flanagan RJ (2004). Influence of dose, cigarette smoking, age, sex and metabolic activity on plasma clozapine concentrations: A predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. J Clin Psychopharmacology, vol24, issue1. These graphs demonstrate the effect of male and female smokers and non-smoker status on plasma concentration of clozapine and therefore impact of dosing regimens.

Figure 1



3. Other factors to consider in prescribing psychotropic drugs during smoking cessation

Considerations should be given to the following:

- Amount of tobacco smoked – i.e. light, moderate, or heavy smoker. This may correlate with the level of nicotine dependence;
- Smoking status;
- Verification of non-smoking status (has the patient actually stopped smoking?);
- Expected changes to smoking status on leave/discharge (will the patient resume smoking on leave or on discharge?);
- Changes to psychotropic doses for other reasons;
- Time delay for changes to CYP1A2 levels on smoking cessation (or resumption) and subsequently the time delay for changes to steady state levels of the psychotropic drug;
- Age - less induction of CYP1A2 enzyme with increasing age;
- Liver dysfunction e.g. acute hepatitis following alcohol binge

Smoking causes induction of hepatic enzymes

Cigarette smoke contains polycyclic aromatic hydrocarbons (PAHs) and it is these (not nicotine) that induce (increase the amount and/or activity of) the hepatic cytochromes enzymes CYP1A1, 1A2 and 2E1.

Induction of these enzymes results in an increase in the metabolism of many drugs that are substrates for these enzymes and causes a subsequent decrease in plasma concentrations of those drugs. Higher doses of these drugs may therefore be required to achieve the same plasma level and therapeutic effect.

It is unclear how quickly the CYP enzymes are induced on commencing smoking. The inducing agent (PAHs in cigarette smoke) causes the synthesis of new enzymes; however, it generally takes more than a week before maximal enzyme induction is seen.

The extent or magnitude of induction varies according to the bioavailability of the cigarette smoke components (unfiltered cigarettes produce higher levels of some PAHs than filtered) and the extent of inhalation. Heavier smokers have the greatest increase in drug clearance. In one study (Chetty et al, 1994), the combination of cigarette and cannabis smoking produced a greater increase in drug clearance than cigarette smoking alone.

Smoking cessation: reversal of hepatic enzymes induction

In a study investigating the time frame for CYP1A2 changes on smoking cessation it was found that on stopping smoking there was a rapid decrease in activity of CYP1A2 with a new steady state being reached after approximately one week (Faber et al, 2004).

Effect of smoking cessation on psychotropic drugs

Smoking cessation can therefore increase levels of drugs that are metabolised via CYP1A2 and so a change in dosing may be necessary. Limited data is available for most drugs. Faber et al recommend that in drugs with a narrow therapeutic index, which are substrates at CYP1A2 (e.g. Clozapine), that a stepwise daily dose reduction of approx 10% until the fourth day after smoking cessation be undertaken. Clear guidelines for clinical practice are not available as there are very few reports on the actual pharmacokinetic changes which occur in psychotropic drugs when patients stop smoking

Appendix 2 - Record of NRT use (for as and when required products)

Patient details (Name and NHS number)

	Date → Time ↓																								
NRT product	01:00																								
	02:00																								
	03:00																								
Strength	04:00																								
	05:00																								
	06:00																								
Dose	07:00																								
	08:00																								
	09:00																								
Frequency	10:00																								
	11:00																								
	12:00																								
Prescriber signature & date	13:00																								
	14:00																								
	15:00																								
	16:00																								
Additional instructions	17:00																								
	18:00																								
	19:00																								
	20:00																								
Pharmacy signature / supply?	21:00																								
	22:00																								
	23:00																								
	24:00																								

Appendix 3 - Using NRT Products at CWP

Treatment should be initiated at a dose appropriate to the number of cigarettes used per day.

- Combination therapy of patches with another form of NRT e.g. lozenges can be tried as a means of increasing efficacy, especially for people who show a high level of dependency or for whom single forms of NRT have been inadequate.

- The choice of product should depend on the patient's history, taking into account previous personal experience and preferences. People unable to tolerate one type of NRT may benefit from a different NRT preparation.

- Details of all NRT products can be found in section 4.10.2 of the British National Formulary (BNF) and are listed briefly below. It is recommended that treatment is prescribed as soon as possible after admission. See section 3.6.1 for prescribing for those with a set quit date and section 3.6.2 for those prescribed NRT for temporary abstinence.

- NRT for inpatients can be prescribed by a nurse trained to level 2 smoking cessation (who has maintained the annual update of training) or by a doctor.

- NRT products will be stocked at the 3 inpatient units on the wards as agreed between the ward manager or NRT lead for each ward and the clinical pharmacy team. Additional stocks will be carried in the emergency/ out of hours cupboard or by local arrangement. Products which are for individual use e.g. inhalators, mouth or nasal sprays will be re-ordered for the individual patients as with other medicines. Gum will not be routinely stocked (see below) and sub-lingual tablets have insufficient usage currently to warrant being held as stock on all wards. These products will be held centrally, as for the additional stock, for the 3 inpatient units. Where more than one brand is available a decision will be made to stock one brand trustwide to reduce waste.

Nicotine Replacement Products

It is anticipated that other formulations will become available as medicinal products in the future. Applications should be made to the CWP formulary for new products. Products available at the time of these guidelines being approved include the following formulations. NRT products can be prescribed following assessment of the risks and benefits for each individual.

Patches	These are available as 16 hour or 24 hour patches. 16 hour patches are advised if sleep disturbances/nightmares are experienced or the 24 hour patch should be removed at bedtime.
Lozenges	These can be used every 1 to 2 hours when the urge to smoke occurs or to prevent cravings. Those who smoke >20cigarettes a day or fail to stop smoking with the lower strength lozenges should use the higher strength lozenges (4mg).
Nasal spray	has a fast onset of action but may cause local irritation. More expensive than patches and lozenges as combined use.
Oral spray	contains <100mg ethanol per dose. More expensive than patches and lozenges as combined use. One spray pack lasts less than 3 days at maximum use.
Sub-lingual tablets	may be useful for those who have difficulty chewing gum or if gum is not allowed. Tablets can be used hourly and should be allowed to dissolve under the tongue. More expensive than patches and lozenges as combined use.
Inhalator	simulates cigarette smoking but may cause local irritation of the mouth and throat. Replacement inhalators cannot be purchased separately. An alternative NRT product may be more suitable for those who regularly misplace the device, as the device will not be replaced through CWP supplies. More expensive than patches and lozenges as combined use. Repeat issuing of inhalators make this an even more expensive and potentially wasteful product

Gum	comes as 2mg and 4mg strength. Those smoking >20cigarettes a day or requiring >15 pieces of the 2mg gum/day should use the 4mg strength. Use is to be assessed on a case by case basis as informed by risk assessment

Not recommended for inpatient use
Note varenicline and bupropion are not NRT but are medicines to assist in smoking cessation.

Varenicline will not be initiated for acute inpatients but can be considered for those patients who are mentally stable and resident on the rehabilitation wards as its use is cautioned in those with a history of mental illness, including depression – see section 3.4.

Bupropion
CWP does not support the prescribing of Bupropion

Combinations of NRT and Varenicline or Bupropion CWP do not utilise NRT, varenicline or bupropion in any combination as per NICE PH10 Smoking Cessation Guidance.