

Introduction

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Smoking rates are significantly higher among people with mental health problems. It is estimated that smoking rates are over double those of the general population and highest in those diagnosed with psychotic disorders. Tobacco smoking has negative effects on the physical, mental and financial well-being of people with mental health problems. Smoking can aggravate symptoms, affect handling of medications and contribute to relapse. Over 50% of smokers with mental health problems want to quit. However, within Mental Health Services, smoking cessation is often overlooked and many smokers do not always receive necessary advice and support required to stop successfully and safely.

National No Smoking legislation came into force in all enclosed public areas and workplaces on 1 July 2007. Under the smoke free regulations mental health in-patient units have been given a time limited exemption until 1 July 2008 to stop smoking. After this date, a total ban on smoking in all enclosed places applies. Mersey Care has been operating a smoke free policy since December 2006 and service users are now offered help to stop smoking. Tobacco smoking can affect the handling of medications. It is recognised that the impact of smoking cessation on medication is often neglected when smoking stops. The purpose of this document is to highlight potential interactions between smoking or smoking cessation and medications which should be considered in clinical and prescribing decisions.

Tobacco smoking is associated with many drug interactions. Drug interactions can occur via pharmacokinetic and pharmacodynamic mechanisms. Pharmacokinetic interactions are those that affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. Such interactions may cause smokers to require larger doses of certain drugs through an increase in plasma clearance, a decrease in absorption, enzyme induction or a combination of these factors. Pharmacodynamic interactions alter the expected response or actions of other drugs. Such interactions may increase the risk of adverse events for example in smokers with cardiovascular disease, and in women who smoke and use oral contraceptives.

The nicotine in tobacco is highly addictive and can cause pharmacodynamic interactions. Polycyclic hydrocarbons and other tar-like compounds in tobacco smoke can increase the activity of several liver enzymes e.g. cytochrome P450 systems - primarily CYP1A2 but also CYP2A6, CYP2B6 and CYP2D6]], which are responsible for metabolising many different types of drugs. Enzyme induction results in faster clearance of medication from the body reducing serum drug levels and decreasing efficacy.

Several studies have shown that smokers require and are prescribed higher doses of psychotropic medication than non-smokers. Increased metabolism and faster clearance of medication implies that higher doses are required to achieve desired therapeutic effects. When smoking is reduced or stopped, enzyme induction reduces or ceases, the rate of metabolism decreases, leading to a rise in serum drug levels. Dose adjustments may be required for certain drugs. This applies also when using therapies for smoking cessation. Therefore, it is important to recognise that on stopping smoking, a person may experience increased side effects despite taking the same dose of medication as that prescribed while smoking.

The implications of smoking cessation on medication can be significant. It is therefore important to assess risks of cutting down or quitting smoking on medication dosing requirements. In the majority of cases, serum drug levels may change necessitating adjustments in the amount of drug prescribed. Not all smoking-related drug interactions are clinically significant. However, the potential for interaction exists and should be borne in mind when smoking is stopped. The risk of drug interactions should however not prevent smokers from quitting. The small risks posed by these interactions are far outweighed by the overall health benefits of quitting. The table below provides information on potential drug reactions that can occur on quitting smoking and offers suggestions for appropriate management.

NB: This table highlights common interactions. It is not a complete listing of all possible interactions.

SMOKING AND HYPNOTICS AND ANXIOLYTICS

Drug/Class	Effects of Smoking	Effect of Smoking cessation	Management on smoking cessation
Benzodiazepines e.g. Aprazolam Chlordiazepoxide Clonazepam Diazepam Loprazolam Lorazepam Lormetazepam Nitrazepam Oxazepam Temazepam	<ul style="list-style-type: none"> Increased clearance due to enzyme induction leading to lowers plasma levels Less sedation and drowsiness with high levels of nicotine Possibly less hypnotic effect in smokers due to central nervous system (CNS) stimulation from nicotine Smokers possibly need larger doses of some benzodiazepines than non-smokers 	<ul style="list-style-type: none"> Plasma levels may rise due to reduced clearance of drug Patients taking benzodiazepines may experience increased sedation after giving up smoking or on using therapies for smoking cessation 	<ul style="list-style-type: none"> Monitor for increased sedation and hangover effects Lower doses of benzodiazepines may be required
Zolpidem	<ul style="list-style-type: none"> Clearance is increased in smokers due to enzyme induction Half life may be 30% shorter Smoking may lower plasma levels Possibly less hypnotic effect due to CNS stimulation from smoking Heavy smokers may require higher doses of zolpidem 	<ul style="list-style-type: none"> Clearance of zolpidem is reduced and plasma levels increase Sedation may increase 	<ul style="list-style-type: none"> Dose reduction may need to be considered especially if there are symptoms of increased sedation and substantial hangover effects
Zopiclone	<ul style="list-style-type: none"> Smoking has no clinically significant effect on the plasma concentration Possibly less hypnotic effect due to CNS stimulation from nicotine 	No known clinically significant effects	Monitor*

SMOKING AND DRUGS USED IN PSYCHOSES AND RELATED DISORDERS

Drug/Class	Effects of smoking	Effect of Smoking cessation	Management on smoking cessation
Antipsychotics - general	<ul style="list-style-type: none"> Smoking reduces the blood levels of some antipsychotics via increased metabolism Smokers may need higher doses Smoking may increase some antipsychotic side effects 	<ul style="list-style-type: none"> Serum levels increase due to reduced clearance Lower doses of antipsychotics may be required on stopping smoking or using therapies for smoking cessation 	<ul style="list-style-type: none"> Monitor response If more sedated or increased side effects, such as hypotension, drowsiness or extrapyramidal side effects [EPSE], then reduce dose
Aripiprazole	<ul style="list-style-type: none"> Smoking appears to have no effect on serum levels 	<ul style="list-style-type: none"> No known clinically significant effects 	<ul style="list-style-type: none"> Monitor*
Amisulpride	Smoking is not thought to have a significant effect on the plasma levels	<ul style="list-style-type: none"> No known clinically significant effects 	<ul style="list-style-type: none"> Monitor*
Chlorpromazine (phenothiazines)	<ul style="list-style-type: none"> Serum levels may be lower in smokers due to increased clearance but clinical significance unclear Less drowsiness and hypotension in smokers 	<ul style="list-style-type: none"> Serum levels increase due to reduced clearance May need lower doses on stopping smoking or using therapies for smoking cessation 	<ul style="list-style-type: none"> Consider dose reduction if side effects such as drowsiness or EPSEs increase Lower doses may be required
Clozapine	<ul style="list-style-type: none"> Serum levels are lower in smokers because smoking induces clozapine metabolism Smokers may need higher doses 	<ul style="list-style-type: none"> Plasma clozapine concentrations increase significantly on stopping smoking or using therapies for smoking cessation Risk of adverse effects increases 	<ul style="list-style-type: none"> Monitor side effects Measure levels before quitting and 2 weeks after; earlier if side effects occur Significantly lower doses may be required
Fluphenazine	<ul style="list-style-type: none"> Serum levels may be lower in smokers 	<ul style="list-style-type: none"> Serum levels may increase on stopping smoking 	<ul style="list-style-type: none"> Consider dose reduction if side effects such as drowsiness or EPSEs increased Lower doses may be required

SMOKING AND DRUGS USED IN PSYCHOSES AND RELATED DISORDERS cont.

Drug/Class	Effects of Smoking	Effect of Smoking cessation	Management on smoking cessation
Haloperidol	<ul style="list-style-type: none"> Serum levels may be around 20% lower in smokers due to increased drug clearance as a result of induction of drug-metabolising enzymes Smokers require higher doses 	<ul style="list-style-type: none"> Serum levels increase due to reduced metabolism Side effects may increase Patients taking haloperidol may require lower doses after stopping smoking 	<ul style="list-style-type: none"> Monitor symptoms Consider dose reduction if adverse effects such as drowsiness, hypotension or EPSEs increase
Olanzapine	<ul style="list-style-type: none"> Smoking increases the clearance of olanzapine as a result of induction of drug-metabolising enzymes Half life may be around 20% shorter in smokers Serum levels lower in smokers 	<ul style="list-style-type: none"> Serum olanzapine levels increase significantly on stopping smoking due to reduced clearance caused by a slower metabolism 	<ul style="list-style-type: none"> Monitor closely Lower doses of olanzapine may be required Consider dose reduction if adverse effects e.g. drowsiness, hypotension occur
Perphenazine	<ul style="list-style-type: none"> Serum levels are lower due to increased metabolism 	<ul style="list-style-type: none"> Serum levels may increase on stopping smoking or using therapies for smoking cessation 	<ul style="list-style-type: none"> Monitor response Lower doses may be required
Quetiapine	<ul style="list-style-type: none"> Smoking does not appear to alter quetiapine metabolism and clearance 	<ul style="list-style-type: none"> No known clinically significant effects 	Monitor*
Risperidone	<ul style="list-style-type: none"> Smoking should not influence the dosing of risperidone 	<ul style="list-style-type: none"> No known clinically significant effects 	Monitor*
Ziprasidone	<ul style="list-style-type: none"> Lack of interaction has been shown 	<ul style="list-style-type: none"> No known clinically significant effects 	Monitor*
Zotepine	<ul style="list-style-type: none"> Smoking seems to have little effect on plasma levels Only a minor fraction of zotepine is metabolised by this enzyme 	<ul style="list-style-type: none"> No known clinically significant effects 	Monitor*

SMOKING AND ANTIDEPRESSANT DRUGS

Drug/Class	Effects of Smoking	Effect of Smoking cessation	Management on smoking cessation
DULOXETINE	<ul style="list-style-type: none"> Smokers may have plasma levels 50% lower than non-smokers due to enzyme induction and increased metabolism 	<ul style="list-style-type: none"> Serum levels may increase on stopping smoking or using therapies for smoking cessation 	<ul style="list-style-type: none"> Monitor for increased side effects Dose reduction may be required
MIRTAZEPINE	<ul style="list-style-type: none"> Cigarette smoke may induce enzymes that metabolise mirtazapine leading to lower blood levels 	<ul style="list-style-type: none"> Clinical significance unclear Serum levels may rise 	<ul style="list-style-type: none"> Monitor for side effects Dose adjustment should be considered if side effects increase
SSRIs fluvoxamine	<ul style="list-style-type: none"> Smoking may alter drug clearance of fluvoxamine as a result of enzyme induction Serum levels are significantly lower in smokers than nonsmokers 	<ul style="list-style-type: none"> Serum levels may increase on stopping smoking or using therapies for smoking cessation 	<ul style="list-style-type: none"> Monitor for side effects and consider dose adjustment, if appropriate
Tricyclics e.g. amitriptyline clomipramine imipramine nortriptyline,	<ul style="list-style-type: none"> Smoking reduces the plasma levels of tricyclics Cigarette smoke may increase drug clearance due to induction of hepatic drug-metabolising enzymes Although serum levels of tricyclic antidepressants fall in smokers, free drug levels rise, minimising the clinical significance 	<ul style="list-style-type: none"> Serum levels may increase on stopping smoking or using therapies for smoking cessation 	<ul style="list-style-type: none"> Monitor for side effects and consider dose adjustment if appropriate

SMOKING AND DRUGS FOR DEMENTIA

Drug/Class	Effects of Smoking	Effect of Smoking cessation	Management on smoking cessation
Acetylcholinesterase Inhibitors Donepezil Galantamine rivastigmine	<ul style="list-style-type: none"> Smoking not thought to have any clinically significant influence on plasma levels of acetylcholinesterase inhibitors Major enzyme systems minimally involved in metabolism – effect not clinically significant 	<ul style="list-style-type: none"> No known clinically significant effects 	<ul style="list-style-type: none"> Monitor*
Memantine	<ul style="list-style-type: none"> Theoretical interaction via competition for transport system exists and there is the potential for increased plasma levels 	<ul style="list-style-type: none"> Clinical significance unclear 	<ul style="list-style-type: none"> Monitor response

SMOKING AND MOOD STABILISERS

Drug/Class	Effects of Smoking	Effect of Smoking cessation	Management on smoking cessation
Anticonvulsants e.g. carbamazepine, valproate	<ul style="list-style-type: none"> Smoking appears to have no important effect on the serum levels A minor fraction of these drugs is metabolized by enzymes. 	<ul style="list-style-type: none"> No important effect on the serum levels 	Monitor*
Lithium	<ul style="list-style-type: none"> Indirect drug-diet interaction Smoking increases caffeine metabolism via enzyme induction Significant changes in amount of caffeine may affect serum-lithium levels 	<ul style="list-style-type: none"> Theoretically , ceasing smoking could indirectly alter lithium excretion 	<ul style="list-style-type: none"> Check levels especially if deterioration evident

SMOKING AND NON-PSYCHOTROPIC DRUGS

Drug/Class	Effects of Smoking	Effect of Smoking cessation	Management on smoking cessation
Analgesics Dextropropoxyphene Codeine Anti-inflammatory Diflunisal phenylbutazone	<ul style="list-style-type: none"> Dextropropoxyphene and pentazocine are less effective as analgesics in smokers than in non-smokers The clearance of diflunisal and phenylbutazone from the body is greater in smokers than in non-smokers. 	<ul style="list-style-type: none"> Improved response to analgesic 	<ul style="list-style-type: none"> Monitor response
Anti-arrythmic drugs Flecainide lignocaine	<ul style="list-style-type: none"> Serum levels may be lower in smokers due to increased clearance Smokers require higher doses to control arrhythmia 	<ul style="list-style-type: none"> Lower doses may be required 	<ul style="list-style-type: none"> Monitor for side effects/toxicity Dose adjustment may be required
Beta-blockers	<ul style="list-style-type: none"> Smoking can reduce the beneficial effect of beta-blockers on blood pressure and heart rate. Smokers may need larger doses due to increased clearance 	<ul style="list-style-type: none"> Effects of beta blockers may be enhanced by quitting smoking Lower doses may be required on stopping smoking 	<ul style="list-style-type: none"> Monitor blood pressure/pulse If a person taking beta-blockers stops smoking, the dose may need to be reduced.
Diuretics furosemide	<ul style="list-style-type: none"> Nicotine inhibits diuresis and diminishes the diuretic effect of furosemide 	<ul style="list-style-type: none"> Clinical significance unclear 	<ul style="list-style-type: none"> Monitor for changes in response
Histamine₂Blockers cimetidine ranitidine famotidine	<ul style="list-style-type: none"> Smoking may reduce the plasma levels of cimetidine and ranitidine, but does not appear to affect famotidine Cimetidine, and to a lesser extent ranitidine, reduce the clearance of nicotine from the body in non-smokers 	<ul style="list-style-type: none"> Improved response to H₂ blocker expected 	<ul style="list-style-type: none"> Monitor response

Drug/Class	Effects of Smoking	Effect of Smoking cessation	Management on smoking cessation
Insulin	<ul style="list-style-type: none"> Smoking decreases the absorption of insulin and may increase insulin resistance Smokers who have insulin-dependent diabetes may need more insulin than non-smokers 	<ul style="list-style-type: none"> Quitting improves glycaemic control Insulin requirement may be reduced Dose may need to be adjusted according to individual need 	<ul style="list-style-type: none"> Monitor for hypoglycaemia Check blood glucose more frequently Insulin-dependent diabetics may need less insulin
Ropinirole	<ul style="list-style-type: none"> Ropinirole is metabolised via CYP1A2 so elimination may be more rapid in smokers. Smokers may need larger doses. 	<ul style="list-style-type: none"> Serum levels may rise on quitting smoking 	<ul style="list-style-type: none"> Dose may need to be reduced.
Theophylline/ Aminophylline	<ul style="list-style-type: none"> Smoking increases theophylline clearance In smokers, the half-life of theophylline is reduced, clearance is considerably more rapid, due to enzyme induction Smokers need higher doses than non-smokers. For heavy smokers the dose may need to be doubled. 	<ul style="list-style-type: none"> The plasma concentration of theophylline will increase significantly when smoking stopped Theophylline has a narrow therapeutic range – so toxicity is possible 	<ul style="list-style-type: none"> Monitor for signs of toxicity e.g palpitations or nausea. The dose will need to be reduced Plasma levels should be checked and dose adjusted accordingly [typically needs reduction by about a third]
Anticoagulants Warfarin Heparin	<ul style="list-style-type: none"> Smoking may slightly increase warfarin metabolism and clearance slightly reducing response to warfarin Reduced half-life and increased elimination of heparin have been reported in smokers Smokers may possibly need higher doses to achieve anticoagulation. 	<ul style="list-style-type: none"> Dose requirements may be slightly increased. International Normalised ratio [INR] /Prothromin time may increase. 	<ul style="list-style-type: none"> Monitor closely The dose of anticoagulant should be adjusted according to each patient's International Normalised Ratio (INR) / Prothrombin time

Bupropion and Varenicline Interactions

Drug interactions between bupropion (Zyban) and varenicline (Champix) and concurrently prescribed medications must also be considered.

Interactions between bupropion and other medications

Bupropion is contraindicated with in patient taking monoamine oxidase inhibitors. It interacts with medications, including antipsychotics and antidepressants. Extreme caution is required if other drugs that lower the seizure threshold, such as antidepressants, antimalarials, antipsychotics, sedating antihistamines, amantadine, levodopa, quinolones, tramadol, theophylline, or systemic corticosteroids are used with bupropion. Carbamazepine or valproate and possibly cimetidine may cause marked changes in the plasma levels of bupropion and its metabolites. The manufacturer also warns about the concurrent use drugs metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP2B6, the possible use of nicotine and following tobacco withdrawal.

Interactions between varenicline and psychotropic medications

The manufacturer of varenicline states that clinical experience in patients receiving varenicline with other drugs has not revealed evidence of clinically important interactions. Pharmacokinetic interactions are reported to be unlikely with drugs metabolized by or affecting cytochrome P-450 (CYP) isoenzymes. It is however important to note that this is a new drug and information is limited. Monitoring is advised.

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