

## What are the clinically significant drug interactions with cigarette smoking?

Prepared by UK Medicines Information ([UKMi](#)) pharmacists for NHS healthcare professionals  
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### Background

Polycyclic aromatic hydrocarbons (PAHs) are some of the major lung carcinogens found in tobacco smoke. They are also potent inducers of cytochrome P450 (CYP) isoenzymes, particularly CYP1A1 and CYP1A2 [1,2]. Many drugs are substrates for CYP1A2 and their metabolism can be induced in smokers, resulting in a clinically significant reduction in their pharmacologic effect [1,2]. Therefore, dose reduction needs to be considered if a patient stops smoking. Conversely, if a patient starts to smoke and is taking a drug that is metabolised by CYP1A2, the dose may need to be increased [1,2].

This Medicines Q&A summarises those drug interactions with cigarette smoking that are considered to be most clinically important.

### Answer

Most interactions between drugs and smoking are not clinically significant.

Drug interactions with cigarette smoking considered to be of most clinical importance are listed in the table below. The table describes the nature of the interaction and advises on appropriate management when a patient taking an interacting drug alters their smoking status. Since most interactions are due to components of cigarette smoke other than nicotine, these interactions are not expected to occur with nicotine replacement therapy or e-cigarettes [2].

The following criteria have been considered in grading clinical relevance of drug interactions:

- High:** Documented pharmacokinetic interaction with clinically important effects in a number of patients.
- Moderate:** Documented pharmacokinetic interaction with minor clinical effects, or isolated reports of clinically important effects.

**Table. Clinically significant drug interactions with cigarette smoking.**

Drug name	Nature of interaction	Clinical relevance	Action
Aminophylline Theophylline	Aminophylline is a stable mixture of theophylline and ethylenediamine [3]. Theophylline and aminophylline are metabolised principally via CYP1A2, therefore clearance is increased in smokers [4].  Heavy smokers (20-40 cigarettes per day) may need much higher doses than non-smokers, due to the shortened theophylline half-life and increased elimination rate [3,4].	<b>High</b>	When stopping smoking, a reduction in theophylline dose of up to 25-33% might be needed after one week. However, it may take several weeks for enzyme induction to dissipate [4].  Monitor plasma theophylline concentrations and adjust theophylline dose accordingly [3].  Advise the patient to seek help if they develop signs of theophylline toxicity such as vomiting, diarrhoea, palpitations, nausea or vomiting [3].

Drug name	Nature of interaction	Clinical relevance	Action
Clozapine	<p>Clozapine is metabolised principally via CYP1A2 therefore clearance is increased in smokers [5].</p> <p>Smoking reduces plasma levels of clozapine by up to 50% so smokers may need higher doses [6]. Likewise, patients who stop smoking may experience a 50% increase in plasma level so will need dose reduction [6]. There have been case reports of adverse effects in patients taking clozapine when they have stopped smoking [6]</p>	<b>High</b>	<p>Blood levels of clozapine should be measured before stopping or re-starting smoking [2].</p> <p>On stopping smoking, reduce dose gradually over a week until around 75% of original dose reached (i.e. reduce by 25%). Repeat plasma level one week after stopping smoking. Anticipate further dose reductions [2].</p> <p>If re-starting smoking take a plasma level before re-starting. Increase dose to previous smoking dose over one week. Repeat plasma level [2].</p>
Olanzapine	<p>Olanzapine is metabolised principally via CYP1A2 and clearance is increased in smokers [7,8]. Serum olanzapine levels are reduced in smokers compared with non-smokers; smokers may need higher doses [7,8].</p> <p>An increase in smoking has been shown to affect olanzapine concentration and efficacy in some patients [8]. There have also been case reports of adverse effects in patients taking olanzapine when they have stopped smoking [8].</p>	<b>High</b>	<p>On stopping smoking, reduce dose by 25%. Consider further dose reductions [2].</p> <p>Be alert for increased adverse effects of olanzapine such as dizziness, sedation, and hypotension. If adverse effects occur, reduce the dose as necessary [7].</p>
Erlotinib	<p>Erlotinib is metabolised primarily by CYP3A4 and to a lesser extent CYP1A2 [9].</p> <p>Smokers have an increased rate of erlotinib clearance leading to decreased drug exposure [9]. Smokers gain less benefit than non-smokers in clinical studies [10].</p>	<b>High</b>	<p>Current smokers should be advised to stop smoking prior to starting treatment [9].</p> <p>When given to patients who smoke, increase the daily dose in 50mg increments at 2-week intervals, up to a maximum dose of 300mg. If the patient stops smoking the dose should be immediately reduced to the initial starting dose [11].</p>
Riociguat	<p>Riociguat is metabolised by CYP1A1, CYP3A4, CYP3A5 and CYP2J2 [12].</p> <p>In cigarette smoking, riociguat exposure is reduced by 50-60% [12].</p>	<b>High</b>	<p>Current smokers should be advised to stop smoking prior to starting treatment [12].</p> <p>A dose increase to the maximum of 2.5mg three times a day may be needed in patients who are smoking or start smoking during treatment [12].</p> <p>If the patient stops smoking during treatment the dose may need to be reduced [12].</p>

Drug name	Nature of interaction	Clinical relevance	Action
Warfarin	<p>Warfarin is partly metabolised via CYP1A2 [13,14].</p> <p>A systematic review and meta-analysis of 13 studies assessing the interaction between smoking and warfarin reported that smoking may potentially increase warfarin clearance, leading to reduced warfarin effects [15].</p>	<b>Moderate</b>	<p>Monitor smoking status during warfarin therapy [14,15]. If a patient taking warfarin changes their smoking status this may increase their INR. In such cases, monitor INR more closely and adjust dose as needed [14].</p> <p>Advise patients to tell the healthcare professional managing their anticoagulant control that they are changing their smoking status [13].</p>
Chlorpromazine	<p>Chlorpromazine is extensively metabolised in the liver [16]. Smokers have lower serum levels of chlorpromazine compared with non-smokers [2].</p> <p>A comparative study found frequency of drowsiness in 403 patients taking chlorpromazine was 16% in non-smokers, 11% in light smokers, and 3% in heavy smokers (&gt;20 cigarettes daily). Another report describes a patient taking chlorpromazine who experienced increased sedation and dizziness and higher plasma chlorpromazine levels when he gave up smoking [17].</p>	<b>Moderate</b>	<p>Monitor patient closely if they plan to abruptly stop smoking and consider a dose reduction [2].</p> <p>Advise patients who smoke or who start to smoke to be alert for increased adverse effects of chlorpromazine (e.g. dizziness, sedation, nausea). If adverse effects occur, reduce the dose as necessary [2,17].</p>
Methadone	<p>Methadone is extensively metabolised in the liver by CYP isoenzymes including CYP1A2 [18,19].</p> <p>There has been a case report of respiratory insufficiency and altered mental status when a patient taking methadone for analgesia stopped smoking [19].</p>	<b>Moderate</b>	<p>Monitor patient closely if they plan to abruptly stop smoking.</p> <p>Advise patients who plan to abruptly stop smoking to be alert for signs of opioid toxicity. Reduce methadone dose accordingly [19].</p>

## Summary

- Most interactions between drugs and smoking are not clinically significant.
- Healthcare professionals giving smoking cessation advice should be aware of a small number of medicines, in particular aminophylline, theophylline, clozapine, olanzapine, erlotinib and riociguat, which may require dose adjustment or increased monitoring when smoking status is altered.
- Patients taking narrow-therapeutic-index drugs should be monitored closely when any lifestyle modification is made.

## Limitations

- This Q&A does not include drugs which have a low risk, theoretical interaction without documented cases and/or drugs metabolised partly by CYP1A2 and with a wide therapeutic range.
- It does not consider interactions with pharmacological agents used for smoking cessation (e.g. bupropion, varenicline), or pharmacodynamics interactions (e.g. effects of smoking on blood pressure). It does not include potential interactions of e-cigarettes.

## References

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## Quality Assurance

### Prepared by

Hannah Al-Jaffar. North West Medicines Information Centre, 70 Pembroke Place, Liverpool, L69 3GF

### Date Prepared

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### Checked by

Dr Leanne Bloxam and Joanne McEntee.

North West Medicines Information Centre, 70 Pembroke Place, Liverpool, L69 3GF

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### Search strategy

1. Embase [Smoking and Drug-Interaction DT2012-2017] on 13/10/2017
2. Medline [Smoking and Drug-Interactions DT2012-2017] on 13/10/2017
3. In-house databases/resources

Available through Specialist Pharmacy Service at [www.sps.nhs.uk](http://www.sps.nhs.uk)

