What are the clinically significant drug interactions with tobacco smoking?

There are multiple constituents to tobacco smoke that may have the potential to induce hepatic cytochrome P450 (CYP) isoenzymes and other metabolic processes (1,2).
Polycyclic aromatic hydrocarbons (PAHs) are a product of incomplete tobacco combustion and an inducer of hepatic enzymes as well being one of the major lung carcinogens found in tobacco smoke (1,2).
Other compounds such as acetone, pyridine, heavy metals, benzene and carbon monoxide may also interact with hepatic enzymes, but their effects appear to be less significant (1).

At present there are data that suggest PAHs induce CYP1A1, 1A2, 1B1, 2B6 and 2E1 as well as uridine diphosphate (UGT)-related metabolism (1-3).
Tobacco smoke also appears to inhibit CYP2A6 (2).
Of the tobacco-induced isoenzymes, CYP1A2 is the most clinically significant as many drugs are substrates for CYP1A2 (1,4).

This document summarises those drug interactions with tobacco smoking that are considered to be most clinically important.

Most interactions between drugs and tobacco smoking are not clinically significant.

If a patient starts to smoke and is taking a drug which is a substrate for an induced enzyme then increased metabolism can lead to a clinically significant reduction in pharmacologic effect and the dose may need to be increased (1,4).
Conversely, if a patient stops smoking then dose reduction needs to be considered due to downregulation of the enzyme-reducing drug metabolism which could lead to an increase in toxicity (1,4).

Even if the degree of induction is weak it can still produce clinically significant events for drugs with a narrow therapeutic index (4).
Any dose adjustments need to be individually tailored. Patients can have different distributions of CYP enzymes, and the amount and type of tobacco smoked along with the degree of smoke inhalation can all vary the degree of enzyme induction (4,5).
Close monitoring of plasma levels (where useful), clinical progress and adverse effect occurrence and severity is essential (4).
Patients taking narrow-therapeutic-index drugs should be monitored closely when any lifestyle modification is made.

Drug interactions with tobacco 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.
If the affected drug is prescribed under the supervision of a specialist, their input should be sought if the patient changes their smoking status.
Since most interactions are due to components of tobacco smoke and not due to nicotine, these interactions are not expected to occur with nicotine replacement therapy or e-cigarettes (vapes).

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.

Clinically significant drug interactions with tobacco smoking.

Drug name	Nature of interaction	Clinical relevance	Action
Aminophylline Theophylline	Theophylline and aminophylline are metabolised in the liver by CYP1A2, 2E1 and 3A3 (6,7). Smoking can increase clearance of theophylline and aminophylline (6-8). Heavy smokers (20-40 cigarettes per day) may need much higher doses of than non-smokers (7). Full normalisation of hepatic function appears to take many months or even years after stopping aminophylline or theophylline (7).	**High** (narrow therapeutic index drug)	When stopping smoking, a reduction in theophylline dose of up to 25-33% might be needed after one week (7). If a patient starts to smoke, their dose may need to be increased as smokers often need higher maintenance doses (6).
Clozapine	Clozapine is almost completely metabolised before excretion by CYP1A2 and 3A4, and to some extent by 2C19 and 2D6 (6,9). Smokers may need higher doses due to increased clearance of clozapine (7,9). There have been case reports of adverse effects in patients who abruptly stopped smoking (6,7,9).	**High**	Take clozapine plasma level before stopping smoking. On stopping, reduce dose gradually (over 1 week) until around 75% of original dose reached (i.e. reduce by 25%). Repeat plasma level 1 week after stopping. Anticipate further dose reductions (4). If a patient has stopped smoking and intends to re-start, take their clozapine plasma level before they do so. Increase dose to previous smoking dose over 1 week. Repeat plasma level (4). If a patient starts smoking it has been suggested a 50% increase in clozapine dose should be anticipated (7).

Drug name	Nature of interaction	Clinical relevance	Action
Erlotinib	1 Erlotinib is metabolised primarily by CYP3A4 and to a lesser extent by A2 (6,10). Cigarette smoking has been shown to reduce erlotinib exposure by 50- 60% (10). Smokers gain less benefit than non-smokers from erlotinib in clinical studies (7).	**High**	Current smokers should be advised to stop smoking as early as possible before initiation of treatment (10). If the patient stops smoking the erlotinib dose should be immediately reduced to the indicated starting dose (6). When given to patients who smoke, increase the daily dose of erlotinib in 50mg increments at 2-week intervals up to a maximum
Olanzapine	Olanzapine is metabolised by glucuronidation and CYP1A2, both of which are induced by smoking, leading to increased clearance of olanzapine (6,7,11). To a lesser extent olanzapine is also metabolised by CYP2D6 (6). Smokers have lower olanzapine serum levels and require higher daily doses compared to non-smokers (7). There are case reports of extrapyramidal symptoms developing when a patient stops smoking (7).	**High**	On stopping smoking reduce dose by 25% (4). Closely monitor patient and consider further dose reductions if necessary, according to patient response (4,7). If restarting smoking, increase dose to previous smoking dose over 1 week (4). Monitor the patient closely making further dose adjustments as needed, dependent upon patient response (4,7,11). If a patient starts smoking monitor them closely and increase dose if required, adjusted to patient response (7,11). If olanzapine plasma level monitoring is available, it may help to take levels before stopping/starting smoking and repeat them one week after the dose change (4).
Riociguat	Riociguat is mainly metabolised by CYP1A1, 2C8, 2J2, 3A4 and 3A5 (6,12). Plasma concentrations of riociguat are reduced by 50-60% in smokers compared to non-smokers (6,12).	**High**	Current smokers should be advised to stop smoking (7,12). A dose decrease may be required in patients who stop smoking (6,7,12). A dose increase to the maximum daily dose of 2.5mg three times daily may be required in patients who are smoking or start smoking during treatment (6,7,12).
Chlorpromazine	Chlorpromazine is extensively metabolised in the liver (13). Studies indicate clearance of chlorpromazine may be increased in patients who smoke (6). A comparative study found smokers	**Moderate**	When stopping smoking, monitor patient closely and consider dose reduction (4,7). If re-starting smoking, monitor patient closely and consider re-starting previous smoking dose

Drug name	Nature of interaction	Clinical relevance	Action
Chlorpromazine	Chlorpromazine is extensively metabolised in the liver (13). Studies indicate clearance of chlorpromazine may be increased in patients who smoke (6). A comparative study found smokers experienced a lower frequency of drowsiness than non-smokers (7). A case report describes a patient experiencing increased sedation and dizziness when they gave up smoking (7).		When stopping smoking, monitor patient closely and consider dose reduction (4,7). If re-starting smoking, monitor patient closely and consider re-starting previous smoking dose (4,7).
Flecainide	*In vitro* studies have shown CYP1A2 to be involved in the metabolism of flecainide (7). CYP2D6 also appears to be involved (6,14). The clearance of flecainide was found to be 50% higher in smokers than in non-smokers (7). Smokers are likely to require larger doses of flecainide than non-smokers to achieve the same therapeutic effects (7).	**Moderate**	If a patient abruptly stops smoking be alert for flecainide adverse effects and be aware that it is likely that the dose of flecainide will need to be reduced (7).
Methadone	Methadone is metabolised in the liver by numerous enzymes including CYP1A2, 2B6 and 3A4 (6,7,15,16). One case report of respiratory insufficiency and altered mental status was reported in a patient taking methadone as an analgesic who stopped smoking (7).	**Moderate**	If a patient, who takes methadone, stops smoking they should be monitored for signs of methadone toxicity. The dose of methadone should be adjusted accordingly (16).
Warfarin	Warfarin is partly metabolised by CYP1A2 and 2C9 (6,7). A systematic review and meta-analysis concluded that smoking can increase warfarin clearance, leading to reduced warfarin effects and smokers requiring slightly higher doses (6).	**Moderate** (narrow therapeutic index drug)	Monitoring of smoking status during warfarin therapy is advised (6,17). Routine INR monitoring should detect any need for dose adjustments (7). Be alert for the need to alter warfarin doses in patients who have changed their smoking status (7,17,18).

Summary

- Most interactions between drugs and tobacco smoking are not clinically significant.
- When giving smoking cessation advice, be aware of a small number of drugs, in particular aminophylline, theophylline, clozapine, erlotinib, olanzapine and riociguat, which may require dose adjustment or increased monitoring when smoking status is altered.
- Close monitoring of plasma levels (where useful), clinical progress and adverse effect occurrence and severity is essential when patients change their smoking status.
- Patients taking narrow-therapeutic-index drugs should be monitored closely when any lifestyle modification is made.
- **If the affected drug is prescribed under the supervision of a specialist, their input should be sought if the patient changes their smoking status.**

Limitations

- This Q&A does not include drugs which have a low risk, theoretical interaction without documented cases and/or drugs metabolised partly by induced CYP enzymes 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 nicotine replacement therapy, using e-cigarettes (vapes) or chewing tobacco.

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