Drug InterACTIONs with Tobacco Smoke

The polycyclic aromatic hydrocarbons (PAHs) found in tobacco smoke induce liver enzymes responsible for the metabolism of drugs (1A2, 2B6, 2E1) resulting in pharmacokinetic (PK) drug interactions. These PK drug interactions are not attributable to nicotine. Pharmacodynamic (PD) drug interactions with the components of tobacco smoke, including nicotine, may also occur.

When supporting quit attempts, it is important to be familiar with the drugs which are affected by tobacco smoke and may require dose adjustment or increased monitoring when smoking status changes. Narrow therapeutic index drugs should be monitored closely.[1,2,3]

Non-Oncology Drugs	Effect of smoking	Change with Smoking Cessation	Clinical Significance	Action
Benzodiazepines[1,2,3,4,9] (e.g., alprazolam, diazepam, clonazepam)	**PK:** Possible increased metabolism may result in lower serum levels of benzodiazepines. **PD:** Stimulation from nicotine may reduce sedative effects of benzodiazepines.	Potential increase in benzodiazepine levels with smoking cessation. Possible increase in sedation due to loss of CNS stimulation with nicotine.	Low to Moderate	Monitor for adverse effects (e.g., excessive sedation and drowsiness). May require dosage reductions if clinically indicated.
Betablockers[1,2,3,4]	**PK:** Propranolol clearance may be increased by smoking, which may lower serum levels. **PD:** Smoking may reduce the effects of beta-blockers on blood pressure and heart rate.	Potential increase in propranolol levels with smoking cessation. The loss of nicotine effect on blood pressure and heart rate may enhance the effects of betablockers.	Low	Monitor for adverse effects (e.g. bradycardia and hypotension). May require dosage reductions if clinically indicated.
Caffeine[1,3,9]	**PK:** Smoking increases the clearance of caffeine by more than 50%.	Potential increase in caffeine levels with smoking cessation.	Moderate to High	Advise patients to reduce caffeine consumption prior to a quit attempt (e.g., reduce by 50%) to lower the risk of caffeine related adverse effects. Monitor for signs of caffeine toxicity (e.g., tremor, nausea, dizziness, agitation, irritability).
First generation antipsychotics (i.e., chlorpromazine, fluphenazine, haloperidol)[1,2,3,4,9]	**PK:** Smoking can reduce antipsychotic serum levels.	Potential increase in antipsychotic levels with smoking cessation.	Low to Moderate	Monitor patients closely for adverse effects (e.g., hypotension, sedation, dizziness, nausea, extra-pyramidal symptoms) particularly with abrupt cessation. May require dosage reductions if clinically indicated (e.g., reduce dose by 25%).
Clopidogrel[1,2,3,4]	**PK:** Smoking-related enzyme induction may increase the metabolism of clopidogrel to its active metabolite. The effect of clopidogrel is enhanced in individuals who smoke 10 or more ciagrettes per day.	Effect of clopidogrel may be diminished by smoking cessation.	Low to high	The clinical relevance of this interaction is variable. Tobacco cessation should still be recommended in at-risk populations needing clopidogrel. Specialist advice is recommended for any dosage adjustments.
Clozapine[1,2,3,4,5]	**PK:** Smoking can increase metabolism and reduce serum levels of clozapine.	Potential increase in clozapine levels with smoking cessation.	High	Any change in smoking status may require dose adjustment. With smoking reduction or cessation, closely monitor drug levels and monitor for subjective symptoms of toxicity (e.g., drowsiness, confusion, rapid heart rate). Specialist consultation is recommended for dosage reductions to avoid toxicity. An average 50% dosage reduction may be needed.
Duloxetine[2,3,5]	**PK:** Smoking may lower plasma levels of duloxetine.	Potential increase in duloxetine levels with smoking cessation.	Low	Monitor for possible increase in adverse effects (e.g., nausea, vomiting, dizziness, and tachycardia). May require dosage reductions if clinically appropriate.
Flecainide[1,2,4,10]	**PK:** Smoking increases clearance and reduces plasma levels of flecainide.	Potential increase in flecainide levels with smoking cessation.	Low to Moderate	Monitor for adverse effects (e.g., dizziness and visual disturbances). May require dosage reductions if clinically indicated.
Fluvoxamine[1,2,3,5,9,10]	**PK:** Smoking may lower plasma levels of fluvoxamine.	Potential increase in fluvoxamine levels with smoking cessation.	Low to Moderate	Monitor for adverse effects (e.g., dizziness, drowsiness, nausea, tremor, nystagmus). May require dosage reductions if clinically indicated.
Heparin[1,2,3,4,9]	**PK and PD:** The mechanism of interaction is unclear, but individuals who smoke may require increased dosages of heparin due to PK and PD effects.	Prothrombin time may increase with smoking cessation which can increase the risk of bleeding.	Low to Moderate	Close monitoring is required along with potential dosage adjustment according to prothrombin time (e.g., monitor for unexplained heavy bleeding, easy bruising, blood spots under the skin).
Insulin, subcutaneous[1,3,4]	**Possibly PK and PD:** Individuals who smoke may have increased insulin resistance and decreased insulin absorption due to vasoconstriction. Higher insulin dosages may be required in individuals who smoke.	Insulin resistance may decrease with smoking cessation which may result in hypoglycemia.	Moderate	More frequent blood glucose monitoring is recommended, particularly for patients prone to hypoglycemia. Advise the patient to monitor for symptoms of hypoglycemia (e.g., shakiness, sweating, headache, hunger or nausea, fatigue, irritability or anxiety). May require dosage reductions if clinically indicated.
Melatonin[2,6]	**PK:** Smoking may reduce plasma levels of melatonin.	Potential increase in melatonin levels with smoking cessation.	Moderate	Monitor for adverse effects (e.g., excessive sedation, dizziness, headache). May require dosage reductions if clinically indicated.
Methadone[1,2,3,4,7]	**Likely PK and PD:** Smoking may increase methadone metabolism (PK); nicotine affects the endogenous opioid system (PD).	Potential increase in methadone levels and sedative effect.	Moderate	Monitor for signs of methadone toxicity (e.g., sedation and respiratory depression) particularly with abrupt cessation and reduce the dose accordingly. May require dosage reductions if clinically indicated.
Mexiletine[1,2]	**PK:** Smoking may increase clearance and decrease plasma levels of mexiletine.	Potential increase in mexiletine levels with smoking cessation.	Low to Moderate	Monitor for adverse effects (e.g., nausea, tremor, hypertension) May require dosage reductions if clinically indicated.

Non-Oncology Drugs	Effect of smoking	Change with Smoking Cessation	Clinical Significance	Action
Mirtazapine[3,5]	**PK:** Smoking reduces plasma levels of mirtazapine.	Potential increase in mirtazapine levels with smoking cessation.	Low	Monitor for adverse effects (e.g., sedation). May require dosage reductions if clinically indicated.
Olanzapine[1,2,3,4,5,7]	**PK:** Smoking increases clearance and reduces plasma levels of olanzapine.	Potential increase in olanzapine levels with smoking cessation.	Moderate to High	Monitor for adverse effects (e.g., dizziness, sedation, hypotension).
Pirfenidone[1,2]	**PK:** Smoking increases metabolism of pirfenidone. Decreased exposure in individuals who smoke might alter efficacy profile.	Potential increase in pirfenidone levels with smoking cessation.	Moderate	Patients should be encouraged to stop smoking before and during treatment with pirfenidone. Specialist advice should be sought for dosage adjustment.
Riociguat[1,2]	**PK:** Smoking reduces plasma levels of riociguat significantly (50% to 60%).	Potential increase in riociguat levels with smoking cessation.	High	Monitor for adverse effects (e.g., dizziness, headache, nausea, diarrhea). May require dosage reductions if clinically indicated.
Ropinirole[1,2]	**PK:** Smoking may reduce plasma levels of ropinirole.	Potential increase in ropinirole levels with smoking cessation.	Moderate	Monitor for adverse effects (e.g. nausea, dizziness). May require dosage reductions if clinically indicated.
Theophylline[1,2,3,4,7]	**PK:** Smoking increases metabolism and reduces plasma levels of theophylline.	Plasma levels of theophylline increase with smoking cessation.	High	Theophylline levels should be monitored if smoking is initiated, discontinued, or changed. Dosage adjustment required according to levels (e.g., 25% to 33% reduction over one week). Monitor for signs of toxicity (e.g., palpitations, nausea, vomiting).
Tricyclic Antidepressants (TCAs)[1,2,3,4,5] (e.g., amitriptyline, imipramine, nortriptyline)	**PK:** Smoking may reduce plasma levels of TCAs.	Potential increase in TCA levels with smoking cessation.	Low	Monitor for adverse effects (e.g. sedation, dry mouth). May require dosage reductions if clinically indicated (e.g., by 10% to 25% over one week).
Warfarin[1,2,3,4,7]	**PK:** Smoking may increase clearance and decrease the serum concentration of warfarin.	INR may increase with smoking cessation.	Moderate	Advise primary care provider or individual monitoring warfarin of the quit attempt. Monitor the INR more closely and monitor for signs of increased warfarin effect (e.g., bleeding). May require dosage reductions if clinically indicated.
Oncology Drugs	**Effect of smoking**	**Change with Smoking Cessation**	**Clinical Significance**	**Action**
Bendamustine[11,12,13]	**PK:** Cigarette smoking may affect the circulating levels of bendamustine and its active metabolites.	Theoretical change in concentration of both bendamustine and its active metabolite.	Unrated	Manufacturer recommends caution should be used in individuals who smoke or consider alternative treatments.
Erlotinib[1,2,3]	**PK:** Smoking increases clearance and reduces plasma levels of erlotinib.	Potential increase in erlotinib levels with smoking cessation.	High	Individuals who smoke should be strongly advised to quit smoking prior to initiation of treatment. Seek specialist advice. Dosage adjustment may be required.
Irinotecan[1,3]	**PK:** Systemic exposure and efficacy of irinotecan may be reduced with smoking.	Potential increase in irinotecan levels with smoking cessation.	High	Seek specialist advice. Dosing should be closely monitored.
Pomalidomide[2,8]	**PK:** Smoking may reduce pomalidomide exposure.	Potential increase in pomalidomide levels with smoking cessation; however, dosages are not usually adjusted in the presence of smoking.	Moderate	Advise patients that smoking may reduce the efficacy of pomalidomide. Smoking should be avoided while using pomalidomide if possible. Patients who smoke should be monitored for reduced effectiveness of pomalidomide.

*The ratings of clinical significance were taken from the cited sources, which varied in definition and severity. A range of ratings have been presented when there was disagreement across citations. The content of this document was current at the time of the review. It may not represent a comprehensive list of all potential drug interactions with tobacco smoke, however, given the volume of drug interactions. The most clinically significant interactions are provided here. For more information on any of the listed interactions or to search for other drug interactions, please refer to drug interactions checkers. Assessment and dosage adjustment must be individualized to the specific patient. Professional judgment must be used in applying the information contained in this document. This material is intended for personal, non-commercial use only provided that the content is not modified in any way. The content is intended for educational and informational purposes and to be used only with permission.

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