DRUG INTERACTIONS WITH TOBACCO SMOKE

Many interactions between tobacco smoke and medications have been identified. In most cases it is the tobacco smoke—not the nicotine—that causes these drug interactions. Tobacco smoke interacts with medications through pharmacokinetic (PK) and pharmacodynamic (PD) mechanisms. PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered response to those drugs. Most PK interactions with smoking result from induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). People who smoke may require higher doses of medications that are CYP1A2 substrates. Upon cessation, dose reductions might be required. PD interactions alter the expected response or actions of other drugs. The amount of tobacco smoking needed to have an effect has not been established, and the assumption is that a person with any level of smoking is susceptible to the same degree of interaction. **The most clinically significant interactions appear in the shaded rows. Commonly available brand names are shown in parentheses.**

DRUG/CLASS	MECHANISM OF INTERACTION AND EFFECTS
Pharmacokinetic Interactions	
Alprazolam (Xanax®)	▪ Conflicting data on significance, but possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Caffeine	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (56%). ▪ Caffeine levels likely ↑ after cessation; recommend reduction in caffeine upon cessation.
Cilostazol	▪ ↓ Plasma concentrations (by 20%).
Chlorpromazine (Thorazine®)	▪ ↓ AUC (36%);↓ plasma concentrations (by 24%). ▪ ↑ Levels upon cessation have been reported causing sedation and hypotension.
Clopidogrel (Plavix®)	▪ ↑ Metabolism (induction of CYP1A2) of clopidogrel to its active metabolite. ▪ Clopidogrel's effects may be enhanced in smokers (≥10 cigarettes/day); may be dependent on CYP1A2 genotype; might also ↑ risk of bleeding. ▪ Smoking cessation should still be recommended in the at-risk populations needing clopidogrel.
Clozapine (Clozaril®)	▪ ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (by 18%). ▪ ↑ Levels upon cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.
Duloxetine (Cymbalta®)	▪ ↓ AUC (33%) ▪ Dosage modifications not routinely recommended.
Erlotinib (Tarceva®)	▪ ↑ Clearance (24%); ↓ trough plasma concentrations (2-fold).
Flecainide	▪ ↑ Clearance (61%); ↓ trough plasma concentrations (by 25%). ▪ Smokers may need ↑ dosages.
Fluvoxamine	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ Cmax (32%) and Css (39%). ▪ Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Haloperidol (Haldol®)	▪ ↑ Clearance (44%); ↓ plasma concentrations (by 70%); data are inconsistent therefore clinical significance is unclear.
Insulin, subcutaneous	▪ Possible ↓ insulin absorption secondary to peripheral vasoconstriction. ▪ Smoking is reported to cause insulin resistance. ▪ PK & PD interactions likely not clinically significant, but smokers may need ↑ dosages.
Irinotecan (Camptosar®)	▪ ↑ Clearance (18%); ↓ AUC of active metabolite, SN-38, by 40% via induction of glucuronidation; ↓ systemic exposure resulting in lower hematologic toxicity and may reduce efficacy. ▪ Smokers may need ↑ dosages.
Methadone	▪ ↑ Metabolism (induction of CYP1A2 [minor pathway for methadone]). ▪ ↑ Levels upon cessation have been reported causing sedation, confusion and labored breathing which required dosage reduction. Carefully monitor response upon cessation.
Mexiletine	▪ ↑ Clearance (25%); ↓ half-life (36%).
Nintedanib (OFEV®)	▪ Decreased exposure (21%) in smokers which may affect efficacy. ▪ No dose adjustment recommended; however, avoid smoking during treatment.
Olanzapine (Zyprexa®)	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (40%); ↓ plasma concentrations (by 12%). ▪ Smokers may need ↑ dosages.

Pharmacokinetic Interactions (continued)	
DRUG/CLASS	**MECHANISM OF INTERACTION AND EFFECTS**
Pirfenidone (Esbriet®)	▪ ↑ Metabolism (induction of CYP1A2); ↓ AUC (54%) and ↓ Cmax (32%) compared to nonsmokers. ▪ Decreased exposure in smokers may decrease efficacy.
Pomalidomide (Pomalyst®)	▪ ↓ AUC 32% compared to nonsmokers.
Propranolol (Inderal®)	▪ ↑ Clearance (77%).
Riluzole (Rilutek®)	▪ ↑ Elimination (20%) ▪ Dosage modifications not routinely recommended.
Riociguat (Adempas®)	▪ ↓ Plasma concentrations (by 50–60%). ▪ Smokers may require dosages higher than 2.5 mg three times daily; consider dose reduction upon cessation.
Ropinirole	▪ ↓ Cmax (30%) and ↓ AUC (38%) in study with patients with restless legs syndrome. ▪ Smokers may need ↑ dosages.
Tasimelteon (Hetlioz®)	▪ ↑ Metabolism (induction of CYP1A2); ↓ drug exposure (40%). ▪ Smokers may need ↑ dosages.
Theophylline	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (58–100%); ↓ half-life (63%). ▪ Monitor levels if smoking is initiated, discontinued, or changed. Maintenance doses are higher in smokers; ↑ clearance with second-hand smoke exposure.
Tizanidine (Zanaflex®)	▪ ↓ AUC (30–40%) and ↓ half-life (10%) observed in male smokers.
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	▪ Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical significance is not established.
Warfarin	▪ ↑ Metabolism (induction of CYP1A2) of R-enantiomer; however, S-enantiomer is more potent and effect on INR is inconclusive. ▪ Shown to impact INR. Consider monitoring INR upon smoking cessation.
Pharmacodynamic Interactions	
Benzodiazepines (diazepam, chlordiazepoxide)	▪ ↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.
Beta-blockers	▪ Less effective blood pressure and heart rate control effects, possibly caused by nicotine-mediated sympathetic activation. ▪ Smokers may need ↑ dosages.
Corticosteroids, inhaled	▪ Smokers with asthma may have less of a response to inhaled corticosteroids.
Hormonal contraceptives (combined)	▪ ↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use combined hormonal contraceptives. Ortho Evra® patch users shown to have 2-fold ↑risk of venous thromboembolism compared to oral contraceptive users, likely due to ↑ estrogen exposure (60% higher levels). ▪ ↑ Risk with age and with heavy smoking (≥ 15 cigarettes per day) and is quite marked in women ≥ 35 years old.
Serotonin 5-HT_1 receptor agonists (triptans)	▪ This class of drugs may cause coronary vasospasm; caution for use in smokers due to possible unrecognized coronary artery disease.

Adapted and updated, from:

Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet* 1999;36:425–38.

Kroon LA. Drug interactions with smoking. *Am J Health-Syst Pharm* 2007;64:1917-21.

Li H, Shi Q. Drugs and diseases interacting with cigarette smoking in US prescription drug labelling. *Clin Pharmacokinet* 2015;54: 493–501.

Information from individual drug package inserts is also used.

Abbreviations: AUC, area under the plasma concentration-time curve; Cmax, maximum plasma concentration; Css, steady-state plasma drug concentration; CYP, cytochrome P450; INR, international normalized ratio.