DRUG INTERACTIONS WITH SMOKING

Many interactions between tobacco smoke and medications have been identified. Note that in most cases it is the tobacco smoke—not the nicotine—that causes these drug interactions. Tobacco smoke may interact with medications through pharmacokinetic (PK) or pharmacodynamic (PD) mechanisms. PK interactions affect the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. The majority of PK interactions with smoking are the result of induction of hepatic cytochrome P450 enzymes (primarily CYP1A2). 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 any smoker is susceptible to the same degree of interaction. The most clinically significant interactions are depicted in the shaded rows.

DRUG/CLASS	MECHANISM OF INTERACTION AND EFFECTS
Pharmacokinetic Interactions	
Alprazolam (Xanax)	▪ Conflicting data on significance of a PK interaction. Possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Caffeine	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (56%). ▪ Likely ↑ caffeine levels after cessation.
Chlorpromazine (Thorazine)	▪ ↓ Area under the curve (AUC) (36%) and serum concentrations (24%). ▪ ↓ Sedation and hypotension possible in smokers; smokers may need ↑ dosages.
Clozapine (Clozaril)	▪ ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (18%).
Flecainide (Tambocor)	▪ ↑ Clearance (61%); ↓ trough serum concentrations (25%). ▪ Smokers may need ↑ dosages.
Fluvoxamine (Luvox)	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ plasma concentrations (32%). ▪ Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Haloperidol (Haldol)	▪ ↑ Clearance (44%); ↓ serum concentrations (70%).
Heparin	▪ Mechanism unknown but ↑ clearance and ↓ half-life are observed. Smoking has prothrombotic effects. ▪ Smokers may need ↑ dosages due to PK and PD interactions.
Insulin, subcutaneous	▪ Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance. ▪ PK & PD interactions likely not clinically significant; smokers may need ↑ dosages.
Insulin, inhaled (Exubera)	▪ Systemic exposure is greatly increased in smokers; greater maximal insulin concentrations (3–5 fold) and faster (by 20-30 minutes) ; ↑AUC 2–3 fold ▪ Contraindicated in smokers and those who have discontinued smoking for less than 6 months.
Mexiletine (Mexitil)	▪ ↑ Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%).
Olanzapine (Zyprexa)	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (98%); ↓ serum concentrations (12%). ▪ Dosage modifications not routinely recommended but smokers may require ↑ dosages.
Propranolol (Inderal)	▪ ↑ Clearance (77%; via side chain oxidation and glucuronidation)
Tacrine (Cognex)	▪ ↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations three-fold lower. ▪ Smokers may need ↑ dosages.
Theophylline (Theo Dur, etc.)	▪ ↑ Metabolism (induction of CYP1A2); ↑ clearance (58–100%); ↓ half-life (63%). ▪ Levels should be monitored if smoking is initiated, discontinued, or changed. ▪ ↑ Clearance with second-hand smoke exposure. ▪ Maintenance doses are considerably higher in smokers.
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	▪ Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical importance is not established.
Pharmacodynamic Interactions	
Benzodiazepines (diazepam, chlordiazepoxide)	▪ ↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.
Beta-blockers	▪ Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation. ▪ Smokers may need ↑ dosages.
Corticosteroids, inhaled	▪ Asthmatic smokers may have less of a response to inhaled corticosteroids.
Hormonal contraceptives	▪ ↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral contraceptives. ▪ ↑ Risk with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women age 35 and older.
Opioids (propoxyphene, pentazocine)	▪ ↓ Analgesic effect; smoking may ↑ the metabolism of propoxyphene (15–20%) and pentazocine (40%). Mechanism unknown. ▪ Smokers may need ↑ opioid dosages for pain relief.

Adapted from Zevin S, Benowitz NL. Drug interactions with tobacco smoking. *Clin Pharmacokinet* 1999;36:425–438.