DRUG INTERACTIONS WITH TOBACCO SMOKE

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 interacts with medications by influencing the absorption, distribution, metabolism, or elimination of other drugs, potentially causing an altered pharmacologic response. Because of these interactions, smokers may require higher doses of medications. Upon cessation, dose reductions might be needed.

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, but possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Bendamustine (Treanda)	• Metabolized by CYP1A2. Manufacturer recommends using with caution in smokers due to likely ↓ bendamustine concentrations, with ↑ concentrations of its two active metabolites.
Caffeine	• Metabolism (induction of CYP1A2); ↑ clearance (56%). Caffeine levels likely ↑ after cessation.
Chlorpromazine (Thorazine)	• ↓ Area under the curve (AUC) (36%) and serum concentrations (24%). • ↓ Sedation and hypotension possible in smokers; smokers may require ↑ dosages.
Clopidogrel (Plavix)	• ↑ Metabolism (induction of CYP1A2) of clopidogrel to its active metabolite. • Clopidogrel's effects are enhanced in smokers (≥10 cigarettes/day): significant ↑ platelet inhibition, ↓ platelet aggregation; improved clinical outcomes have been shown (smokers' paradox; may be dependent on CYP1A2 genotype); tobacco cessation should still be recommended in at-risk populations needing clopidogrel.
Clozapine (Clozaril)	• ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (18%). • ↑ Levels upon cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.
Erlotinib (Tarceva)	• ↑ Clearance (24%); ↓ trough serum concentrations (2-fold).
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.
Irinotecan (Camptosar)	• ↑ Clearance (18%); ↓ serum concentrations of active metabolite, SN-38 (~40%; via induction of glucuronidation); ↓ systemic exposure resulting in lower hematologic toxicity and may reduce efficacy. • Smokers may need ↑ dosages.
Mexiletine (Mexitil)	• ↑ Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%).
Nintedanib (OFEV®)	• Decreased exposure (21%) in smokers. • No dose adjustment recommended; however, patients should not smoke during use.

Pharmacokinetic Interactions, continued	
Olanzapine (Zyprexa)	• ↑ Metabolism (induction of CYP1A2); ↑ clearance (98%); ↓ serum concentrations (12%). • Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Pirfenidone (Esbriet®)	• ↑ Metabolism (induction of CYP1A2); ↓ AUC (46%) and ↓ Cmax (68%). • Decreased exposure in smokers might alter efficacy profile.
Propranolol (Inderal)	• ↑ Clearance (77%; via side-chain oxidation and glucuronidation).
Ropinirole (Requip)	• ↓ Cmax (30%) and AUC (38%) in study with patients with restless legs syndrome. • Smokers may need ↑ dosages.
Tacrine (Cognex)	• ↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations 3-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. Maintenance doses are considerably higher in smokers. • ↑ Clearance with second-hand smoke exposure.
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	• Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical significance is not established.
Tizanidine (Zanaflex)	• ↓ AUC (30–40%) and ↓ half-life (10%) observed in male smokers.
Warfarin	• ↑ Metabolism (induction of CYP1A2) of R-enantiomer; however, S-enantiomer is more potent and effect on INR is inconclusive. 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 antihypertensive 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	• ↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral 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.
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.

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AMERICAN ACADEMY OF FAMILY PHYSICIANS
Rx for Change
Smoking Cessation Leadership Center
UCSF
University of California San Francisco