DRUG INTERACTIONS with TOBACCO SMOKE

PHARMACOKINETIC DRUG INTERACTIONS with TOBACCO SMOKE

Drugs that may have a *decreased effect* due to induction of CYP1A2:

- Caffeine
- Clozapine
- Erlotinib
- Fluvoxamine
- Irinotecan*
- Haloperidol
- Olanzapine
- Pirfenidone
- Pomalidomide
- Riociguat
- Ropinirole
- Tasimelteon
- Theophylline

*induction of glucuronidation

Smoking cessation will reverse these effects.

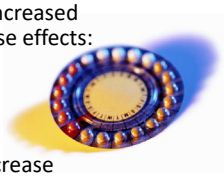
DRUG INTERACTION: TOBACCO SMOKE and CAFFEINE

- Constituents in tobacco smoke induce CYP1A2 enzymes, which metabolize caffeine
  - Caffeine levels increase ~56% upon quitting
- Challenges:
  - Nicotine withdrawal effects might be enhanced by increased caffeine levels
  - Insomnia can be due to ↑ caffeine levels or a side effect of a smoking cessation drug (e.g., varenicline or bupropion)
- Decrease caffeine intake (e.g., roughly half) when quitting
- For individuals with a typical bedtime, suggest eliminating caffeine by early afternoon

PHARMACODYNAMIC DRUG INTERACTIONS with TOBACCO SMOKE

Individuals who smoke and use combined hormonal contraceptives have an increased risk of serious cardiovascular adverse effects:

- Stroke
- Myocardial infarction
- Thromboembolism



This interaction **does not** decrease the efficacy of hormonal contraceptives.

Women who are 35 years of age or older AND smoke at least 15 cigarettes per day are at significantly elevated risk.

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.

The shaded rows indicate clinically significant drug interactions.

DRUG INTERACTIONS with TOBACCO SMOKE: SUMMARY

Clinicians should be aware of their patients' smoking status:

- Clinically significant interactions result the combustion products of tobacco smoke, not from nicotine.
- Constituents in tobacco smoke (e.g., polycyclic aromatic hydrocarbons; PAHs) may enhance the metabolism of other drugs, resulting in an altered pharmacologic response.
- Changes in smoking status might alter the clinical response to the treatment of a wide variety of conditions.
- Drug interactions with smoking should be considered when patients start smoking, quit smoking, or markedly alter their levels of smoking.