

Drug interactions with smoking

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Tobacco smoke consists of two phases: the vapor (or gaseous) and particulate phases. Of the estimated 4800 compounds in tobacco smoke, the majority are found in the particulate phase.¹ Nicotine, a natural substance found in tobacco leaves, is the major component of the particulate phase.² Nicotine comprises 1.5% of the total weight of a commercial cigarette and is the primary alkaloid found in tobacco. The carcinogens are found in tar, which is the particulate matter minus nicotine and water.³ Of the 69 carcinogens identified in tobacco smoke, 11 are known human carcinogens and 7 are probably carcinogenic in humans.¹

Numerous drug interactions have been identified with tobacco smoke. Therefore, clinicians should routinely ask their patients if they are current smokers. Patients who smoke or have recently quit should be screened for potential drug interactions with smoking. One of the quality performance measures of the Joint Commission is the provision of smoking-cessation counseling to adult patients with heart failure, myocardial infarction, or pneumonia. Therefore, information regarding a patient's smoking habits may be more readily available in institutional settings.

Purpose. The mechanisms for drug interactions with smoking and clinically significant pharmacokinetic and pharmacodynamic drug interactions with smoking are reviewed.

Summary. Polycyclic aromatic hydrocarbons (PAHs) are some of the major lung carcinogens found in tobacco smoke. PAHs are potent inducers of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and, possibly, 2E1. After a person quits smoking, an important consideration is how quickly the induction of CYP1A2 dissipates. The primary pharmacokinetic interactions with smoking occur with drugs that are CYP1A2 substrates, such as caffeine, clozapine, fluvoxamine, olanzapine, tacrine, and theophylline. Inhaled insulin's pharmacokinetic profile is significantly affected, peaking faster and reaching higher concentrations in smokers compared with nonsmokers, achieving significantly faster onset and higher insulin levels. The primary pharmacodynamic drug interactions with smoking

are hormonal contraceptives and inhaled corticosteroids. The most clinically significant interaction occurs with combined hormonal contraceptives. The use of hormonal contraceptives of any kind in women who are 35 years or older and smoke 15 or more cigarettes daily is considered contraindicated because of the increased risk of serious cardiovascular adverse effects. The efficacy of inhaled corticosteroids may be reduced in patients with asthma who smoke.

Conclusion. Numerous drug interactions exist with smoking. Therefore, smokers taking a medication that interacts with smoking may require higher dosages than nonsmokers. Conversely, upon smoking cessation, smokers may require a reduction in the dosage of an interacting medication.

Index terms: Contraceptives; Dosage; Drug interactions; Insulin; Insulins; Pharmacodynamics; Pharmacokinetics; Smoking; Steroids, cortico-; Toxicity

Am J Health-Syst Pharm. 2007;64:1917-21

Mechanisms for drug interactions with smoking

Polycyclic aromatic hydrocarbons (PAHs)—products of incomplete combustion—are some of the major lung carcinogens found in tobacco smoke.⁴ PAHs are also potent inducers of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and,

possibly, 2E1.³ Other compounds such as acetone, pyridine, heavy metals, benzene, carbon monoxide, and nicotine may also interact with hepatic enzymes but their effects appear to be less significant. Many drugs are substrates for hepatic CYP1A2, and their metabolism can be induced in smokers, resulting in

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Supported in part by grant R25 CA90720 from the National Cancer Institute and awarded to Karen Suchanek Hudmon, Dr.P.H.,

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DOI 10.2146/ajhp060414

a clinically significant decrease in pharmacologic effects. Thus, smokers may require higher doses of drugs that are CYP1A2 substrates. Another metabolic pathway, glucuronide conjugation, can also be induced by PAHs.³ It is important to recognize that these pharmacokinetic drug interactions are caused by the PAHs in tobacco smoke, not the nicotine. Nicotine-replacement therapy does not contribute to the pharmacokinetic drug interactions discussed in this article. However, pharmacodynamic drug interactions with tobacco smoke are largely due to nicotine. Because it activates the sympathetic nervous system, nicotine can counter the pharmacologic actions of certain drugs.⁵

Potential for drug interactions after smoking cessation

After a person quits smoking, an important consideration is how quickly the induction of CYP1A2 dissipates. This is particularly important when a patient is hospitalized and abruptly quits smoking. Faber and Fuhr⁶ studied CYP1A2 activity, using caffeine clearance, in 12 subjects who smoked at least 20 cigarettes daily (range, 22.3–27.7 cigarettes). At days 1, 2, 3, and 4 and at steady state (approximately one week), the relative reduction in CYP1A2 activity was 12.3%, 20.1%, 25.0%, 28.2%, and 36.1%, respectively. The half-life of CYP1A2 activity after smoking cessation was 38.6 hours. The authors recommended a 10% daily-dose reduction for drugs that are CYP1A2 substrates until the fourth day after smoking cessation. This is a conservative approach and can be considered for drugs with a narrow therapeutic range, such as theophylline. It is important to note that the subjects in the Faber and Fuhr⁶ study were heavy smokers. It is not known how the amount of cigarettes smoked daily or interindividual variation affects CYP1A2 induction. Given the short length of stay for many hospitalized

patients, practitioners should consider the potential for some degree of persistence of CYP1A2 induction during hospitalization.

As a general approach, practitioners should consider a dosage reduction of drugs that are CYP1A2 substrates for a person who quits smoking. Conversely, if a person begins smoking and is taking a drug that is a CYP1A2 substrate, the dosage may need to be increased.

Pharmacokinetic drug interactions

Figure 1 lists the pharmacokinetic drug interactions with smoking. The most clinically significant interactions appear in the shaded rows and are discussed below.

Caffeine is >99% metabolized by CYP1A2 and often used in studies as a marker for CYP1A2 activity.⁷ Its clearance is increased by 56% in smokers.³ After controlling for caffeine intake, since smokers consume more caffeine, the median caffeine concentrations are twofold to threefold higher in nonsmokers.⁸ When a patient quits smoking, the patient's caffeine intake should be reduced by half to avoid excessive caffeine levels. Symptoms of caffeine toxicity, such as irritability and insomnia, can mimic those of nicotine withdrawal and may confound the assessment of whether a person is experiencing nicotine withdrawal. Careful evaluation of a patient's total daily caffeine intake is important, so all sources of caffeine, such as nonprescription drugs and dietary supplements, should be examined.

Clozapine, an atypical antipsychotic drug with a narrow therapeutic range, is metabolized primarily by CYP1A2 but also by CYP2C19 and possibly CYP3A4.^{7,9} One study found that at a given dose, the average plasma clozapine levels of smokers were 81.8% of those of nonsmokers ($p = 0.022$).¹⁰ In male smokers, the plasma clozapine levels were only 67.9% of the concentrations of nonsmokers

($p = 0.0083$).¹⁰ Another study found that nonsmokers had 3.2-fold higher plasma clozapine levels compared with smokers.⁷ Heavy smoking (30 or more cigarettes daily) significantly affected mean intraindividual variation in plasma clozapine concentrations at a daily dose of 100 mg. The mean coefficient of variation for clozapine concentrations was significantly higher for heavy smokers than non-heavy-smokers ($32\% \pm 3\%$ versus $19\% \pm 8\%$, $p = 0.03$).⁹ There were no significant differences observed between smokers and nonsmokers receiving the 300- and 600-mg doses.

Olanzapine, a widely used atypical antipsychotic, is extensively metabolized by direct *N*-glucuronidation, with CYP1A2 and CYP2D6 being minor metabolic pathways.^{11,12} Smokers have been found to have an approximate fivefold-lower dose-corrected steady-state plasma olanzapine concentration compared with nonsmokers.¹¹ Another study found the dose-corrected plasma concentrations of olanzapine to be 12% lower in patients who smoke. Olanzapine's clearance is increased by 98% in smokers.¹³

De Leon¹⁴ recommended an average dosage-correction factor of 1.5 for clozapine and olanzapine in smokers. For example, if a patient is taking clozapine and starts smoking, the clozapine dosage may need to be increased by 1.5 within two to four weeks.¹⁴ Clozapine levels should be monitored in this situation or if the patient quits smoking. Of note, smoking does not affect the metabolism of quetiapine, a more widely used atypical antipsychotic.¹⁵

Fluvoxamine is extensively metabolized by CYP1A2 and polymorphic CYP2D6 and is a potent inhibitor of CYP1A2.^{16,17} Fluvoxamine's maximum serum concentration, steady-state serum concentration (C_{ss}), and area under the concentration–time curve are significantly lower (32%, 39%, and 31%, respectively) in

Figure 1. Pharmacokinetic and pharmacodynamic interactions with smoking. Reprinted, with permission, from the Regents of the University of California, University of Southern California, and Western University of Health Sciences. All rights reserved.



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)	<ul style="list-style-type: none"> Conflicting data on significance of a PK interaction. Possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%).
Caffeine	<ul style="list-style-type: none"> ↑ Metabolism (induction of CYP1A2); ↑ clearance (56%). Likely ↑ caffeine levels after cessation.
Chlorpromazine (Thorazine)	<ul style="list-style-type: none"> ↓ Area under the curve (AUC) (36%) and serum concentrations (24%). ↓ Sedation and hypotension possible in smokers; smokers may need ↑ dosages.
Clozapine (Clozaril)	<ul style="list-style-type: none"> ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (18%).
Flecainide (Tambocor)	<ul style="list-style-type: none"> ↑ Clearance (61%); ↓ trough serum concentrations (25%). Smokers may need ↑ dosages.
Fluvoxamine (Luvox)	<ul style="list-style-type: none"> ↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ plasma concentrations (32%). Dosage modifications not routinely recommended but smokers may need ↑ dosages.
Haloperidol (Haldol)	<ul style="list-style-type: none"> ↑ Clearance (44%); ↓ serum concentrations (70%).
Heparin	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> ↑ Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%).
Olanzapine (Zyprexa)	<ul style="list-style-type: none"> ↑ Metabolism (induction of CYP1A2); ↑ clearance (98%); ↓ serum concentrations (12%). Dosage modifications not routinely recommended but smokers may require ↑ dosages.
Propranolol (Inderal)	<ul style="list-style-type: none"> ↑ Clearance (77%; via side chain oxidation and glucuronidation)
Tacrine (Cognex)	<ul style="list-style-type: none"> ↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations three-fold lower. Smokers may need ↑ dosages.
Theophylline (Theo Dur, etc.)	<ul style="list-style-type: none"> ↑ 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)	<ul style="list-style-type: none"> Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical importance is not established.
Pharmacodynamic Interactions	
Benzodiazepines (diazepam, chlordiazepoxide)	<ul style="list-style-type: none"> ↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system.
Beta-blockers	<ul style="list-style-type: none"> Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation. Smokers may need ↑ dosages.
Corticosteroids, inhaled	<ul style="list-style-type: none"> Asthmatic smokers may have less of a response to inhaled corticosteroids.
Hormonal contraceptives	<ul style="list-style-type: none"> ↑ 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)	<ul style="list-style-type: none"> ↓ 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.

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smokers than in nonsmokers.^{16,18} Another study found no significant difference in the C_{ss} of smokers compared with nonsmokers.¹⁷ These inconsistent findings may be explained by the small sample sizes, possible saturation of CYP1A2 in smokers, and CYP2D6 genotype differences.¹⁷ While dosage modification is not routinely recommended, smokers may require higher dosages of this infrequently used antidepressant.

Tacrine, an infrequently used drug for the treatment of Alzheimer's disease, significantly interacts with smoking. The half-life of tacrine is decreased by 50%,³ and serum tacrine concentrations are threefold lower in patients who smoke.¹⁹

Theophylline's clearance is increased by 58–100% and its half-life is decreased by 63% in smokers compared with nonsmokers.³ This is because it is highly metabolized by CYP1A2. One week after a patient quit smoking, theophylline's clearance was decreased by 38% and its half-life was increased by 36%.²⁰ After only 24–36 hours of smoking cessation, theophylline's pharmacokinetics are not significantly changed.²¹ However, Faber and Fuhr⁶ found that CYP1A2 activity was reduced by 20% after only two days of smoking cessation. Theophylline's clearance increases by 51% in children exposed to the secondhand smoke of parents who smoke at least 20 cigarettes daily. Further, when receiving the same i.v. dose of aminophylline, the C_{ss} was approximately 25% lower in children exposed to secondhand smoke compared with children not exposed to tobacco smoke.²² Theophylline, while used much less frequently for the outpatient management of asthma, is still used in the inpatient setting. Plasma theophylline levels should be routinely monitored in smokers, and dosages should be adjusted accordingly.

Inhaled insulin is contraindicated for use in smokers and in patients who have stopped smoking for less

than six months. Inhaled insulin peaks faster and reaches higher concentrations in smokers compared with nonsmokers.^{23,24} This leads to a systemic exposure that is twofold to fivefold higher in smokers, thus increasing the risk of hypoglycemia.²⁵ If a person resumes smoking, an alternative form of insulin delivery (i.e., subcutaneous injection) must be used.

Pharmacodynamic drug interactions

Figure 1 also lists the pharmacodynamic drug interactions with smoking. The most clinically significant interaction occurs with combined hormonal contraceptives. The use of oral contraceptives increases the risk of cardiovascular adverse effects, specifically thromboembolism (e.g., venous thrombosis, pulmonary embolism), ischemic stroke, and myocardial infarction (MI), but the risk is lower than that associated with the higher-dose oral contraceptives used in the past.^{26–28} Smoking increases the risk of arterial adverse events (i.e., ischemic stroke and MI) associated with oral contraceptive use.²⁶ The risk for cardiovascular events with oral contraceptive use substantially increases in older women who are heavy smokers. For women who use low-dose oral contraceptives (20–50 µg of estrogen), the absolute risk of death from cardiovascular disease in nonsmoking women ages 15–34 years is 0.65 per 100,000 and 6.21 per 100,000 for women ages 35–44 years.²⁹ This risk greatly increases in women who smoke: 3.3 per 100,000 women ages 15–34 years versus 29.4 per 100,000 women ages 35–44 years. In a case-control study assessing the risk of a first nonfatal MI in oral contraceptive users younger than 45 years, the odds ratio among heavy smokers (≥25 cigarettes a day) was 2.5 (95% confidence interval, 0.9–7.5) and close to 1.0 among light smokers and nonsmokers.³⁰ The use of oral contraceptives is contraindi-

cated in women age 35 years or older who smoke 15 or more cigarettes daily.^{31,32} Practitioners should target smoking-cessation interventions toward women in this high-risk population. If unsuccessful, an alternative form of contraception should be recommended, such as a progestin-only contraceptive.^{33,34} Of note, the clinical efficacy of hormonal contraceptives is not reduced in smokers.

Labeling for the Ortho Evra (Ortho-McNeil) contraceptive patch (containing ethinyl estradiol and norelgestromin) was revised in 2005 to indicate that the patch results in 60% higher estrogen levels compared with levels achieved using an oral contraceptive containing 35 µg of estrogen.³⁵ While the published data on this increased cardiovascular risk mainly deal with oral contraceptives, this risk is presumed to be associated with other dosage forms of hormonal contraceptives, such as a patch and ring. The labeling for Ortho Evra and NuvaRing (Organon) warns against use in women over age 35 years who smoke 15 or more cigarettes daily.^{35,36} Women who use combined hormonal contraceptives of any kind should be strongly advised to quit smoking or use an alternative form of contraception if they cannot quit.

The efficacy of inhaled corticosteroids may be reduced in patients with asthma who smoke. In patients with mild asthma receiving 1000 µg daily of inhaled fluticasone (as two puffs twice daily with a metered-dose inhaler), the increase in peak expiratory flow at three months was significantly greater in nonsmokers (27 L/min), compared with a decrease of 5 L/min in smokers ($p = 0.006$).³⁷ Another study of patients with mild, persistent asthma demonstrated significantly less improvement in morning peak expiratory function in smokers taking low-dose inhaled beclomethasone (400 µg daily) than in nonsmokers ($p = 0.019$).³⁸ However, these differences were not significant in patients receiving 2000

µg daily of inhaled beclomethasone ($p = 0.661$).³⁸ Practitioners should be aware that patients with chronic asthma may be less responsive to inhaled corticosteroids and should be a targeted priority for smoking-cessation interventions.

Conclusion

Numerous drug interactions exist with smoking. Therefore smokers taking a medication that interacts with smoking may require higher dosages than nonsmokers. Conversely, upon cessation, smokers may require a reduction in the dosage of an interacting medication.

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