

REVIEW ARTICLE

*Smoking and Drug Intraction : A Literature Review*Amit Tirth¹, Md Nazamuddin Tafadar², Vaibhav Tandon³, Supinder Sudan²**Abstract**

Cigarette smoking remains highly prevalent in most countries. It can affect drug therapy by both pharmacokinetic and pharmacodynamic mechanisms. When patients enter hospital they may have to stop smoking abruptly if the hospital has a 'no smoking' policy. Abrupt smoking cessation can affect the metabolism of drugs. Cigarette smoking induces the activity of human cytochromes P450 (CYP) 1A2 and 2B6. These enzymes metabolise several clinically important drugs, including clozapine, olanzapine and methadone. Decreased CYP1A2 activity after smoking cessation increases the risk of adverse drug reactions, with reports of increased toxicity from clozapine and olanzapine. Predicting the required dose reduction of drugs metabolised by CYP1A2 after smoking cessation is challenging. 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.

Keywords: CYP1A2, Drug interaction, smoking cessation**Introduction**

Tobacco (smoking or smokeless) use is one of the biggest public health threats the world has ever faced and it is one of the major users in the world, 70% of whom are in low-income countries.² 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.³ Nicotine, the major component of the particulate phase, 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.⁴ Of the 69 carcinogens identified in tobacco smoke, 11 are known human carcinogens and 7 are probably carcinogenic in humans.³

Many interactions between tobacco smoke and medications have been identified. 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. Hence, 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.

Mechanism for drug interaction with smoking

Polycyclic aromatic hydrocarbons (PAHs)-products of incomplete combustion-are some of the major lung carcinogens found in tobacco smoke.⁵ PAHs are also potent inducers of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and, possibly, 2E1.⁴ 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 cytochrome P450 family 1 subfamily A member 2 CYP1A2, and their metabolism can be induced in smokers, resulting in 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.⁴ It is important to recognize that these pharmacokinetic drug interactions are caused by the PAHs in tobacco smoke, not the nicotine. Pharmacokinetics is the movement of the drug through the body's biological systems over a period of time, including the processes by which drugs are absorbed, distributed in the body, localized in the tissues, and excreted. Nicotine-replacement therapy does not contribute

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to the pharmacokinetic drug interactions. 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.⁶ Pharmacodynamics is the study of a drug's molecular, biochemical and physiologic effects or actions.

Effect of smoking abstinence on medications

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.

As discussed earlier, pharmacokinetic interactions are primarily due to substances in tobacco smoke, such as hydrocarbons or tar-like products that cause induction of some liver enzymes (CYP 1A2, in particular). Therefore, medicines metabolized by these enzymes are broken down faster and can result in reduced concentrations in the blood. When a person stops smoking, the enzyme activity returns to normal (slows down) which may result in increased levels of these medicines in the blood.

Literature recommends 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 not known how the amount of cigarettes smoked daily or inters individual 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.⁷ Drugs that are CYP1A2 substrates include propranolol, clozapine, tizanidine, theophylline, caffeine etc.

Pharmacokinetic drug interactions

[Mechanism of Interaction and Effects	Clinical significance
Alprazolam (Xanax) • Benzodiazepines used to treat Anxiety and Panic disorder	Possible ↓ in plasma concentrations (up to 50%); ↓ half-life (35%).	Conflicting data
Caffeine • Psychoactive drug	Metabolism (induction of CYP1A2); increase clearance (56%). Caffeine levels likely increase after cessation.	High
Chlorpromazine (Thorazine) • Antipsychotic drug	↓Area under the curve (AUC) (36%) and serum concentrations (24%). ↓Sedation and hypotension possible in smokers; smokers may require increase dosages.	Low

Clopidogrel (Plavix) • Antiplatelet medication used for prevention of heart attack and stroke and peripheral vascular disease	↑Metabolism (induction of CYP1A2) of clopidogrel to its active metabolite. Clopidogrel's effects are enhanced in smokers (≥10 cigarettes/day): significant increase platelet inhibition, decrease platelet aggregation; improved clinical outcomes have been shown (smokers' paradox; may be dependent on CYP1A2 genotype);	High
Clozapine (Clozaril) • Antipsychotics used in the treatment of schizophrenia	↑Metabolism (induction of CYP1A2); ↓plasma concentrations (18%). ↑Levels upon cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.	High
Erlotinib (Tarceva) • Anticancer medication	↑Clearance (24%); ↓trough serum concentrations (2-fold).	High
Flecainide (Tambocor) • Antiarrhythmic medicine used in the treatment of Arrhythmia	↑Clearance (61%); ↓trough serum concentrations (25%). Smokers may need ↑ dosages.	Low
Fluvoxamine (Luvox) • Selective serotonin reuptake inhibitor (SSRI) antidepressant	↑Metabolism (induction of CYP1A2); ↑clearance (24%); ↓AUC (31%); ↓plasma concentrations (32%). Dosage modifications not routinely recommended but smokers may need ↑dosages.	High
Haloperidol (Haldol) • Antipsychotic used in the treatment of Schizophrenia	↑Clearance (44%); ↓serum concentrations (70%).	Low
Heparin • Anticoagulant	Mechanism unknown but ↑clearance and ↓ half-life are observed. Smoking has prothrombotic effects. Smokers may need ↑dosages due to PK and PD interactions.	Low
Insulin, subcutaneous • Used in the treatment of diabetes mellitus Type (1 & Type 2)	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	Low

	may need ↑dosages	
Mexiletine (Mexitil) • Anti-arrhythmic medication	↑Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%).	Low
Propranolol (Inderal) • Beta blocker used in the treatment of Hypertension.	↑Clearance (77%; via side-chain oxidation and glucuronidation).	Low
Theophylline (Theo-Dur, etc.) • Bronchodilator used in the treatment and prevention of chronic obstructive disease and asthma	↑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.	High
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical significance is not established.	Low
Tizanidine (Zanaflex) • Muscle relaxant	↓AUC (30-40%) and ↓ half-life (10%) observed in male smokers.	Low
Warfarin • Anticoagulant	↑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.	Low

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

Pharmacodynamic drug interactions

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; possibly caused by nicotine-mediated sympathetic activation. Smokers may need ↑ dosages.
Corticosteroids, inhaled	<ul style="list-style-type: none"> Smokers with asthma may have less of a response to inhaled corticosteroids.
Hormonal	<ul style="list-style-type: none"> ↑ Risk of cardiovascular

contraceptives	<p>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).</p> <ul style="list-style-type: none"> ↑Risk with age and with heavy smoking (≥15 cigarettes per day) and is quite marked in women ≥35 years old.
Opioids (propoxyphene, pentazocine) • Analgesics used for moderate to severe pain.	<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.

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Drugs for nicotine dependence

Drugs used to aid smoking cessation are not without their hazards, particularly in patients with psychiatric disorders. Bupropion, a selective catecholamine reuptake inhibitor, is associated with a dose-related risk of seizures. Predisposing risk factors include concomitant administration of antipsychotics, antidepressants, excessive alcohol or those sedatives which lower the seizure threshold. Psychiatric symptoms, in particular psychosis or mania, have been observed, mainly in patients with a history of psychiatric illness, particularly bipolar disorder.

Bupropion is metabolised by CYP2B6 and inhibits the CYP2D6 pathway. Drugs predominantly metabolised by 2D6 (including metoprolol, many antidepressants and antipsychotics) should be started at the lower end of the dose range if bupropion is used. Co-administration of drugs known to induce metabolism (for example, carbamazepine and phenytoin) or inhibit metabolism (for example, valproate) may affect the activity of bupropion. Nortriptyline, a tricyclic antidepressant shown to aid smoking cessation, also interacts with other drugs metabolised by CYP2D6.

Varenicline, a partial agonist at neuronal nicotinic acetylcholine receptors, has no known clinically significant drug interactions. However, using nicotine replacement therapy while taking varenicline can exacerbate adverse effects such as nausea and headache. As with bupropion, serious neuropsychiatric symptoms have been reported (although a causal association has not been established).⁸

Conclusion

Smoking can cause medications to become sub therapeutic, leading to slower improvement in disease states. Smoking not only has the potential to cause death, but it also decreases the efficacy of many medications. For that reason, it's important for medical professionals to know which medications are affected by smoking so that appropriate counselling measures and dosage adjustments can be provided to patients.

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