Drug interactions with tobacco smoke: Implications for patient care

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Series Editor

Mrs. C, age 51, experiences exacerbated asthma and difficulty breathing and is admitted to a non-smoking hospital. She also has chronic obstructive pulmonary disease, type 2 diabetes mellitus, hypertension, hypercholesterolemia, hypothyroidism, gastroesophageal reflux disease, overactive bladder, muscle spasms, fibromyalgia, bipolar disorder, insomnia, and nicotine and caffeine dependence. She takes 19 prescribed and over-the-counter medications, drinks up to 8 cups of coffee per day, and smokes 20 to 30 cigarettes per day. In the emergency room, she receives albuterol/ipratropium inhalation therapy to help her breathing and a 21-mg nicotine replacement patch to avoid nicotine withdrawal.

In the United States, 19% of adults smoke cigarettes.[1] Heavy tobacco smoking and nicotine dependence are common among psychiatric patients and contribute to higher rates of tobacco-related morbidity and mortality.[2] When smokers stop smoking or are admitted to smoke-free facilities and are forced to abstain, nicotine withdrawal symptoms and changes in drug metabolism can develop over several days.[3-5]

Smokers such as Mrs. C are at risk for cytochrome (CYP) P450 drug interactions when they are admitted to or discharged from a smoke-free facility. Nine of Mrs. C's medications are substrates of CYP1A2 (acetaminophen, caffeine, cyclobenzaprine, diazepam, duloxetine, melatonin, olanzapine, ondansetron, and zolpidem). When Mrs. C stops smoking while in the hospital, she could experience higher serum concentrations and adverse effects of these medications. If Mrs. C resumes smoking after bring discharged, metabolism and clearance of any medications started while she was hospitalized that are substrates of CYP1A2 enzymes could be increased, which could lead to reduced efficacy and poor clinical outcomes.

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Pharmacokinetic effects

Polycyclic aromatic hydrocarbons in tobacco smoke induce hepatic CYP1A1, 1A2, and possibly 2E1 isoenzymes.[6-12] CYP1A2 is a hepatic enzyme responsible for me-

Practice Points

- Tobacco smokers often are treated with medications that are metabolized by hepatic cytochrome (CYP) 1A2 enzymes. **Starting or stopping tobacco smoking may cause drug interactions** because polycyclic aromatic hydrocarbons in cigarette smoke induce CYP1A2 enzymes.
- **Drugs that are significantly metabolized by CYP1A2 (major substrates)** are more likely to be impacted by changes in tobacco smoking compared with minor substrates.
- **Induction of hepatic CYP1A2 enzymes may be greater in heavy or moderate smokers** compared with light smokers (eg, <10 cigarettes per day).
- Evidence-based approaches for treating tobacco use in health care settings should **address the risk of CYP1A2 drug interactions in tobacco smokers** and how this impacts their clinical care.

Table 1

Common major cytochrome P450 (CYP) 1A2 substrates

Drug	Class
Alosetron[3,5,6]	Irritable bowel syndrome: serotonin 3 antagonist
Aminophylline[3,5]	Bronchodilator: theophylline derivative
Betaxolol[3,5]	β-1 selective adrenergic receptor blocking agent
Caffeine[3-9]	Stimulant
Clomipramine[3-11]	Tricyclic antidepressant
Clozapine[3-10]	Second-generation antipsychotic
Cyclobenzaprine[3-7]	Skeletal muscle relaxant
Doxepin[3,7,10,11]	Tricyclic antidepressant
Duloxetine[3-6]	Serotonin-norepinephrine reuptake inhibitor
Estradiol[3,5-8]	Estrogen (active)
Estrogens: conjugated and estropipate[3,5]; estrone[3,7]	Estrogen (derivatives)
Fluvoxamine[3,8,9]	Selective serotonin reuptake inhibitor
Guanabenz[3,5-7]	α-2 adrenergic agonist
Mirtazapine[3-7]	Antidepressant: α-2 antagonist, serotonin 2A, 2C antagonist
Olanzapine[3-11]	Second-generation antipsychotic
Pimozide[3,5,7]	First-generation antipsychotic
Propranolol[3-11]	β-adrenergic blocker
Ramelteon[3,5,10]	Melatonin receptor agonist
Rasagiline[3,5]	Antiparkinson: type B monoamine oxidase inhibitor
Riluzole[3-7,10]	Glutamate inhibitor
Ropinirole[3,5-7]	Antiparkinson: dopamine agonist
Theophylline[3-6,8-11]	Bronchodilator: methylxanthine
Thiothixene[3,5]	First-generation antipsychotic
Trifluoperazine[3,5,9]	First-generation antipsychotic

Several classes of CYP1A2 substrates are not included and may cause toxicity with smoking cessation or require dosage increases in tobacco smokers (eg, antiarrhythmic, antifungal, antimalarial, antineoplastic, antiretroviral, and anthelmintic agents and the antibiotic quinolone). Clinicians should be most concerned about drugs with a narrow therapeutic index and those that may be toxic with smoking cessation (eg, bleeding from warfarin and clopidogrel; high serum concentrations of caffeine, clozapine, olanzapine, propranolol, and theophylline)

tabolizing and eliminating several classes of substrates (eg, drugs, hormones, endogenous compounds, and procarcinogens).[6,13] Genetic, epigenetic, and environmental factors such as smoking impact the expression and activity of CYP1A2 and result in large interpatient variability in pharmacokinetic drug interactions.[6,12,13] CYP1A2 enzymes can be induced or inhibited by drugs and substances, which can result in decreased or increased serum concentrations of substrates, respectively. When individuals stop smoking and switch to other nicotine products or devices, CYP1A2 induction of hepatic enzymes will revert to normal metabolism over several weeks to a month.[10] Besides tobacco smoke, other CYP1A2 inducers include charbroiled food, carbamazepine, omeprazole, phenobarbital, primidone, and rifampin.[4,5] Nicotine replacement products—such as gum, inhalers, lozenges, patches, and nasal spray—and nicotine delivery devices such as electronic cigarettes do not induce hepatic CYP1A2 enzymes or cause the same drug interactions as cigarette smoking.

Table 1[3-11] and ***Table 2*** (***page 14***)[3-11] list commonly prescribed CYP1A2 substrates that could be affected by tobacco smoke. There

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Clinical Point

Polycyclic aromatic hydrocarbons in tobacco smoke induce hepatic CYP1A1, 1A2, and possibly 2E1 isoenzymes

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Clinical Point

Nicotine products do not induce hepatic CYP1A2 enzymes or cause the same drug interactions as cigarette smoking

Table 2

Common minor cytochrome P450 (CYP) 1A2 substrates

Drug	Class
Acetaminophen[3-9]	Analgesic
Almotriptan[6]	Antimigraine: serotonin 1B, 1D receptor agonist
Amitriptyline[3-7,9-11]	Tricyclic antidepressant
Asenapine[9]	Second-generation antipsychotic
Carvedilol[5-7]	β and α adrenergic blocking activity
Chlorpromazine[3,4,7-9,11]	First-generation antipsychotic
Chlorzoxazone[4,7]	Skeletal muscle relaxant
Clopidogrel[5]	Antiplatelet
Desipramine[4,7,10,11]	Tricyclic antidepressant
Diazepam[4,7,9,10]	Benzodiazepine
Diclofenac[5,7]	Nonsteroidal anti-inflammatory drug
Diphenhydramine[6]	Antihistamine
Febuxostat[5]	Xanthine oxidase inhibitor
Fluphenazine[3,9]	First-generation antipsychotic
Frovatriptan[3]	Antimigraine: serotonin 1 agonist
Haloperidol[3,4,6,8,9]	First-generation antipsychotic
Imipramine[3,4,6-11]	Tricyclic antidepressant
Maprotiline[6]	Tetracyclic antidepressant
Melatonin[3,4,6,7]	Sleep-regulating hormone
Metoclopramide[3]	Antiemetic: prokinetic gastrointestinal agent
Nabumetone[6]	Nonsteroidal anti-inflammatory drug
Naproxen[3,4,6,7]	Nonsteroidal anti-inflammatory drug
Naratriptan[10]	Antimigraine: serotonin 1B, 1D receptor agonist
Nicardipine[3,7]	Calcium channel blocker
Nortriptyline[4,6,7,9-11]	Tricyclic antidepressant
Ondansetron[3,4,6,7]	Antiemetic: serotonin 3 antagonist
Palonosetron[5]	Antiemetic: serotonin 3 antagonist
Perphenazine[3,7]	First-generation antipsychotic
Progesterone[5,7]	Progestin
Propofol[4,6,7]	General anesthetic
Ranitidine[5,7]	H2 antagonist
Rivastigmine[10]	Acetylcholinesterase inhibitor
Selegiline[6,7]	Antiparkinson: type B monoamine oxidase inhibitor
Thioridazine[3,4,6]	First-generation antipsychotic
Tizanidine[3-6]	Skeletal muscle relaxant: α-2 adrenergic agonist
Trazodone[6,9]	Serotonin reuptake inhibitor and antagonist
Triamterene[6]	Diuretic: potassium sparing
Verapamil[3,4,6,7,10]	Calcium channel blocker
Warfarin[3,4,6-10]	Anticoagulant: coumarin derivative
Zileuton[3,4,6,7]	Asthma agent: 5-lipoxygenase inhibitor
Ziprasidone[3,4]	Second-generation antipsychotic
Zolmitriptan[3,6,7]	Antimigraine: serotonin 1B, 1D receptor agonist
Zolpidem[4,6,7]	Nonbenzodiazepine hypnotic

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are no specific guidelines for how to assess, monitor, or manage pharmacokinetic drug interactions with tobacco smoke.[6-13] Induction of hepatic CYP1A2 enzymes by cigarette smoke may require increased dosages of some psychotropics—such as tricyclic antidepressants, duloxetine, mirtazapine, and some first- and second-generation antipsychotics (SGAs)—to achieve serum concentrations adequate for clinical efficacy. Serum concentrations may increase to toxic levels and result in adverse effects when a person quits smoking cigarettes or if a CYP1A2 inhibitor, such as amlodipine, cimetidine, ciprofloxacin, diclofenac, fluoxetine, fluvoxamine, or nifedipine, is added.[5]

SGA such as clozapine and olanzapine are major substrates of CYP1A2 and dosages may need to be adjusted when smoking status changes, depending on clinical efficacy and adverse effects.[10,14,15] Maximum induction of clozapine and olanzapine metabolism may occur with 7 to 12 cigarettes per day and smokers may have 40% to 50% lower serum concentrations compared with nonsmokers.[14] When a patient stops smoking, clozapine and olanzapine dosages may need to be reduced by 30% to 40% (eg, a stepwise 10% reduction in daily dose until day 4) to avoid elevated serum concentrations and risk of toxicity symptoms.[15]

Tobacco smokers can tolerate high daily intake of caffeinated beverages because of increased metabolism and clearance of caffeine, a major substrate of CYP1A2.[11] When patients stop smoking, increased caffeine serum concentrations may cause anxiety, irritability, restlessness, insomnia, tremors, palpitations, and tachycardia. Caffeine toxicity also can mimic symptoms of nicotine withdrawal; therefore, smokers should be advised to reduce their caffeine intake by half to avoid adverse effects when they stop smoking.[10,11]

Adjusting dosing

Factors such as the amount and frequency of tobacco smoking, how quickly CYP1A2 enzymes change when starting and stopping smoking, exposure to secondhand smoke, and other concomitant drugs contribute to variability in pharmacokinetic drug interactions. Heavy smokers (≥30 cigarettes per day) should be closely monitored because variations in drug serum concentrations may be affected significantly by changes in smoking status.[4,9,11]

continued

Related Resources

- Rx for Change. Drug interactions with smoking. http://smokingcessationleadership.ucsf.edu/interactions.pdf.
- Fiore MC, Baker TB. Treating smokers in the health care setting. N Engl J Med. 2011;365(13):1222-1231.

Drug Brand Names

Albuterol/ipratropium • Combivent
Almotriptan • Axert
Alosetron • Lotronex
Aminophylline • Phyllocontin, Truphylline
Amitriptyline • Elavil
Amlodipine • Norvasc
Asenapine • Saphris
Betaxolol • Kerlone
Carbamazepine • Carbatrol, Tegretol
Carvedilol • Coreg
Chlorpromazine • Thorazine
Chlorzoxazone • Parafon Forte
Cimetidine • Tagamet
Ciprofloxacin • Cipro
Clomipramine • Anafranil
Clopidogrel • Plavix
Clozapine • Clozaril
Cyclobenzaprine • Flexeril
Desipramine • Norpramin
Diazepam • Valium
Diclofenac • Voltaren
Diphenhydramine • Benadryl
Doxepin • Silenor, Sinequan
Duloxetine • Cymbalta
Estradiol • Estrace
Estrogens (conjugated) • Cenestin, Premarin
Estropipate • Ogen
Febuxostat • Uloric
Fluoxetine • Prozac
Fluphenazine • Prolixin
Fluvoxamine • Luvox
Frovatriptan • Frova
Guanabenz • Wytensin
Haloperidol • Haldol
Imipramine • Tofranil
Maprotiline • Ludiomil
Metoclopramide • Reglan
Mirtazapine • Remeron
Nabumetone • Relafen
Naratriptan • Amerge
Nicardipine • Cardene
Nifedipine • Adalat, Procardia
Nortriptyline • Aventyl, Pamelor
Olanzapine • Zyprexa
Omeprazole • Prilosec
Ondansetron • Zofran
Palonosetron • Aloxi
Perphenazine • Trilafon
Pimozide • Orap
Primidone • Mysoline
Progesterone • Prometrium
Propofol • Diprivan
Propranolol • Inderal
Ramelteon • Rozerem
Ranitidine • Zantac
Rasagiline • Azilect
Rifampin • Rifadin, Rimactane
Riluzole • Rilutek
Rivastigmine • Exelon
Ropinirole • Requip
Selegiline • Eldepryl, EMSAM, others
Theophylline • Elixophyllin
Thioridazine • Mellaril
Thiothixene • Navane
Tizanidine • Zanaflex
Trazodone • Desyrel, Oleptro
Triamterene • Dyrenium
Trifluoperazine • Stelazine
Verapamil • Calan, Verelan
Warfarin • Coumadin, Jantoven
Zileuton • Zyflo
Ziprasidone • Geodon
Zolmitriptan • Zomig
Zolpidem • Ambien, Edluar

Disclosure

Ms. Fankhauser reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

When a patient stops smoking, clozapine and olanzapine dosages may need to be reduced by 30% to 40%

Clinical Point

Those exposed to secondhand smoke, which induces hepatic CYP1A2 enzymes, may experience changes in drug metabolism

Dosage reductions of potentially toxic drugs should be done immediately when a heavy tobacco user stops smoking.[10] For CYP1A2 substrates with a narrow therapeutic range, a conservative approach is to reduce the daily dose by 10% per day for several days after smoking cessation.[11,16] The impact on drug metabolism may continue for weeks to a month after the person stops smoking; therefore, there may be a delay until CYP1A2 enzymes return to normal hepatic metabolism.[4,8,9,15] In most situations, smoking cessation reverses induction of hepatic CYP1A2 enzymes back to normal metabolism and causes serum drug concentrations to increase.[10] Because secondhand smoke induces hepatic CYP1A2 enzymes, those exposed to smoke may have changes in drug metabolism due to environmental smoke exposure.[11]

Tobacco smokers who take medications and hormones that are metabolized by CYP1A2 enzymes should be closely monitored because dosage adjustments may be necessary when they start or stop smoking cigarettes. An assessment of CYP drug interactions and routine monitoring of efficacy and/or toxicity should be done to avoid potential adverse effects from medications and to determine if changes in dosages and disease state management are required.

References

1. Centers for Disease Control and Prevention (CDC). Vital signs: current cigarette smoking among adults aged ≥18 years—United States, 2005-2010. MMWR Morb Mortal Wkly Rep. 2011;60(35):1207-1212.
2. Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine Tob Res. 2008;10(12):1691-1715.
3. Choe JY. Drug actions and interactions. New York, NY: McGraw-Hill Medical; 2011.
4. Tatro DS. Drug interaction facts. St. Louis, MO: Wolters Kluwer Health; 2011.
5. Lacy CF, Armstrong LL, Goldman MP, et al, eds. Drug information handbook, 20th ed. Hudson, OH: Lexicomp; 2011.
6. Zhou SF, Yang LP, Zhou ZW, et al. Insights into the substrate specificity, inhibitors, regulation, and polymorphisms and the clinical impact of human cytochrome P450 1A2. AAPS J. 2009;11(3):481-494.
7. Rendic S. Summary of information on human CYP enzymes: human P450 metabolism data. Drug Metab Rev. 2002;34(1-2):83-448.
8. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. Clin Pharmacokinet. 1999:36(6):425-438.
9. Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. CNS Drugs. 2001;15(6):469-494.
10. Schaffer SD, Yoon S, Zadezensky I. A review of smoking cessation: potentially risky effects on prescribed medications. J Clin Nurs. 2009;18(11):1533-1540.
11. Kroon LA. Drug interactions with smoking. Am J Health Syst Pharm. 2007;64(18):1917-1921.
12. Plowchalk DR, Yeo KR. Prediction of drug clearance in a smoking population: modeling the impact of variable cigarette consumption on the induction of CYP1A2. Eur J Pharmacol. 2012;68(6):951-960.
13. Faber MS, Jetter A, Fuhr U. Assessment of CYP1A2 activity in clinical practice: why, how, and when? Basic Clin Pharmacol Toxicol. 2005;97(3):125-134.
14. Haslemo T, Eikeseth PH, Tanum L, et al. The effect of variable cigarette consumption on the interaction with clozapine and olanzapine. Eur J Clin Pharmacol. 2006;62(12):1049-1053.
15. Lowe EJ, Ackman ML. Impact of tobacco smoking cessation on stable clozapine or olanzapine treatment. Ann Pharmacother. 2010;44(4):727-732.
16. Faber MS, Fuhr U. Time response of cytochrome P4501A2 activity on cessation of heavy smoking. Clin Pharmacol Ther. 2004;76(2):178-184.