

## ARTICLE

# Smoking and drug interactions

## Catherine Lucas

Clinical pharmacology registrar<sup>1</sup>

## Jennifer Martin

Clinical pharmacologist<sup>1,2</sup>

Consultant physician  
Internal Medicine<sup>2</sup>

Associate professor of  
Medicine<sup>3</sup>

<sup>1</sup>Royal Brisbane and  
Women's Hospital  
Brisbane

<sup>2</sup>Princess Alexandra  
Hospital  
Brisbane

<sup>3</sup>The University of  
Queensland

## Key words

clozapine, cytochrome  
P450, nicotine

*Aust Prescr* 2013;36:102-4

## SUMMARY

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. Therapeutic drug monitoring should be used when possible.

Nicotine replacement therapy does not influence CYP1A2 activity.

## Introduction

Despite anti-smoking campaigns, there are about 1.3 billion cigarette smokers worldwide and this number is still increasing.<sup>1</sup> Both smoking prevalence and daily tobacco consumption are very high in patients with psychiatric disorders.<sup>2</sup> Over two-thirds of Australians with psychosis smoke cigarettes, compared with one quarter of the general population.<sup>3</sup>

Smoking restriction or cessation is now commonly imposed on patients by 'no smoking' policies in Australian hospitals. Stopping smoking is particularly important in patients with mental health problems as they often have an adverse cardiovascular risk profile (from factors including obesity, dyslipidaemia, insulin resistance and hypertension). This is associated with high rates of premature mortality from cardiovascular disease.<sup>4</sup>

Even with nicotine replacement therapy as a cessation aid, patients with psychiatric illness appear to have more difficulty maintaining long-term abstinence than other smokers.<sup>5</sup> Most resume smoking within five weeks of hospital discharge.<sup>6</sup> These patients should be regularly asked about their smoking status, as an additional risk of resuming or abruptly ceasing cigarette smoking has the potential for drug interactions.<sup>7</sup>

## Drug interactions

The chemicals in smoke may interact with antipsychotics, antidepressants, benzodiazepines,<sup>8</sup> oral contraceptives, inhaled corticosteroids and beta blockers via pharmacokinetic and pharmacodynamic (often nicotine-mediated) mechanisms.<sup>9</sup>

## Pharmacokinetic interactions

Cigarette smoking induces the activity of cytochrome P450 (CYP) 1A2 (via chemicals in cigarette smoke such as polycyclic aromatic hydrocarbons)<sup>10</sup> and also CYP2B6.<sup>11</sup> These enzymes metabolise several clinically important drugs (such as antidepressants and antipsychotics) (Box) and a number of procarcinogens (such as those in cigarettes).<sup>10,12</sup>

The effect of smoking on hepatic enzymes is not related to the nicotine component of tobacco. Nicotine replacement therapy does not influence CYP1A2 activity.<sup>13</sup>

Genetic polymorphisms of the CYP1A2 gene contribute to extensive inter-individual variability in drug metabolism<sup>14,15</sup> and are associated with altered inducibility of gene expression in smokers.<sup>7,16</sup> There are also marked ethnic differences in the distribution of CYP1A2 mutations,<sup>10,17</sup> meaning that different ethnic groups respond differently when the patient stops smoking.

CYP1A2 activity is significantly higher in heavy smokers (more than 20 cigarettes/day) than in non-smokers.<sup>18</sup> This is likely to be clinically relevant for some drugs which have a narrow therapeutic index and are metabolised by CYP1A2, such as clozapine. The induction varies depending on the bioavailability of the components of cigarette smoke and the extent of inhalation.<sup>8</sup> It is not known how the number of cigarettes smoked daily or inter-individual variation affects CYP1A2 induction,<sup>9</sup> but heavier smokers appear to have a greater increase in the clearance of drugs.<sup>19</sup>

This enzyme induction is rapidly reversed when patients abruptly stop smoking, with a new steady state of CYP1A2 activity reached after approximately one week.<sup>20</sup> This reduction in enzyme activity reduces clearance and increases the risk of adverse drug reactions for patients taking drugs metabolised by CYP1A2.<sup>20,21</sup> These patients should be regularly asked about their smoking and the extent of their cigarette consumption.<sup>16</sup>

## Clozapine and olanzapine

Cigarette smoking induces the metabolism of

clozapine and olanzapine,<sup>22</sup> resulting in lower plasma concentrations.<sup>7,16,21</sup> The daily consumption of 7–12 cigarettes is probably sufficient to cause the maximum induction of clozapine and olanzapine metabolism.<sup>22</sup> A 50% difference in the mean daily dose of clozapine needed by smokers and non-smokers to reach a given blood concentration has been reported.<sup>23</sup>

Irrespective of smoking status, the mean oral bioavailability of clozapine is 27–47% and clozapine plasma concentrations have more than a 45-fold variability amongst individuals during chronic treatment.<sup>24</sup> There are also large inter-patient differences in olanzapine exposure, with gender and genetic factors contributing.<sup>25</sup>

Non-smokers are at higher risk of adverse effects if treated with standard doses, suggesting that there is an interaction between smoking, olanzapine and clozapine.<sup>20,22</sup> In one case report, a patient receiving olanzapine experienced extrapyramidal symptoms (including akathisia, akinesia and bradyphrenia) within days of significantly reducing tobacco consumption.<sup>21</sup> Case reports on smoking discontinuation by patients taking clozapine outline effects including confusion,<sup>21</sup> tonic-clonic seizures, stupor, coma<sup>26</sup> or aspiration pneumonia.<sup>27</sup>

Clearance of clozapine has been shown to decrease when smoking is ceased, with a mean increase of 72% in plasma clozapine concentrations.<sup>27</sup> It is suggested that daily dose reductions (of approximately 10% until the fourth day after smoking cessation) should be made whenever patients cease smoking during treatment with clozapine.<sup>20</sup> Patients who resume smoking after leaving hospital may need their drugs and doses reviewed to account for this change.<sup>28</sup> Therapeutic drug monitoring of clozapine is useful.

### Antidepressants

As fluvoxamine is metabolised by CYP1A2, smokers might require higher doses than those recommended from clinical trial data.<sup>8</sup> Smoking is not anticipated to alter the pharmacokinetics of other selective serotonin reuptake inhibitors as they are not substrates of CYP450 isoenzymes induced by smoking.<sup>8</sup>

Smokers might require higher than normal doses of the tricyclic antidepressant imipramine. They do not appear to require dose adjustments of amitriptyline, nortriptyline or clomipramine.<sup>8</sup>

### Warfarin

Warfarin's less active R isomer is eliminated to a minor extent by CYP1A2.<sup>29</sup> Smoking may therefore potentially interact with warfarin by increasing its clearance and reducing its effect. A recent meta-analysis showed that smoking appeared to increase

## Box Substrates of some cytochrome P450 enzymes induced by smoking

### CYP1A2

amitriptyline, caffeine, clozapine, duloxetine, fluvoxamine, haloperidol, imipramine, olanzapine, ondansetron, paracetamol, propranolol, theophylline, warfarin (R-isomer)

### CYP2B6

bupropion, clopidogrel, cyclophosphamide, efavirenz, ifosfamide, methadone, nevirapine

More comprehensive lists are available<sup>8,17</sup>

Adapted from Australian Medicines Handbook 2013

the warfarin dose requirement by 12%, resulting in an extra 2.26 mg per week compared with non-smoking.<sup>30</sup> Consequently, INR should be closely monitored when there is a change in patients' smoking status.

### Clonidine and prasugrel

CYP isoenzymes (including CYP2C19, 3A4/5, 1A2, 2B6 and 2C9) convert clopidogrel and prasugrel into their active metabolites, which bind irreversibly to the receptors on platelets. As smoking is known to enhance CYP1A2 activity, theoretically it could increase the antiplatelet efficacy of these thienopyridine drugs.<sup>31</sup>

An enhanced response to clopidogrel has been seen in smokers who are CYP1A2 (163CA) A-allele carriers.<sup>32</sup> Two retrospective analyses of large randomised clinical trials of clopidogrel showed that clopidogrel might be more effective in active smokers.<sup>33,34</sup> However, a systematic review concluded that smoking is not associated with reduced platelet reactivity in patients on clopidogrel.<sup>31</sup> Genetic polymorphisms seem not to impact on the activity of prasugrel.<sup>31</sup>

### Caffeine

Caffeine is highly dependent on CYP1A2 for its metabolism. Smokers require up to four times as much caffeine as non-smokers to achieve the same plasma caffeine concentration. Caffeine can increase the concentration of clozapine and olanzapine.<sup>35</sup>

### Pharmacodynamic drug interactions

Pharmacodynamic drug interactions with tobacco smoke are largely due to nicotine.<sup>9</sup>

### Methadone

The vast majority of patients using methadone maintenance therapy also smoke tobacco.<sup>36</sup> Methadone doses have been found to be higher in heavy smokers<sup>37</sup> and methadone has been shown to increase both smoking rates and smoking satisfaction.<sup>38</sup> Patients report less methadone-induced

sedation when they smoke around the time of their methadone dose.<sup>39</sup>

Although methadone is a CYP2B6 substrate (Box), nicotine affects the endogenous opioid system. Cigarette smoking enhances the effect of methadone on opioid withdrawal symptoms.<sup>40</sup>

Methadone attenuates nicotine withdrawal. Reducing methadone doses when the patient is trying to stop smoking could be detrimental.<sup>40</sup>

### Benzodiazepines

Nicotine activates the central nervous system<sup>9</sup> and this may explain the attenuated sedation observed in smokers compared to non-smokers taking benzodiazepines.<sup>41</sup> Prescribers should be aware that when patients taking benzodiazepines stop smoking, there is a risk of central nervous system depression.

### Oral contraception

Smoking increases the adverse effects of the combined oral contraceptive pill (specifically thromboembolism, ischaemic stroke and myocardial infarction). The combined oral contraceptive pill is contraindicated in women aged 35 years or older who smoke 15 or more cigarettes a day.<sup>9</sup> For smokers who use combined low-dose oral contraceptives, the attributable risk of death from cardiovascular disease is 19.4 per 100 000 women aged 35–44 years (vs 3.03 per 100 000 for non-smoking women of the same age).<sup>42</sup> This risk is also presumed to be associated with other contraceptives containing oestrogen.<sup>9</sup>

Limited data suggest no convincing association between cardiovascular disease and progestogen-only pill use.<sup>43</sup> If smoking cessation is unsuccessful, non-hormonal or progestogen-only contraceptives are preferred from a cardiovascular perspective.<sup>9</sup>

### Other drugs

The efficacy of inhaled corticosteroids may be reduced in asthmatic patients who smoke,<sup>9</sup> so these patients might require higher doses of inhaled corticosteroids to attain asthma control.<sup>44</sup>

Proposed mechanisms of corticosteroid insensitivity include suppression of histone deacetylase expression and activity by cigarette smoking, causing inflammatory gene expression and a reduction in glucocorticoid function.<sup>45</sup> Clearance of corticosteroids from the lungs may be altered by increased mucus secretion or airway permeability.<sup>46</sup>

Smokers may require higher doses of beta blockers. Although propranolol is a CYP1A2 substrate (Box), nicotine-mediated central nervous system activation may diminish the effect of beta blockers on blood pressure and heart rate.<sup>9</sup>

## 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).

## Conclusion

Cigarette smoking can affect drug metabolism via pharmacokinetic and pharmacodynamic mechanisms, and a change in smoking status can render patients at risk of serious adverse reactions.

Patients should be regularly monitored with regard to their smoking status and extent of cigarette consumption and doses of relevant medications adjusted accordingly. ◀

*No relevant potential conflict of interest declared*

*Acknowledgement: Dr Peter Donovan and Nicky Foxlee (Manager, Herston Health Sciences Library and The University of Queensland Dentistry Library)*



### SELF-TEST QUESTIONS

#### True or false?

9. As smoking induces cytochrome P450 1A2, smokers need lower doses of drugs metabolised by this enzyme.

10. The pharmacokinetic effects caused by stopping smoking can be avoided by giving the patient a nicotine patch.

Answers on page 107

## REFERENCES

1. Guindon GE, Boisclair D. Past, current and future trends in tobacco use. Health, Nutrition and Population (NHP) discussion paper. Economics of tobacco control paper No. 6. Washington DC: World Bank; 2003.
2. Keizer I, Eytan A. Variations in smoking during hospitalization in psychiatric in-patient units and smoking prevalence in patients and health-care staff. *Int J Soc Psychiatry* 2005;51:317-28.
3. Morgan VA, Waterreus A, Jablensky A, Mackinnon A, McGrath JJ, Carr V, et al. People living with psychotic illness 2010. Report on the second Australian national survey. Canberra: Department of Health and Ageing; 2011.
4. Hennekens CH, Hennekens AR, Hollar D, Casey DE. Schizophrenia and increased risks of cardiovascular disease. *Am Heart J* 2005;150:1115-21.
5. Siru R, Hulse GK, Khan RJ, Tait RJ. Motivation to quit smoking among hospitalised individuals with and without mental health disorders. *Aust N Z J Psychiatry* 2010;44:640-7.
6. Prochaska JJ, Fletcher L, Hall SE, Hall SM. Return to smoking following a smoke-free psychiatric hospitalization. *Am J Addict* 2006;15:15-22.
7. Dobrinas M, Cornuz J, Oneda B, Kohler Serra M, Puhl M, Eap CB. Impact of smoking, smoking cessation, and genetic polymorphisms on CYP1A2 activity and inducibility. *Clin Pharmacol Ther* 2011;90:117-25.
8. Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS Drugs* 2001;15:469-94.
9. Kroon LA. Drug interactions with smoking. *Am J Health Syst Pharm* 2007;64:1917-21.
10. Zhou SF, Yang LP, Zhou ZW, Liu YH, Chan E. Insights into the substrate specificity, inhibitors, regulation, and polymorphisms and the clinical impact of human cytochrome P450 1A2. *AAPS J* 2009;11:481-94.
11. Washio I, Maeda M, Sugiura C, Shiga R, Yoshida M, Nonen S, et al. Cigarette smoke extract induces CYP2B6 through constitutive androstane receptor in hepatocytes. *Drug Metab Dispos* 2011;39:1-3.
12. Rendic S. Summary of information on human CYP enzymes: human P450 metabolism data. *Drug Metab Rev* 2002;34:83-448.
13. Schaffer SD, Yoon S, Zadezensky I. A review of smoking cessation: potentially risky effects on prescribed medications. *J Clin Nurs* 2009;18:1533-40.
14. Cascorbi I. Genetic basis of toxic reactions to drugs and chemicals. *Toxicol Lett* 2006;162:16-28.
15. Palma BB, Silva e Sousa M, Vosmeer CR, Lastdrager J, Rueff J, Vermeulen NP, et al. Functional characterization of eight human cytochrome P450 1A2 gene variants by recombinant protein expression. *Pharmacogenomics J* 2010;10:478-88.
16. Bondolfi G, Morel F, Crettol S, Rachid F, Baumann P, Eap CB. Increased clozapine plasma concentrations and side effects induced by smoking cessation in 2 CYP1A2 genotyped patients. *Ther Drug Monit* 2005;27:539-43.
17. Zhou SF, Wang B, Yang LP, Liu JP. Structure, function, regulation and polymorphism and the clinical significance of human cytochrome P450 1A2. *Drug Metab Rev* 2010;42:268-354.
18. Tantcheva-Poor I, Zaigler M, Rietbrook S, Fuhr U. Estimation of cytochrome P-450 CYP1A2 activity in 863 healthy Caucasians using a saliva-based caffeine test. *Pharmacogenetics* 1999;9:131-44.
19. Jusko WJ. Influence of cigarette smoking on drug metabolism in man. *Drug Metab Rev* 1979;9:221-36.
20. Faber MS, Fuhr U. Time response of cytochrome P450 1A2 activity on cessation of heavy smoking. *Clin Pharmacol Ther* 2004;76:178-84.
21. Zullino DF, Delessert D, Eap CB, Preisig M, Baumann P. Tobacco and cannabis smoking cessation can lead to intoxication with clozapine or olanzapine. *Int Clin Psychopharmacol* 2002;17:141-3.
22. Haslemo T, Eikeseth PH, Tanum L, Molden E, Refsum H. The effect of variable cigarette consumption on the interaction with clozapine and olanzapine. *Eur J Clin Pharmacol* 2006;62:1049-53.
23. van der Weide J, Steijns LS, van Weelden MJ. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. *Pharmacogenetics* 2003;13:169-72.
24. Potkin SG, Bera R, Gulasekaram B, Costa J, Hayes S, Jin Y, et al. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. *J Clin Psychiatry* 1994;55 Suppl B:133-6.
25. Ghotbi R, Mannheimer B, Akiillu E, Suda A, Bertilsson L, Eliasson E, et al. Carriers of the UGT1A4 142T>G gene variant are predisposed to reduced olanzapine exposure – an impact similar to male gender or smoking in schizophrenic patients. *Eur J Clin Pharmacol* 2010;66:465-74.
26. Skogh E, Bengtsson F, Nordin C. Could discontinuing smoking be hazardous for patients administered clozapine medication? A case report. *Ther Drug Monit* 1999;21:580-2.
27. Meyer JM. Individual changes in clozapine levels after smoking cessation: results and a predictive model. *J Clin Psychopharmacol* 2001;21:569-74.
28. Lawn S, Pols R. Smoking bans in psychiatric inpatient settings? A review of the research. *Aust N Z J Psychiatry* 2005;39:866-85.
29. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005;165:1095-106.
30. Nathisuwan S, Dilokthornsakul P, Chaiyakunapruk N, Morarai T, Yodtong T, Piriyananansorn N. Assessing evidence of interaction between smoking and warfarin: a systematic review and meta-analysis. *Chest* 2011;139:1130-9.
31. Hochholzer W, Trenk D, Mega JL, Morath T, Stratz C, Valina CM, et al. Impact of smoking on antiplatelet effect of clopidogrel and prasugrel after loading dose and on maintenance therapy. *Am Heart J* 2011;162:518-26.
32. Park KW, Park JJ, Jeon KH, Kang SH, Oh IY, Yang HM, et al. Enhanced clopidogrel responsiveness in smokers: smokers' paradox is dependent on cytochrome P450 CYP1A2 status. *Arterioscler Thromb Vasc Biol* 2011;31:665-71.
33. Desai NR, Mega JL, Jiang S, Cannon CP, Sabatine MS. Interaction between cigarette smoking and clinical benefit of clopidogrel. *J Am Coll Cardiol* 2009;53:1273-8.
34. Berger JS, Bhatt DL, Steinhilb SR, Shao M, Steg PG, Montalescot G, et al. Smoking, clopidogrel, and mortality in patients with established cardiovascular disease. *Circulation* 2009;120:2337-44.
35. de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. *Psychiatric Serv* 2004;55:491-3.
36. Richter KP, Gibson CA, Ahluwalia JS, Schmelzle KH. Tobacco use and quit attempts among methadone maintenance clients. *Am J Public Health* 2001;91:296-9.
37. Frosch DL, Stopshaw S, Nahom D, Jarvik ME. Associations between tobacco smoking and illicit drug use among methadone-maintained opiate-dependent individuals. *Exp Clin Psychopharmacol* 2000;8:97-103.
38. Chait LD, Griffiths RR. Effects of methadone on human cigarette smoking and subjective ratings. *J Pharmacol Exp Ther* 1984;229:636-40.
39. McCool RM, Paschall Richter K. Why do so many drug users smoke? *J Subst Abuse Treat* 2003;25:43-9.
40. Elkader AK, Brands B, Selby P, Sproule BA. Methadone-nicotine interactions in methadone maintenance treatment patients. *J Clin Psychopharmacol* 2009;29:231-8.
41. Olivier D, Lubman DI, Fraser R. Tobacco smoking within psychiatric inpatient settings: biopsychosocial perspective. *Aust N Z J Psychiatry* 2007;41:572-80.
42. Schwingl PJ, Ory HW, Visness CM. Estimates of the risk of cardiovascular death attributable to low-dose oral contraceptives in the United States. *Am J Obstet Gynecol* 1999;180:241-9.
43. Heinemann LA, Assmann A, DoMinh T, Garbe E. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. *Eur J Contracept Reprod Health Care* 1999;4:67-73.
44. Lazarus S, Chinchilli V, Rollings N, Boushey H, Cherniack R, Craig T, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;175:783-90.
45. Ito K, Lim S, Caramori G, Chung KF, Barnes PJ, Adcock IM. Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression, and inhibits glucocorticoid actions in alveolar macrophages. *FASEB J* 2001;15:1110-2.
46. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002;57:226-30.