REVIEW

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# A review of smoking cessation: potentially risky effects on prescribed medications

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**Aims and objectives.** To identify prescription drugs that require dosage adjustment or monitoring in patients who quit smoking and to provide recommendations for dosage adjustment based on available evidence.

**Background.** Health care providers are urged to facilitate smoking cessation for patients who smoke, but the effects of smoking cessation on the metabolism of some drugs is not routinely considered.

**Design.** A comprehensive literature review.

**Methods.** The review was conducted in 2008 using a computerised drug interaction program and multiple PubMed and CINAHL searches to identify prescription drugs with clinically significant pharmacokinetic or pharmacodynamic changes caused by smoking cessation.

**Results.** Although much of the evidence is case report, dosage adjustments are clearly indicated for warfarin, olanzapine, clozapine and theophylline since they are metabolised by cytochrome P450 CYP1A2 and also have narrow therapeutic ratios. Careful monitoring is recommended for other CYP1A2 metabolised drugs, including those for hypertension and Alzheimer's disease. For many affected drugs, smoking cessation reverses smoking-induced CYP1A2 hepatic enzyme levels to normal, increasing plasma concentrations in patients whose dose was established while smoking. Because the effect on hepatic microsomal enzymes is not related to the nicotine component of tobacco, nicotine replacement will not alter the effect.

**Conclusions.** The effects of smoking cessation on drugs metabolised by CYP1A2 have been under-appreciated by health care providers. Smoking cessation may increase plasma levels of some drugs to potentially toxic levels. Further research is warranted to clarify this effect.

**Relevance to clinical practice.** When patients stop smoking, providers should carefully review prescribed drug regimens and adjust or monitor drugs whose metabolism is affected by smoking cessation. This is particularly important for patients who abruptly stop smoking due to hospitalisation and for older patients who are likely to be taking multiple medications.

**Key words:** CYP1A2, cytochrome P 450, drug interaction, nurses, nursing, smoking cessation

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## Introduction

Cigarette smoking is well recognised as a health hazard causing various cancers and a risk factor for the development of coronary artery disease, cerebrovascular disease and chronic obstructive lung disease (Sherman 1991). It is estimated that about one third of all adults worldwide are smokers although cigarette smoking rates somewhat vary by gender and countries' income level (Slama 2008). These high smoking rates have important implications for health care providers

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in many countries including the USA. The World Health Organization (WHO 2003) proposed recommendations for smoking cessation and treatment of tobacco dependence including behavioural and pharmacological interventions. In the USA, one of the goals of *Healthy People 2010, A document outlining national health priorities* is to decrease smoking prevalence from 24 percent to 12 percent by the year 2010 (U. S. Department of Health and Human Services 2000). Health care providers are urged to assess all patients for tobacco use, to strongly recommend tobacco cessation and to prescribe nicotine replacement or bupropion to help patients quit smoking (Fiore 1996, WHO 2003). However, it is not well recognised that the metabolism of many prescribed drugs are affected by tobacco smoking and that smoking cessation may necessitate dosage adjustment for these drugs.

### Objectives

The purpose of this paper is to report the current evidence related to the effect of smoking cessation on prescribed drug metabolism, with emphasis on those interactions that are likely to be of the most clinical significance.

## Background

### Effects of smoking cessation on pharmacokinetics

Cytochrome P450 (CYP) enzymes in the liver are responsible for the detoxification of foreign chemicals and the metabolism of drugs. Some drugs can 'induce' P450 by enhancing the rate of its synthesis or reducing its rate of degradation, while others 'inhibit' P450 by slowing metabolism and extending half-life. Among various P450 hepatic enzymes, CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4 isoforms seem to play an important role for hepatic drug metabolism (Turkoski 2002, Correia 2007, Kroon 2007).

Tobacco smoke contains polycyclic aromatic hydrocarbons that have been shown to induce cytochrome P450 enzymes, particularly CYP1A2, resulting in faster metabolism of some drugs (Zevin & Benowitz 1999). Thus, smokers may require higher doses of certain drugs due to increased plasma clearance, attributed to an induction of P450 first pass metabolism enzymes (Schein 1995, Zevin & Benowitz 1999, Kroon 2007). Smoking cessation reverses induced hepatic enzyme levels to normal (MacLeod *et al.* 1997) and also reverses other smoking-induced effects, markedly augmenting plasma drug concentrations in patients whose dose was established while smoking (Faber & Fuhr 2004). Nicotine replacement treatment to assist smoking cessation will not ameliorate this effect in most cases because the effect on hepatic microsomal enzymes is not related to the nicotine component of tobacco, but is related to aromatic hydrocarbons in tobacco smoke (Clinical Pharmacology 2008).

Drugs affected by CYP 1A2 include those with central nervous system (CNS) activity (e.g. imipramine, clozapine), opioid analgesics (e.g. propoxyphene), anti-hypertensive drugs (e.g. propranolol, verapamil) and others. Although aromatic hydrocarbons in tobacco smoke also induce cytochrome P450 CYP 1A1 and possibly CYP2E1, these enzymes are primarily involved in the activation of procarcinogens (Zevin & Benowitz 1999).

In addition to cytochrome P450 mechanisms affecting plasma concentration of drugs related smoking status, tobacco smoking may also reduce blood flow to the skin and subcutaneous tissue, slowing the absorption of injected medications such as insulin. Tobacco smoking results in faster clearance of heparin, possibly related to activation of thrombosis with enhanced heparin binding to antithrombin III (Zevin & Benowitz 1999).

Increased plasma concentrations after smoking cessation may cause serious clinical consequences, particularly in drugs with narrow therapeutic ratios. Narrow therapeutic ratio is defined according to 21 CFR 320·33(c) (United States Code of Federal Regulations) as drugs having a less than twofold difference between the median lethal (LD50) and median effective dose (ED50) or a less than two-fold difference between the minimum toxic and minimum effective concentration in the blood. Examples of drugs with narrow therapeutic ratios include warfarin, clozapine, olanzapine and theophylline (Burns 1999, Faber & Fuhr 2004).

### Changes in pharmacokinetics and pharmacodynamics in older adults

Older adults are generally more susceptible to drug effects, with adverse drug reactions occurring 2–3 times more frequently in persons over age 65 (Turnheim 1998). Although the activities of cytochrome P450 enzymes are reduced in older adults, conjugation mechanisms are maintained (Cusack 2004). Changes in pharmacodynamic effects of drugs in older adults may result in increased activity of drugs, such as central nervous system depressants, at a given plasma concentration (Buxton 2006). Reduced renal drug elimination (about 50%), decreased hepatic drug clearance, changes in body water content and changes in body fat content also increase risks of adverse drug effects in older adults (Turnheim 2004, Oates 2006). For example, Ramelteon plasma concentrations can be up to 97% higher in older adults (Rozerem® 2006). Given these pharmacodynamic and

  

pharmacokinetic changes, the high prevalence of comorbidities and use of multiple prescribed drugs in older adults, prediction of drug safety and efficacy after smoking cessation becomes complex.

### Evidence for drug dosing with smoking cessation

Faber and Fuhr (2004) studied CYP1A2 activity using caffeine clearance in smokers subjected to sudden smoking cessation, since caffeine is metabolised primarily by CYP1A2. A decrease in caffeine clearance of 20% by day 2 and 36% by day 7 was documented, leading the authors to conclude that immediate dose reductions be made whenever patients cease smoking under treatment with CYP1A2 metabolised drugs, particularly those with a narrow therapeutic ratio (Faber & Fuhr 2004).

### Design & methods

This article presents results of a comprehensive search for drug-tobacco interactions using a web-based program (Clinical Pharmacology 2008). Tobacco was entered as a search term and every interaction between tobacco/smoking and a drug listed by the program was reviewed and categorised in January 2008. This search was supplemented by PubMed and CINAHL searches done in January and February 2008 using various combinations of smoking cessation, smoking, tobacco, pharmacokinetics and drug interaction, as well as individual searches of all drugs that are primarily metabolised by CYP 1A2 as search terms. Drugs metabolised by CYP1A2 were determined from Hansten and Horn (2006). Additionally, related articles suggested by PubMed and reference lists were reviewed. Where not substantiated by smoking cessation studies, recommendations for dose reduction were made by using published estimates of smoking effects on drug metabolism.

## Results

Although no randomised controlled trials were found to document increased plasma concentrations due to smoking cessation, available studies (e.g. case studies, quasi-experimental studies) provide some evidence (Table 1). The drugs for which data exist demonstrate blood level increases of as much as 40% after smoking cessation, which is particularly significant for drugs with a narrow therapeutic ratio (Faber & Fuhr 2004). Interactions between drugs and smoking cessation are summarised in the following table, with drug categories, generic drug names, mechanisms of interaction and recommendations for dose reduction when evidence was found in the literature. Interactions that are not related to cytochrome P450 are explained.

### Cardiovascular medications

An early prospective study and case reports documented the effects of smoking cessation on warfarin requirements. Although Bachmann *et al.* (1979) reported that smoking cessation did not affect prothrombin time in healthy smokers given a subtherapeutic dose of warfarin, this study did report a 13% increase in average study-state warfarin level and a 13% decrease in warfarin clearance rate when smokers stopped smoking. However, Colucci and Knapp (2001) and Evans and Lewis (2005) reported INR prolongation and need to reduce warfarin dose 14–23% in individuals who stopped smoking after previously achieving a stable warfarin dose.

Smoking cessation decreases verapamil clearance by eight fold (Fuhr *et al.* 2002) and similarly decreases propanolol clearance by 77% (Zevin & Benowitz 1999). However, clinical effects are difficult to predict since propanolol dosage varies from 80–640 mg daily. Thus, it may be crucial to observe for signs and symptoms of overdose. For example, bradycardia, fatigue, dizziness and other symptoms of overdose suggest a need to decrease doses of propanolol and verapamil. Mexiletine, flecanamide and lidocaine are antiarrhythmic drugs that are induced through CYP1A2. Although no studies quantify dosage changes that should be made upon smoking cessation, patients should be monitored for dizziness, nervousness, tremor and worsening arrhythmias which may suggest overdose.

### Mental health/neurological medications

Important clinical evidence (several case reports and a non-randomised study) was found for the effects of smoking cessation and the metabolism of atypical anti-psychotic drugs clozapine and olanzapine (Meyer 2001, Zullino *et al.* 2002, Bondolfi *et al.* 2005, Derenne & Baldessarini 2005, Sandson *et al.* 2007, Brownlowe & Sola 2008). Dose reductions of approximately 36% should be implemented within one week of smoking cessation to avoid toxicity with these drugs (Skogh *et al.* 1999, Meyer 2001, de Leon *et al.* 2005). Although no studies have substantiated the effects of smoking cessation and diazepam plasma levels, smoking increases the clearance of diazepam up to threefold (Clinical Pharmacology 2008). Patients who stop smoking while taking diazepam should be carefully monitored for central nervous system (CNS) depression. However, other benzodiazepines are not affected by smoking cessation.

Tobacco smoking increases the clearance of naratriptan by roughly 30% (Amerge® package insert 2003). Increased plasma levels of naratriptan after smoking cessation may

**Table 1** Drugs affected by smoking cessation

| Drug categories | Generic drug name | Mechanism of interaction | Evidence for dosage adjustment after smoking cessation |
|---|---|---|---|
| Cardiovascular medications | | | |
| Antihypertensive | Propranolol | Propranolol is mainly metabolised by CYP 1A2. Smoking also increases side-chain oxidation and glucuronidation (Zevin & Benowitz 1999). | Smoking increases clearance of propanolol by 77% (Zevin & Benowitz 1999). The clinical implication of increased blood drug levels is not well understood since recommended dosage varies from 80–640 mgs/day, however the clinical effect should be closely monitored. |
| | Verapamil | Verapamil is metabolised by CYP 1A2. | A 0·8 fold decrease in AUC (tau,ss) was observed for smokers. Dose should be closely monitored, especially in heavy smokers receiving a high dose of Verapamil (Fuhr *et al.* 2002). |
| Anticoagulant | Warfarin | Possible induction of multiple CYP enzymes (Evans & Lewis 2005). | Dose reductions of 14 and 23% were needed in individuals after smoking cessation. INRs should be closely monitored (Colucci & Knapp 2001, Evans & Lewis 2005). |
| Antiarrhythmic | Mexiletine*<br>Flecainide<br>Lidocaine | Cigarette smoking induces drug elimination through CYP 1A2 and selectively induces conjugation of mexiletine with glucuronic acid (Grech-Belanger *et al.* 1985). | Dosage may need to be decreased, but no specific recommendations available. Use caution with older adults taking Mexiletine. |
| Mental health /neurological medications | | | |
| Antianxiety | Diazepam* | Diazepam is a substrate of CYP 1A2 and CYP2C19. Smoking increases clearance up to 3-fold (Clinical Pharmacology 2008). Tobacco smoke accelerates the metabolism of diazepam's major active metabolite, N-desmethyldiazepam to oxazepam (Hansten & Horn 2006). | No studies recommend specific dose reductions, however the clinical effect should be closely monitored, especially in older adults. |
| Anti-migraine | Naratriptan | Naratriptan undergoes P450 oxidation (Sanders-Bush & Mayer 2006). | Tobacco smoking increases the clearance of naratriptan by roughly 30% (Amerge® package insert 2003). Increased plasma levels after smoking cessation might increase the incidence of CNS side effects (Dodick & Martin 2004). |
| Anti-psychotics | Clozapine<br>Olanzapine | Induction of Cytochrome P450 CYP1A2 (Jann *et al.* 1986, Meyer 2001, de Leon *et al.* 2005). Polymorphism of CYP 1A2 may confer a high inducibility of CYP1A2 by smoking (Bondolfi *et al.* 2005). | Case studies and a non-randomised study documented need for approximately 36% dose reduction of Clozapine and Olanzapine to avoid toxicity (Derenne & Baldessarini 2005). |
| Hypnotic | Ramelteon | Smoking is an inducer of the CYP1A2 isozyme, decreasing ramelteon efficacy (Clinical Pharmacology 2008). | Dosage may need to be decreased, but no specific recommendations are available. Special consideration for older adults as ramelteon plasma concentrations can be 97% higher in older adults (Rozerem® package insert 2006). |
| Antidepressants | Fluvoxamine | Fluvoxamine is metabolised by CYP 1A2 (Spigset *et al.* 1995). | Plasma area under the curve (AUC) after smoking is decreased by 30% and might increase after smoking cessation (Spigset *et al.* 1995). Close monitoring for adverse events is recommended. |
| | Amitriptyline* and other tri-cyclic antidepressants | Smoking increases the clearance of tricyclic antidepressants via hepatic microsomal enzymes (Clinical Pharmacology 2008) | No data to suggest dose reduction, but caution is advised. |

  

**Table 1** (Continued)

| Drug categories | Generic drug name | Mechanism of interaction | Evidence for dosage adjustment after smoking cessation |
|---|---|---|---|
| Alzheimer's | Rivastigmine | Cigarette smoking induces hepatic CYP450 microsomal enzymes (Clinical Pharmacology 2008). | Smoking cessation decreases Rivastigmine oral clearance by 23% (Exelon® package insert 2004). Decreased dose of approximately 23% may be needed. (Exelon® package insert 2004). |
| | Tacrine | Cigarette smoking induces hepatic CYP450 microsomal enzymes (Clinical Pharmacology 2008). | Serum concentrations are three-fold lower in smokers (Zevin & Benowitz 1999). Dose reduction of up to threefold may be needed. |
| Analgesic medications | | | |
| Opioid analgesics | Propoxyphene* | Tobacco smoking increases hepatic metabolism of propoxyphene although mechanisms are unclear; sudden smoking cessation may cause an increase in the effects of propoxyphene as hepatic enzyme activities return to normal. Nicotine replacement does not alter (Clinical Pharmacology 2008). | No data to base dosage recommendations is available, but caution advised with older adults. |
| Respiratory medications | | | |
| Bronchodilators | Theophylline | Induction of Cytochrome P450 CYP1A2 (Zevin & Benowitz 1999). | Quasi-experimental study demonstrated 36·6% decrease in clearance after smoking cessation. Nicotine gum had no effect. It was recommended that theophylline dose be decreased by 25–33% after smoking cessation (Lee *et al.* 1987). |
| Endocrine medications | | | |
| Anti-diabetic | Insulin | Tobacco smoking may reduce blood flow to the skin and subcutaneous tissue, slowing the absorption of insulin from injection sites. (Madsbad *et al.* 1980). Nicotine activates neuroendocrine pathways (e.g. increases in circulating cortisol and catecholamine levels) and may increase plasma glucose (Clinical Pharmacology 2008). | Insulin sensitivity increased significantly after smoking cessation in an open parallel study (Eliasson *et al.* 1997). No recommendations for dose reduction were found, however, diabetics who maintain tight control of their blood sugar levels should monitor blood glucose more frequently and should be prepared to decrease dose. |
| | Repaglinide Nateglinide | Nicotine activates neuroendocrine pathways (e.g. increases in circulating cortisol and catecholamine levels) and may increase plasma glucose (Clinical Pharmacology 2008). | Decreased dose may be needed, but no specific recommendations available. |
| | Pioglitazone Rosiglitazone | Nicotine may increase plasma glucose (see above). | Decreased dose may be needed, but no specific recommendations available. These drugs do not cause hypoglycemia when used alone, but may in combination with other agents. |
| | Metformin | Nicotine may increase plasma glucose (see above). | Decreased dose may be needed, but no specific recommendations available. Does not cause hypoglycemia when used alone, but may in combination with other agents. |
| | Glyburide, Glipizide & others | Nicotine may increase plasma glucose (see above). | Decreased dose may be needed, but no specific recommendations available. |
| Uncategorised medications | | | |
| Anti- amyotrophic lateral sclerosis | Riluzole | Possible induction of CYP 1A2 due to smoking (Tatro 2008). | Pharmacokinetic modeling showed a 36% increased clearance in smokers; clinical effect should be closely monitored (Bruno *et al.* 1997). |

*Drugs listed on Beer's List (Fick *et al.* 2003), meaning that the drugs should generally be avoided in persons 65 years or older because they pose unnecessarily high risk.

increase the incidence of CNS side effects such as decreased mental acuity, drowsiness, dizziness and somnolence (Dodick & Martin 2004). Smoking decreases efficacy of ramelteon through induction of CYP1A2, although this effect has not been quantified. Persons using ramelteon who stop smoking should be monitored for somnolence, dizziness and fatigue. Caution is particularly advised for older patients since systemic exposure to ramelteon is higher in older individuals (Clinical Pharmacology 2008).

Fluvoxamine inhibits the activity of hepatic isoenzyme CYP1A2; smokers have a 25% increase in metabolism of fluvoxamine over non-smokers (Clinical Pharmacology 2008). Effects of smoking cessation have not been described, but monitoring for somnolence is recommended. Clearance of rivastigmine is decreased by 23% after smoking cessation (Exelon® package insert 2004), so monitoring for GI upset, dizziness and cholinergic effects is recommended after smoking cessation. However, dose reductions of up to three-fold may be needed for patients stabilised on tacrine, since serum concentrations are three-fold lower in smokers (Zevin & Benowitz 1999).

### Analgesic medications

Clearance of propoxyphene is increased in smokers, although this effect has not been quantified (Clinical Pharmacology 2008). Patients who stop smoking while taking propoxyphene should be monitored for central nervous system (CNS) depression.

### Respiratory medications

A single quasi-experimental study documented a 36·6% decrease in clearance of theophylline after smoking cessation. It was recommended that theophylline dose be decreased by 25–33% after smoking cessation to maintain therapeutic drug levels in the narrow range of 10–20 μ/ml (Lee *et al.* 1987).

### Endocrine medications

Although CYP1A2 is not involved in metabolism of insulin and oral hypoglycemic (anti-diabetic) drugs, the elimination of elevated glucose levels caused by nicotine on neuroendocrine pathways may cause dangerous hypoglycemia in patients who are maintaining tight control of their diabetes. However, no studies were found to document this risk. It is recommended that glucose levels be carefully monitored whenever patients taking hypoglycemic drugs stop smoking.

## Discussion and conclusions

It is clear that smoking cessation can have an effect on drugs metabolised by CYP 1A2 as well as some other drugs. Although research has not documented appropriate post-smoking dose changes for many of these drugs, clinically significant drug interactions may be anticipated based on pharmacokinetic knowledge: 'The absence of evidence is not evidence of absence' (de Leon *et al.* 2005). Further research is warranted to clarify these effects. Drug metabolism changes related to smoking cessation could be particularly important in diabetics who are maintaining tight control or in older adults, whose drug metabolism is affected by aging and who are more likely to be taking multiple drugs.

Although no evidence of clinical problems and no dosage recommendations were found for propoxyphene, mexilitine, amitriptyline and diazepam, these have been identified as drugs that should be avoided in older adults because they pose unnecessarily high risks according to Beers criteria (Fick *et al.* 2003), supporting the need for caution when prescribing them for older adults who quit smoking.

### Relevance to clinical practice

Since population smoking rates remain high worldwide, it is important for health care providers in the community and in acute care settings to determine a patient's smoking status and to obtain a list of all current medications. Immediate dose reductions should be made whenever patients cease smoking under treatment with CYP1A2 metabolised drugs with a narrow therapeutic ratio such as olanzapine, clozapine and theophylline. Although an early warfarin study failed to document changes in prothrombin time, this study did find increased serum levels and decreased warfarin clearance rates of 13%, consistent with later case studies documenting increased INR and a need to adjust doses by 14 and 23%. Based on this evidence, health care providers should anticipate the need to decrease warfarin by 13–23% in persons who stop smoking. Careful monitoring for signs of overdose or increased adverse drug effects should be instituted for other drugs listed in this article, especially for older adults who use multiple medications. This recommendation has particular relevance for hospitalised patients who are abruptly subjected to involuntary smoking cessation due to the speed at which the induction of CYP1A2 dissipates.

## Contributions

Study design: SS, SY; data collection and analysis: SS, SY, IZ; and manuscript preparation: SS, SY.

  

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