

Graylands Hospital Drug Bulletin

Psychotropic drugs- *the effect of Smoking and Caffeine*

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Introduction

Both cigarette smoking and the consumption of caffeine can have a significant effect on the metabolism of a wide variety of drugs used to treat mental illness.¹ Cigarette smoke constituents have been shown to induce certain liver enzymes, which play a central role in drug metabolism, whereas caffeine can inhibit the metabolism of certain drugs through the competitive inhibition of such enzyme systems.^{1,2}

Such interactions are clinically relevant and may influence both the effectiveness and safety of psychiatric medication.¹ In addition, health-care professionals are focused on the benefits and challenges of quitting smoking from the patient perspective, so might fail to consider the potential problems related to drug metabolism that can result from cessation of smoking.

In this bulletin, we review the impact of smoking and caffeine on psychiatric medication. This includes a detailed list of medications known to interact and suggests practical strategies on how to manage patients who change their smoking status or caffeine consumption.

Mechanisms for drug interactions with smoking

Tobacco smoke contains polycyclic aromatic hydrocarbons (PAHs) that induce (increase the activity of) certain hepatic enzymes CYP1A1, CYP1A2 and possibly CYP2E1 (CYP1A2 in particular).¹ Other compounds such as acetone, pyridine, heavy metals, benzene, carbon monoxide, may also interact with hepatic enzymes but their effects appear to be less significant.¹

The effect of smoking on hepatic enzymes is not related to the nicotine component of tobacco. Therefore, nicotine replacement therapy does not influence enzyme activity.¹

Many drugs are substrates for hepatic CYP1A2, and their metabolism can be induced in smokers, resulting in a clinically significant decrease in pharmacological effects.¹ Thus, smokers may require higher doses of drugs that are CYP1A2 substrates.

Antipsychotics

Clozapine and olanzapine

Cigarette smoking significantly induces the metabolism of both clozapine and olanzapine resulting in lower plasma concentrations.³ A cohort study of schizophrenia inpatients found that daily consumption of 7-12 cigarettes is sufficient for maximum induction of clozapine and olanzapine metabolism.³ This induction is clinically relevant, as smokers frequently require higher doses of these medications to achieve therapeutic effect.¹

Clozapine plasma levels have been found to be 50% lower in smokers than in non-smokers, and among patient demographic factors smoking is second in importance only to dose in its influence on serum clozapine levels.³ Interestingly, a small prospective open study (55 smokers; 15 non-smokers) has suggested that smokers may respond better to clozapine than non-smokers and clozapine may reduce smoking frequency.⁴

Olanzapine's clearance is increased and its half-life shortened in smokers. Smokers have been shown to have an approximately five-fold lower dose corrected steady-state plasma olanzapine concentration compared with non-smokers.³ Another study found the dose-corrected plasma concentration of olanzapine to be 12% lower in patients who smoke.⁵

Chlorpromazine (CPZ)

Cigarette smoking has been shown to increase CPZ clearance with smokers experiencing less sedation and orthostatic hypotension compared with non-smokers.¹ A case report of a 25-year old patient controlled on CPZ described more severe side effects following abrupt cessation of smoking, which was correlated with an increase in plasma CPZ concentration. The patient's serum CPZ concentration was 10 mcg/L during her smoking history and 106 mcg/L within one week after smoking cessation.⁶

Fluphenazine

The effect of smoking on drug clearance in psychiatric inpatients maintained on oral fluphenazine and fluphenazine decanoate was described in a retrospective longitudinal review.⁷ Plasma concentrations were significantly lower (by around 50%) and clearance was significantly higher

in the smoking group compared with the non-smoking group.⁷

Haloperidol

Steady-state plasma concentrations of haloperidol and its metabolite (reduced haloperidol) were investigated in 50 patients with schizophrenia (23 smokers, 27 non-smokers) in a retrospective, longitudinal review.⁸ Smokers had significantly lower haloperidol and reduced haloperidol plasma concentrations than non-smokers.⁸ Clearance of haloperidol was significantly greater in smokers compared to non-smokers.⁸

Antidepressants

Duloxetine

Fric and colleagues examined the effects of smoking on serum duloxetine levels in 28 patients under naturalistic conditions.⁹ Smokers were found to have significantly lower serum concentrations (approx 50%) than non-smokers. They suggest that in smokers, higher doses of duloxetine seem to be necessary to reach adequate serum levels.

Fluvoxamine

Spigset *et al* investigated the pharmacokinetics of a single dose of fluvoxamine 50 mg in 12 smokers and 12 non-smokers.¹⁰ Smokers had significantly lower serum concentrations (about 30%) of fluvoxamine than non-smokers after a single oral dose. The authors suggested that there might be a need for higher dosages of fluvoxamine in smokers than in non-smokers.¹⁰

Other SSRIs

The effects of smoking on the metabolism of other SSRIs have not been extensively evaluated. However, based upon the CYP isozyme information smoking would not be expected to significantly affect their plasma levels.¹

Mirtazapine

A recent study in 95 patients with depression reported that smokers had significantly lower plasma mirtazapine concentrations (approx 25% lower) than non-smokers, confirming the role of CYP1A2, which is induced by cigarette smoking, in the metabolism of mirtazapine.¹¹

Tricyclic antidepressants (TCA)

Studies on the effects of smoking on TCA levels have shown inconsistent findings. For example, two published studies did not find any correlation between smoking and the plasma concentrations of either amitriptyline or imipramine.^{12,13} However, Linnoila *et al* found that smokers had significantly lower mean nortriptyline and mean combined amitriptyline and nortriptyline concentrations than did non-smokers.¹⁴

Imipramine plasma concentrations were shown to be lower in smokers compared with non-smokers.¹⁵ However, they were still within the therapeutic range, and the free concentrations were not measured. The clinical significance of this interaction remains unclear.

Mean plasma concentrations of clomipramine have been shown to be significantly lower in smokers compared with non-smokers.¹⁶ In addition, it has been shown that clomipramine is better tolerated in smokers than non-smokers.¹⁶

Benzodiazepines

Early studies suggested an increased clearance of benzodiazepines in smokers.¹⁷ Plasma levels may be reduced by 0-50% depending upon the drug and smoking status.¹⁷ In addition, smokers taking benzodiazepines appear to experience less sedation and drowsiness compared with non-smokers.¹⁷ This is most likely due to the fact that nicotine activates the central nervous system.¹⁷ Therefore, prescribers should be aware that when patients taking benzodiazepines stop smoking, there is an increased risk of CNS depression.

Effects of smoking cessation on psychiatric medication

If smokers who are stable on a drug metabolised by CYP1A2 enzymes stop smoking, enzyme activity reduces over several days, less medication is metabolised and plasma levels increase. Toxic levels of medication can accumulate in a matter of days.

Stopping smoking while on clozapine and olanzapine can be dangerous. Serum levels of clozapine can rise by approximately 70% in 2-4 weeks after smoking cessation.¹⁸ A case report has described the occurrence of clozapine-induced seizures in a man who abruptly stopped smoking.¹⁹

In another patient, admission to intensive care was required for the management of severe hypotension after cessation of smoking whilst receiving clozapine. There has also been reports of urinary hesitancy, constipation, sexual dysfunction, pneumonia and confusion in patients who stop or reduce smoking whilst taking clozapine.²⁰

A recent study reported the case of a patient who, after reducing his tobacco consumption from 40 cigarettes to 10 cigarettes, showed severe extrapyramidal symptoms while receiving olanzapine treatment.²¹ It is therefore recommended that plasma levels are measured before smoking cessation and, for clozapine, olanzapine and fluphenazine, the dose of medication is gradually reduced to 75% over the subsequent week and a further plasma level is taken one week after cessation.¹⁸

Table 1: Psychotropic drugs affected by smoking status¹⁸

Drug	Effect of smoking	Action to be taken on stopping smoking
Benzodiazepines	Smokers may require larger doses to achieve sedative effects equivalent to those in non-smokers. May be due to increased clearance or nicotine CNS stimulation. Plasma levels may be reduced by 0-50% depending upon the drug and smoking status	Monitor closely and consider dose reduction by up to 25% over one week.
Carbamazepine	Unclear, but smoking may reduce plasma levels to a small extent. Carbamazepine may lower nicotine levels leading to increased smoking	Monitor for changes in severity of adverse effects
Chlorpromazine	Plasma levels reduced. Clinical significance is unclear. Reduced sedation & hypotension possible in smokers	Monitor closely, consider dose reduction
Clozapine	Reduces plasma levels by up to 50%	Take plasma level before stopping smoking. On stopping, reduce dose slowly (over a week) until around 75% of original dose reached. Repeat plasma level one week after stopping. Anticipate further dose reductions
Duloxetine	Plasma levels may be reduced by up to 50%	Monitor closely. Dose may need to be reduced
Fluphenazine	Reduces plasma levels by up to 50%	Reduce dose by 25% upon stopping smoking
Fluvoxamine	Plasma levels reduced by around a third	Monitor closely. Dose may need to be reduced
Haloperidol	Reduces plasma levels by around 20%	Reduce dose by around 10% and monitor carefully
Mirtazapine	Reduces plasma levels by around 25%	Monitor closely. Dose may need to be reduced
Olanzapine	Reduces plasma levels by up to 50%	Take plasma level before stopping. On stopping, reduce dose by 25% over one week.
Tricyclic antidepressants	Plasma levels reduced by 25-50%	Monitor closely; consider reducing dose by 10-25%

The change in plasma clozapine levels can (in 80% of cases) be predicted by using the formula:

$$\text{Non-smoking level} = 45.3 + (1.474 \times \text{smoking level})^{22}$$

Nomograms also exist to help predict doses in people on clozapine who smoke.²²

For benzodiazepines, doses may be reduced by up to 25% in the first week, and for tricyclic antidepressants dose reductions of 10-25% over the first week may be required.¹⁸ For all these medications, further dose reductions may be needed.

Table 2: Interactions of caffeine¹⁸

Drug	Effect of caffeine on drug
Clozapine	Plasma levels increased by up to 60%
Olanzapine	Increased risk of toxicity (theoretical)
Lithium	High doses of caffeine may reduce lithium levels. Lithium levels may rise upon caffeine withdrawal
SSRIs	Large doses of caffeine may increase risk serotonin syndrome
Benzodiazepines	Reduced efficacy. Caffeine may bind to GABA receptor, acting as an antagonist.
MAOIs	Caffeine may enhance stimulant CNS effects
Imipramine/Clomipramine	May increase plasma levels

Caffeine: the forgotten variable

Patients with mental illness have been reported to drink large amounts of caffeinated drinks. Possible explanations for this include polydipsia with schizophrenia, and compensating for the side effects of antipsychotics such as dry mouth and sedation.² Another possible reason may be due to the fact that smoking increases the elimination of caffeine (note: when smoking is ceased, caffeine levels rise accordingly and there is an increased risk of CNS related adverse effects). Thus individuals who smoke may use more caffeine to make up for increased elimination of caffeine due to heavy smoking.²

Mechanism of drug interactions with caffeine

The most likely explanation is competitive inhibition of CYP1A2 by caffeine. In addition, high doses of caffeine may inhibit benzodiazepine receptor binding. Long-term use of caffeine leads to the up-regulation of 5HT1, 5HT2, nicotinic, muscarinic and GABA receptors and down-regulation of Beta-adrenergic receptors.²

Clozapine

Caffeine increases serum clozapine levels. A study by Hägg *et al* reported a 19% average increase in serum clozapine levels with doses of 400-1000 mg/d of caffeine in healthy subjects.²³ Two case studies have reported significant fluctuations in clozapine levels with the consumption and cessation of lower doses of caffeine (150-180 mg/d).²⁴ A study by Carillo *et al* described a 50% reduction of serum clozapine levels following the removal of an average of 160mg/d caffeine.²⁵

Lithium

A study of 11 patients on lithium carbonate (600 to 1200 mg/day) who were regular coffee drinkers (4-8 cups/day) showed that when coffee was withdrawn, their serum lithium levels rose by an average of 24%.²⁶ These findings are consistent with another report of two patients who had an aggravation of their lithium-induced tremor when they stopped taking caffeine.²⁷

Benzodiazepines

Caffeine has been shown to counteract the drowsiness induced by diazepam.¹⁸ There is also evidence that caffeine and clonazepam or triazolam have mutually opposing effects. Caffeine may interact similarly with zopiclone.¹⁸

Fluvoxamine

The clearance of caffeine is considerably reduced by fluvoxamine (approx 80%).² An increase in the stimulant and side effects of caffeine would be expected.

Conclusion

We have shown that smoking and caffeine affects the metabolism of a wide variety of psychiatric drugs. In addition, serious adverse consequences have occurred in individuals who suddenly stop or reduce the amount they smoke. This is particularly relevant given that many hospitalised patients are forced to reduce their cigarette intake due to non-smoking hospital policies.

It would be prudent to always enquire about smoking status and caffeine intake and to monitor patients closely. Side effect rating scales, such as the Glasgow Antipsychotic Side Effect-Scale (GASS)²⁸ for clozapine, prompt health professionals to enquire and record both smoking and caffeine intake. Such rating scales can then be used on an on-going basis and are a valuable aid for anticipating future problems.

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References are available on request.

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