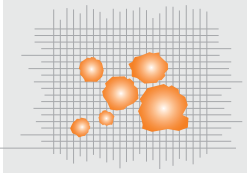
The dangers of smoking cessation… and medicines



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The problem

Approximately 17% of people over 15 years old in New Zealand smoke tobacco. The highest prevalence is in the more deprived populations.[1] Striving for New Zealand to be smoke-free by 2025 means that there is still a large number of people who will be giving up smoking. This is positive, but we need to be cognisant of the potential harm from smoking cessation for those people on some medicines, particularly clozapine and olanzapine.

Polycyclic aromatic hydrocarbons (PAHs), which are found in tobacco smoke, are potent inducers of cytochrome P450 1A2 enzyme CYP1A2, and CYP1A1, CYP2B6 and to a lesser extent CYP2E1. As CYP1A2 metabolises medicines such as clozapine, olanzapine and theophylline, induction by smoking means that the serum concentrations for an equivalent dosage is lower in smokers than non-smokers.[2–5] Smoking seven to 12 cigarettes daily appears to be sufficient to cause the maximal induction of CYP1A2 and hence concern with stopping smoking, even from relatively low cigarette consumption.[6]

While clozapine and olanzapine are of primary concern because of toxicity—especially clozapine—other medicines are metabolised by CYP1A2, but may have alternative metabolism pathways. As a result, the impact is somewhat less, or the medicines themselves are less toxic in higher dose, as they have a larger therapeutic index.

There are also interactions that are not related to the enzyme metabolism but are more due to the effect of smoking itself, such as smoking reducing the subcutaneous absorption of insulin or impairing blood pressure control due to vasoconstriction.

The management: smoking cessation for those on olanzapine or clozapine

Abrupt smoking cessation

Smoking reduces serum concentrations of clozapine and olanzapine 36–50%.[6,7]

When a person stops smoking, there is a time delay while the excess induced CYP1A2 enzyme is eliminated. This enzyme has a half-life of approximately 40 hours and, hence, the effect of the reduced enzymes will become apparent starting at about three to five days post–smoking cessation. Empirically, there should be a pre-emptive dosage reduction by 30–40% three to five days after stopping smoking, and monitoring of the serum concentration in seven days.[8] Close contact is required with the patient because of the risk of stopping and starting smoking, and the dose titration and clinical monitoring that is required with this.

The interaction is due to the smoke from cigarettes and so a switch from smoking to nicotine replacement therapy equates to abrupt cessation of smoking.

Smoking seven to 12 cigarettes daily appears to be sufficient to cause the maximal induction of CYP1A2

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KEY POINTS

- Smoking reduces serum concentrations of clozapine and olanzapine 36–50% and hence stopping smoking can result in toxic, and potentially fatal, adverse effects.
- Smoking more than seven cigarettes a day is likely to result in a significant interaction with clozapine and olanzapine.
- Using nicotine replacement therapy has the same effect as not smoking for drug interactions, as the interaction is usually due to the smoke rather than the nicotine.
- For people on olanzapine and clozapine, check their smoking status at every consultation and take a planned, intensive approach to smoking cessation.

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Table 1. Smoking and medicines interactions

Medicine	Effect of smoking	If smoking stopped	Actions
Major interaction: extreme caution if starting or stopping smoking			
Clozapine	Increases metabolism	Serum concentrations likely to increase	Reduce dose 30–40% three to five days after smoking cessation. Check serum concentrations after one week
Olanzapine	Increases metabolism	Serum concentrations likely to increase	Reduce dose 30–40% three to five days after smoking cessation. Monitor clinically
Theophylline	Increases metabolism	Serum concentrations likely to increase	Requires dose reduction. Be wary of nausea, palpitations
Thioridazine	Increases metabolism	Serum concentrations likely to increase	Reduce dose 30–40% three to five days after smoking cessation. Monitor clinically
Moderate interaction: be very wary if starting or stopping smoking			
Caffeine	Increases metabolism	Caffeine will have a greater effect	May notice tremors, headache. Try and also reduce caffeine intake
Chlorpromazine	Increases metabolism	May get some increase in serum concentration	Monitor for increased drowsiness and extrapyramidal effects
Fluphenazine	Increases metabolism	May get some increase in serum concentration	Monitor for increased drowsiness and extrapyramidal effects
Haloperidol	Increases metabolism	May get some increase in serum concentration	Monitor for increased drowsiness, extrapyramidal effects and hypotension. May require a dose reduction
Insulin	May increase insulin resistance, reduce absorption	Improved glycaemic control but risk of hypoglycaemia	Monitor blood glucose more closely and be alert for hypoglycaemia. May need dose reduction
Methadone	Potential increased metabolism	Potential for increased effect of methadone	Monitor for adverse effects of methadone (sedation, respiratory depression) as dose reduction may be necessary
Minor interaction			
Benzodiazepines	Increased metabolism	May increase sedation	Effect through glucuronidation induction rather than CYP1A2
Tricyclic antidepressants	Increased metabolism	May increase sedation	Likely minor effect
Blood pressure lowering	Pharmacodynamic effect	Reduced blood pressure	May be a longer-term change
No apparent interaction			
Quetiapine			
Risperidone			
Ziprasidone			
Conflicting reports			
Clopidogrel			Limited information
Phenytoin			Conflicting reports
Valproate			Conflicting reports
Warfarin			Conflicting reports. Check INR weekly for two weeks

Slow reduction in cigarettes

This is pharmacokinetically more difficult to address, but while still smoking 10 or more cigarettes a day, CYP1A2 enzyme induction is still likely. Monitor clinically for adverse effects, preferably with weekly contact, and monitor serum concentrations according to the rate of reduction of cigarettes. If a person reduces from 20+ cigarettes a day to 10 a day within one week, then check the serum concentration about one week later.

Once a person is smoking less than 10 cigarettes a day, the extent of enzyme induction will be reducing and closer clinical monitoring is required with a dosage reduction.

Passive smoking

This is a confounder that has not been investigated.

Smoking cessation and other medicines

Clozapine and olanzapine are the most problematic medicines with respect to smoking cessation. However, it is important to manage and monitor smoking cessation for patients taking other medicines where a major or moderate interaction is expected (see Table 1). Dose reduction may be necessary in some cases.

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