Tees, Esk and Wear Valleys NHS
NHS Foundation Trust

Medication Safety Series: MSS 25

Tobacco smoking, smoking cessation & psychotropic drugs

- Patients must be advised to notify prescribers **ASAP** of any changes to smoking status.
- ***Why?*** A number of psychotropic drugs, and some used for physical health conditions, can be affected by changes in smoking status (See **Appendix 1**); the most significantly affected psychotropic drugs are **clozapine** and **olanzapine**.
- ***How?*** Some components of tobacco smoke (not nicotine) induce hepatic cytochrome P450 enzymes, increasing metabolism of their substrates; of these CYP1A2 is the most clinically significant, as it metabolises many drugs. (See blue box below for advice re: vapes)
- ***So what?*** A change in smoking status can significantly impact on drug metabolism with the potential to reduce the therapeutic effect (if smoking more), or cause significant toxicity (if smoking less), e.g. increased sedation, muscle stiffness, tremor, dizziness, hypersalivation & constipation with clozapine
- ***When?*** As few as 7-12 cigarettes/day is sufficient for a full effect on CYP1A2 activity and it takes around 8 days for CYP1A2 activity to return to normal following smoking cessation
- ***What do patients need to know?*** Information on the impact of smoking on clozapine/olanzapine is available as handy fact sheets via the choice and medication website.

Clozapine *Target level = 350-500 micrograms per litre (trough) But……. always treat the patient, not the level*

- Plasma levels in a smoker taking a constant clozapine dose are on average 50% lower than non-smokers on the same dose
- Stopping or starting smoking suddenly can result in plasma level changes within 3-5 days.
- In patients also taking valproate, the enzyme induction effects of smoking may be stronger & the effect on plasma levels more marked on smoking cessation

If a patient stops smoking:

- Take a plasma level (prior to cessation where possible) and check for any adverse effects.
- **At the point of stopping smoking or as soon as possible afterwards:** Check for any recent levels at current dose. Based on information on levels and patient risks, consider reducing clozapine dose by 25% gradually over one or two weeks.
- Re-check plasma level at next appointment (usually in 2-4 weeks)
- Make further dose adjustments dependent on emerging side effects or toxicity.
- Further plasma levels & dose adjustments may be necessary.
- Advise patient to be alert for increased adverse effects which may indicate toxicity & report them to their HCP ASAP e.g. ↑sedation, hypersalivation, constipation & dizziness.

If a patient restarts smoking*:

- Take a plasma level prior to restarting (if possible).
- Increase clozapine dose to previous "smoking dose" over one or two weeks.
- Re-check plasma level & adjust dose as appropriate, usually at next appointment in 2-4 weeks.

**if clozapine has been started in a smoker while an inpatient, dose increase may be required after discharge when smoking resumes*

Olanzapine and Haloperidol

Clearance higher & half-life shorter in smokers compared to non-smokers probably due to CYP induction.

- Smoking cessation can lead to toxicity through removal of CYP1A2 induction.
- Dose reduction of 30-50% may be necessary if a patient stops smoking.

If a patient stops smoking:

- **At the point of stopping smoking,** offer information leaflet to outline side effects
- Advise patient to be alert for increased adverse effects which may indicate toxicity, e.g. ↑sedation, muscle stiffness, tremor & dizziness, and report them to their HCP ASAP.
- Monitor for effectiveness & for adverse effects.
- If quit attempt successful at 4 weeks (or sooner if side- effects present), reduce dose by 25%*.
- Make further dose adjustments where appropriate if side effects still present.

If a patient restarts smoking:

- Increase dose to previous "smoking dose" over one week.
- Monitor for effectiveness & for adverse effects.
- Make further dose adjustments where appropriate.

**if olanzapine has been started in a smoker while an inpatient, dose increase may be required after discharge when / if smoking resumes*

Please note: Only tobacco (or cannabis) smoking (including passive smoking) induces hepatic enzymes; cannabis vaping devices may also have an effect. Nicotine replacement, nicotine vaping devices & electronic cigarettes have no effect on enzyme activity.

Title	MSS25: Tobacco smoking/smoking cessation & psychotropics v2	
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Appendix 1: Smoking and the effect on medicines including clozapine (From TEWV Stop Smoking Products Guidance)

The MHRA advised in October 2009 that the most important medicines to consider in those who smoke, or are trying to quit, include THEOPHYLLINE, OLANZAPINE, CLOZAPINE, CAFFEINE and WARFARIN. In 2020, the MHRA issued a reminder to prescribers of the impact of smoking/changes to smoking status on CLOZAPINE.

Drug	Effect of smoking	Action to be taken on stopping smoking	Action to be taken on re-starting smoking
Antipsychotics			
Chlorpromazine	Plasma levels ↓ (Varied estimates of exact effect)	Monitor closely, consider ↓dose	Monitor closely; consider re-starting previous smoking dose
Clozapine	Plasma levels ↓ by up to 50%; plasma level reduction may be greater in those receiving valproate	Take plasma level before stopping; On stopping ↓ dose gradually (over 1 week) until around 75% original dose reached (i.e., 25% reduction). Repeat plasma level 1 week after stopping & anticipate further dose reductions.	Take plasma level before re-starting. Increase dose to previous smoking dose over 1 week. Repeat plasma level.
Fluphenazine	Plasma levels ↓ by up to 50%	On stopping, reduce dose by 25%. Monitor carefully over 4-8 weeks; consider further dose reductions	On re-starting, increase dose to previous smoking dose
Haloperidol	Plasma levels ↓ by around 25-50%	Reduce dose by around 25%. Monitor carefully. Consider further dose reductions	On re-starting, increase dose to previous smoking dose over 1 week.
Loxapine (Inhaled)	Half-life ↓ from 15.7 hours to 13.6 hours	Monitor	Monitor
Olanzapine	Plasma levels ↓ by up to 50%	On stopping reduce dose by 25%. Monitor carefully. Consider further dose reductions.	Increase dose to previous smoking dose over 1 week.
Risperidone/paliperidone	Active moiety concentrations probably lower in smokers. Minor effect (possibly via induction of CYP3A4)	Monitor closely	Monitor closely
Zuclopenthixol	Unclear, but effect probably minimal	Monitor	Monitor

Drug	Effect of smoking	Action to be taken on stopping smoking	Action to be taken on re-starting smoking
Antidepressants			
Agomelatine	Plasma level ↓	Monitor closely; may need to ↓ dose	Consider re-introducing previous smoking dose
Doxepin	Plasma levels may be ↓ by up to 25% (levels of nordoxepin metabolite increased)	Monitor closely; may need to ↓ dose	Consider re-introducing previous dose
Duloxetine	Plasma levels may be ↓ by up to 50%	Monitor closely; dose may need to be reduced	Consider re-introducing previous smoking dose
Escitalopram	In practice smokers have lower blood levels despite being given higher doses. Reduction in levels may be up to 50% (possibly via induction of CYP2C19)	Monitor closely, consider 25% dose ↓	Monitor closely. Reinstate smoking dose.
Fluvoxamine	Plasma levels ↓by around 1/3	Monitor closely; dose may need to be reduced	Dose may need to be increased to previous level
Mirtazapine	Unclear, but effect probably minimal	Monitor	Monitor
Trazodone	Around 25% reduction	Monitor for increased sedation. Consider dose reduction.	Monitor closely, consider increasing dose.
Tricyclic antidepressants	Plasma levels ↓ by 25-50%	Monitor closely. Consider reducing dose by 10-25% over 1 week. Consider further dose reductions.	Monitor closely, consider re-starting previous smoking dose.
Other Psychotropics			
Benzodiazepines	Plasma level ↓ by 0-50%; depends on drug/smoking status.	Monitor closely, consider ↓ dose by up to 25% over 1 week	Monitor closely; consider re-starting “normal” smoking dose
Carbamazepine	Unclear; may ↓ levels to a small extent	Monitor for changes in severity of adverse effects	Monitor plasma levels

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