Smoking Cessation – Effect on Psychotropic Medication including Clozapine

Summary.
A guide to the adjustment of dose in patients who stop smoking – e.g. on admission to an inpatient unit.

Background.
The hydrocarbons in tobacco smoke induce the production or activity of various liver enzymes, in particular cytochrome CYP1A2, an enzyme associated with the metabolism of several psychotropic drugs including clozapine. Therefore, in response to smoking cessation it is possible that the metabolism of these drugs will decrease and plasma levels will rise. This is particularly the case for clozapine where it is possible that plasma levels may be elevated to toxicity.

Note – CYP1A2 activity is affected by hydrocarbons and not by nicotine. Therefore nicotine replacement therapy (NRT) will not affect drug metabolism and there are no known interactions between NRT and drug therapy.

Drugs Most Affected.

<table>
<thead>
<tr>
<th>Plasma level of these drugs:--</th>
<th>Psychotropic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is likely to rise, therefore</strong>...</td>
<td>chlorpromazine, fluphenazine, haloperidol, olanzapine, duloxetine, fluvoxamine, clozapine – see overleaf.</td>
</tr>
<tr>
<td>a dose reduction may be required. The patient must be monitored for adverse effects and plasma drug levels should be monitored if appropriate</td>
<td></td>
</tr>
<tr>
<td><strong>May possibly rise, but...</strong></td>
<td>flupentixol, zuclopenthixol, trifluoperazine, mirtazapine, tricyclic antidepressants, lamotrigine, valproate, most benzodiazepines, zolpidem, propranolol</td>
</tr>
<tr>
<td>this is not generally found to be clinically significant. If adverse effects occur, consider decreasing dose.</td>
<td></td>
</tr>
<tr>
<td><strong>Is unlikely to rise, therefore...</strong></td>
<td>amisulpride, aripiprazole, quetiapine, risperidone, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, moclobemide, reboxetine, venlafaxine, carbamazepine, chlor Diazepoxide. (Note – lithium levels may reduce).</td>
</tr>
<tr>
<td>no interaction is expected. However, data are often limited so patients should be monitored for adverse effects.</td>
<td></td>
</tr>
</tbody>
</table>

The most significant effects on plasma levels are seen with clozapine and olanzapine where increases of up to 70% and 20% respectively have been reported. For olanzapine patients, a reduction in dose of 2.5 – 5mg may be indicated. For clozapine patients far more drastic dose reductions may be necessary, as described overleaf.

Action recommended on admission / assessment.
- Ascertain pre-admission smoking status and recent medication compliance
- Determine effect of smoking cessation from the table above
- Consider adjustment of dose, based also on age, hepatic function, and the time delay for drug plasma level changes to occur – usually not within the first 7 days. Continue to monitor for emergence of adverse effects
- Ascertain and monitor smoking status on leave / discharge. Readjust dose if indicated

If you require this document in an alternative format, i.e. easy read, large text, audio or Braille please contact the pharmacy team on 01243 623349.
For clozapine:

1. **Review** latest (outpatient) serum clozapine levels (if available) and order a new baseline serum clozapine level as soon as practicable. *(Note – no ‘call-out’ is required, as dose reduction need not be immediate. Arrange bloods in normal ‘office hours’).*

2. **Review** side-effects history and, if possible, check against the serum clozapine levels at which they occurred.

3. **Assess** the risk of toxicity (i.e. if level exceeds 1000ng/ml) by estimating the non-smoking serum clozapine level using the formula below:

   \[
   \text{Serum clozapine}^{(\text{Non-smoker})} = [1.5 \times \text{Serum clozapine}^{(\text{Smoker})}] + 50
   \]

   *e.g. smoking level of 500ng/ml gives a non-smoking level of 800ng/ml*

   **Note** The formula is considered to give a suitably accurate result in approximately 80% of cases. However, in patients with higher smoking clozapine levels or doses, (e.g. above 700ng/ml or above 700mg daily), the CYP1A2 enzyme may have been saturated resulting in much higher rates of metabolism. Greatly increased levels may then occur in these patients when they stop smoking and the formula may be wildly inaccurate.

4. **Set a target** (non-smoking) serum clozapine level, taking into consideration the patient’s current condition and clinical response to current dose / level. If indicated, adjust the clozapine dose accordingly. *(Note – if compliance has been poor prior to admission, the baseline level may be artificially low. This should be taken into consideration).*

   For example

   Smoker admitted on clozapine 600mg daily and serum level found to be 480ng/ml. Compliant with medication but clinically unwell on this dose and considered to need a higher level. Estimated serum level on cessation of smoking is \((1.5 \times 480) + 50 = 770\text{ng/ml}\). If clinician considers that a target serum level of 770ng/ml is appropriate then no adjustment of dose may be necessary. However, if it is felt that the target level should be in the region of 600ng/ml, then the patient’s dose may need reducing to 450mg or 475mg daily. For levels above 500ng/mL consider seizure prophylaxis.

5. Necessary reductions in daily dose should normally be made at a rate of approximately 10% per day.

6. If possible, **monitor** serum clozapine level at day 3 and then weekly (until stabilised to target level). Also, pre-discharge level (unless done in previous 48 hours).

7. **Monitor** for adverse effects – bearing in mind that some may take as long as 2 to 3 weeks after adjustment of dose to become apparent.

8. **On discharge or leave**, reassess patient’s likelihood to recommence smoking and the potential reduction in serum clozapine level in response. If this occurs it is likely that the clozapine dose will have to be increased.

9. **Post-discharge**, where possible, monitor serum clozapine level once each week, (or fortnightly if total dose change was less than 20%), until stable.

**References:**
Psychotropic Drug Directory 2014 – S.Bazire

Original version: April 2007    Reviewed: January 2011 and July 15    Next review: July 2018