



Schizophrenia and Smoking

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- Smoking induces the CYP1A2 enzyme, leading to reduced levels of olanzapine, clozapine, and other drugs metabolized by CYP1A2.
- This article gives guidance on clinical issues that may arise in the treatment of patients with schizophrenia who smoke.

Mr B is a 25-year-old outpatient. He has been newly diagnosed with schizophrenia.

What lifestyle habit should be assessed before starting the patient on antipsychotic medication?

Guidance. Smoking behavior should be assessed in all patients, irrespective of diagnosis, because smoking adversely affects a wide range of health outcomes. Smoking is common in schizophrenia,¹ and in such patients is associated with an additional concern: it induces the metabolism of olanzapine and clozapine, thereby reducing the chances of benefit with standard doses of these drugs.

The cytochrome P450 (CYP) 1A2 enzyme plays an important (although not exclusive) role in the metabolism of olanzapine² and clozapine.^{2,3} Carcinogenic polycyclic aromatic hydrocarbons (and not nicotine) in cigarette smoke are potent inducers of CYP1A1, 1A2, and possibly 2E1, as well.⁴ So, in heavy smokers, heightened CYP1A2 activity would result in diminished drug levels⁵ and hence potentially lower efficacy of olanzapine and clozapine. Clinicians would therefore need to be aware of this interaction in heavy smokers who require antipsychotic medication.

Action

Mr B was prescribed risperidone but showed little response despite 8 weeks of treatment with this drug at a dose of 4–6 mg/d. He admits to smoking about 10 cigarettes per day.

Is there a risk that this patient's level of smoking would have an impact on the metabolism of olanzapine if risperidone were replaced by olanzapine?

Guidance. The answer to this question would probably vary with the tar content in the brand of cigarettes smoked. However, in a pharmacokinetic study of the dose-dependent effects of cigarette smoking on serum olanzapine and clozapine levels, Haslemo et al⁶ found that smoking just 7–12 cigarettes per day sufficed for maximum induction of drug metabolism; in nonsmokers relative to smokers, the concentration-to-dose ratio was 50% higher for clozapine and 67% higher for olanzapine. Haslemo et al⁶ therefore concluded that the target doses of these drugs should be increased by about 50% in those who smoke at this level or higher (ie, 7 or more cigarettes a day).

Follow-Up

Mr B failed to respond to olanzapine despite 8 weeks of treatment at a suitably high dose (30 mg/d). He was therefore prescribed clozapine and was eventually satisfactorily stabilized on this drug at a dose of 450 mg/d. However, he continued to smoke. After much encouragement, he agreed to try quitting the habit. Bupropion was initiated, and a quit-smoking date was set.

In this column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to JCP readers in psychiatric and general medical settings.



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What could be the clinical consequences of smoking cessation in this patient?

Guidance. Smoking cessation is associated with the cessation of CYP1A2 induction and with a consequent rise in clozapine levels in patients who are receiving this drug. Patients may experience clozapine-related adverse effects and even clozapine toxicity if the dose of the drug is not compensatorily decreased.⁷ In the case of Mr B, there is also the risk of additive lowering of the seizure threshold by bupropion⁸ and the higher levels of clozapine,⁹ resulting in an increased risk of seizures.

If Mr B stops smoking, when would the induction of clozapine metabolism wear off?

Guidance. Faber and Fuhr¹⁰ showed that, in heavy smokers (20 or more cigarettes per day) who quit smoking, the apparent half-life of CYP1A2 activity decrease was 39 (27–54) hours. Although Mr B is not a heavy smoker, it might be prudent to monitor him for clozapine-related emergent adverse effects starting 1 to 2 days after smoking cessation.

What are the clinical features of rising clozapine levels or clozapine toxicity for which Mr B should be monitored?

Guidance. When clozapine-treated patients quit smoking, possible clozapine-related emergent adverse effects⁵ include

- worsening of psychiatric symptoms
- somnolence
- hypersalivation
- extreme fatigue
- extrapyramidal effects
- seizures

To avoid the risk of clozapine-related adverse effects, it is logically advisable to reduce the dose of clozapine when Mr B quits smoking. How should this be done?

Guidance. Faber and Fuhr¹⁰ suggested that the dose of CYP1A2 substrates should be reduced by about 10% each day until the fourth day after smoking cessation; this dose reduction should be accompanied by therapeutic drug monitoring. Lowe and Ackman⁵ opined that, after smoking stops, the dose of clozapine will need to be reduced by about 30%–40% to achieve precessation clozapine concentrations. Should Mr B resume smoking at a later date, the dose of clozapine would need to be compensatorily increased.

Parting Notes

1. The study of Haslemo et al⁶ was not designed to assess the metabolic effects of fluctuations in the level of smoking in individual subjects. It is possible that such fluctuations may result in fluctuations in levels of CYP1A2 substrates such as clozapine and olanzapine and hence in fluctuations in the adverse effects of these medications. Additionally, the efficacy of clozapine or olanzapine may diminish if smoking levels increase and are maintained at higher levels. This means that

smoking behavior should be assessed not only at the time of initiation of olanzapine or clozapine but also throughout the course of therapy with these drugs.

2. Bupropion is a safe and effective treatment for smoking cessation in schizophrenia.¹¹ Mr B was scheduled to quit smoking with the help of bupropion, which inhibits CYP2D6.¹² Although CYP1A2 is the principal CYP enzyme involved in the metabolism of clozapine, CYP2D6 also plays a role.² Therefore, smoking cessation (resulting in decreased induction of CYP1A2) and initiation of bupropion (resulting in inhibition of CYP2D6) could have additive effects in raising clozapine levels and hence the risk of clozapine adverse effects and toxicity.
3. Mr B quit smoking voluntarily. What if, instead, he had been admitted to the hospital for some reason such as medical investigations or minor surgery? Most hospitals are smoke-free zones, and so Mr B would undergo forced abstinence from smoking during his inpatient stay; however, clozapine therapy would most likely be continued. In such an event, all that was discussed in the context of voluntary quitting would still apply. In many parts of the world, the psychiatric team may not be brought into the picture when such medical admissions occur; therefore, smokers who receive clozapine (and their families or significant others) should know about the interaction between smoking and clozapine.
4. CYP1A2 probably plays but a minor role in the metabolism of haloperidol^{13,14}; nevertheless, smoking has been suggested to lower haloperidol levels.¹⁵ Thiothixene is metabolized by CYP1A2 and 2D6,¹⁶ and fluphenazine is metabolized by CYP2D6¹⁷; the clearance of both drugs may be increased in smokers.¹⁵ Thus, some of the discussion in this article may also apply to patients receiving haloperidol, thiothixene, and fluphenazine.
5. As an unrelated note, what if a smoker with schizophrenia is admitted to the hospital in an acutely psychotic state? As already mentioned, most hospitals are smoke-free zones and the patient would be unable to smoke during the inpatient stay. Therefore, nicotine withdrawal could heighten the agitation associated with psychosis. In such circumstances, irrespective of the antipsychotic prescribed, the use of a nicotine patch may decrease acute agitation over and above the decrease associated with antipsychotic therapy.¹⁸

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