

What to do when your patient who takes clozapine enters a smoke-free facility

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Mr. D, age 30, has a 12-year history of schizophrenia and is experiencing worsening auditory hallucinations despite reported medication adherence. He has been taking clozapine, maintenance dosages 500 to 700 mg/d, for 4 years and smokes 2 packs of cigarettes a day. When Mr. D is admitted to a nonsmoking inpatient psychiatric facility, he receives nicotine transdermal patches, 21 mg/d, for nicotine withdrawal. Mr. D's most recent outpatient clozapine dosage, 700 mg/d, is resumed. All laboratory tests, including complete blood count with differential, are within normal limits at admission.

Five days later Mr. D is tachycardic with a heart rate of 109 beats per minute. When assessing Mr. D, we notice he has alogia and that, when he does speak, his speech is slowed with a 4 to 5 second delay in response. He also appears sedated. We observe occasional mild jerking of his shoulder and lower legs.

Mr. D reports that his auditory hallucinations have lessened since his admission, but complains of difficulty remembering information and feeling tired during the day. The treatment team suspects clozapine toxicity; his trough clozapine level is 1,350 ng/mL (therapeutic range, 350 to 1,000 ng/mL).

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It is well documented that cigarette smoke can induce cytochrome P450 (CYP) isoenzymes, specifically CYP1A1, CYP1A2, and CYP2E1. Because clozapine is primarily metabolized by CYP1A2 (approximately 70%), smoking can induce clozapine metabolism and abruptly stopping smoking can increase clozapine levels.¹ The polycyclic aromatic hydrocarbons, not the nicotine, found in cigarettes are thought to be responsible for CYP1A2 induction; therefore, use of a nicotine replacement product did not prevent the increase in Mr. D's clozapine levels.

Examining the evidence

Meyer¹ evaluated clozapine levels before and after implementation of a hospital-wide smoking ban (N = 11). Clozapine



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Practice Points

- **Smoking induces the CYP1A2 isoenzyme** and can lead to lower levels of clozapine.
- **Nicotine replacement products** (patches, lozenges, nasal spray, inhalers, and gum) and electronic cigarettes **do not induce CYP1A2**.
- A patient who smokes at least 7 to 12 cigarettes a day and is on a stable dosage of clozapine may require a lower daily clozapine dosage when admitted to a smoke-free facility. Practitioners should **consider lowering the clozapine dosage by 30% to 40%** over 4 to 7 days to reduce the risk of clozapine toxicity.
- Upon resumption of cigarette smoking, **the clozapine dosage may need to be increased** by as much as 1.5 times over 2 to 4 weeks.

Clinical Point

Smoking as few as 7 to 12 cigarettes a day is sufficient for maximum induction of CYP1A2



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Table 1

Possible clozapine-related side effects associated with smoking cessation

Extreme fatigue
Myoclonus
Orthostatic hypotension
Seizure
Sialorrhea
Somnolence
Tachycardia
Worsening psychiatric symptoms
Source: Reference 4

Table 2

More than 60% of schizophrenia patients smoke cigarettes. Why?

Sociologic barriers to quitting
<ul style="list-style-type: none"> • Their social groups often include a high percentage of heavy smokers • Some fear nicotine replacement therapy is 'unhealthy,' causes cardiac arrest, or increases nicotine craving⁹ • They are unlikely to achieve sustained abstinence from a single cessation attempt
Physiologic reinforcers and disease factors
<ul style="list-style-type: none"> • Nicotine might modulate schizophrenia's cognitive dysfunction, including sensory gating (a measure of ability to filter out irrelevant environmental stimuli) and attention^{10,11} • Nicotine may increase disease-associated reduction in nicotinic acetylcholine receptor activity^{12,13} • Smoking (but not nicotine) reduces antipsychotic blood levels by increasing metabolism and may reduce side effects of antipsychotic medications¹⁴ • Schizophrenia's cognitive impairment can make smoking cessation strategies difficult to follow

dosages were not adjusted at the time of the smoking ban, which resulted in a mean 72% increase in clozapine levels after a minimum of 2 weeks as nonsmokers. Even after eliminating 2 outliers, the mean increase in clozapine levels was 36.1%. Murayama-Sung et al² reported a statistically significant increase in the level of clozapine (46%,

$P = .004$) and the level of norclozapine (23%, $P = .02$) after a hospital-wide smoking ban was instituted ($N = 14$). However, the pre-change and post-change in the ratio of clozapine to norclozapine level was not found to be statistically significant.

Haslemo et al³ found that smoking as few as 7 to 12 cigarettes a day was sufficient for maximum induction of CYP1A2. Because Mr. D was smoking 2 packs of cigarettes a day (40 cigarettes) with a clozapine dosage 700 mg/d as an outpatient, he likely experienced significant induction of clozapine metabolism through CYP1A2, which was no longer present when he stopped smoking.

Therapeutic clozapine concentrations are typically above 350 and 420 ng/mL.⁴ Concentrations >700 ng/mL are associated with increased adverse effects, but generally are not associated with a higher response; levels >900 ng/mL have been associated with toxicity.⁴ Clozapine-treated patients on a stable dosage who smoke can experience clozapine-related adverse effects after admission to a smoke-free facility secondary to an increase in the clozapine concentration (Table 1).⁴

Five days after admission to the facility, Mr. D was noted to have myoclonus, somnolence, and tachycardia, with a clozapine level of 1,350 ng/mL. Additional adverse effects that can be seen include orthostatic hypotension, sialorrhea, worsening psychiatric symptoms (eg, hallucinations), and seizures.⁵ Although there is variability in the timing of the decrease in CYP1A2 activity after smoking cessation, practitioners should begin to monitor for clozapine-related adverse effects 1 or 2 days after smoking cessation.⁶

Treatment recommendations

Monitoring of the clozapine concentration and adjustment of the dosage might be needed to account for the fluctuation seen with smoking cessation to maintain efficacy and minimize adverse effects. However, a test of the clozapine level may not be available at all facilities, often

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requiring that the specimen be sent to an outside laboratory, taking 3 to 7 days to receive results.

Faber and Fuhr⁶ recommended reducing the dosage of a CYP1A2 substrate medication, such as clozapine, olanzapine, or theophylline, by 10% each day until the dosage has been reduced by 40% in patients who stop smoking. Lowe and Ackman⁵ proposed reducing the clozapine dosage by 30% to 40% to achieve a pre-cessation serum concentration at 1 week. For Mr. D, this would mean decreasing the clozapine dosage to 425 to 500 mg/d.

Assuming that Mr. D's clozapine dosage is decreased during his hospitalization and that he resumes smoking after discharge, it is likely the dosage will need to be increased. It may take several weeks to see maximal induction, because new CYP enzymes need to be synthesized when the patient resumes smoking.⁷ One recommendation is to increase the clozapine dosage by a factor of 1.5 over 2 to 4 weeks, with close monitoring of the clozapine concentration and adverse effects because this increase is approximate.⁷ Depending on when Mr. D's follow-up appointment is scheduled, the practitioner may need to plan a dosage adjustment to prevent a decrease in his clozapine level caused by smoking to prevent a worsening of symptoms and rehospitalization.

This case emphasizes the importance of asking clozapine-treated patients about their smoking history when they are admitted to a smoke-free facility. For several reasons, >60% of patients with schizophrenia smoke cigarettes⁸ (Table 2, page 48).⁹⁻¹⁴ Patients who smoke and are on a stable dosage of clozapine might require a dosage reduction when they are admitted to a smoke-free facility to avoid adverse effects. If the dosage is not adjusted, a patient may experience clozapine-induced adverse effects, such as tachycardia, sedation, and seizures. It is likely that patients such as Mr. D will experience fluctuation in the clozapine level and possibly changes in efficacy and tolerability transitioning between

Related Resources

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Drug Brand Names

Clozapine • Clozaril	Theophylline • Theo-Dur
Olanzapine • Zyprexa	

inpatient and outpatient settings if the dosage is not adjusted.

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Clinical Point

When a patient resumes smoking after discharge, it may take several weeks to see maximal CYP1A2 induction