Atypical Antipsychotic Dosing: The Effect of Smoking and Caffeine

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A previous Psychopharmacology column focused on the effect of co-prescribing anticonvulsant inducers with atypical antipsychotics and argued that the dosing recommendations for atypical antipsychotics that are provided on package inserts do not apply well to patients with unusual genetic profiles or to patients who are exposed to environmental factors that change the concentration-dose ratio (C/D) (1).

Severe mental illnesses are associated with tobacco smoking and, among smokers, with heavy smoking. Is smoking relevant to atypical antipsychotic dosing? Certainly. Byproducts of tobacco smoking, particularly the polycyclic aromatic hydrocarbons, are metabolic inducers. These byproducts are inducers of the cytochrome P450 isoenzyme 1A2 (CYP1A2) and of the less understood UDP-glucuronosyltransferases (UGTs). The metabolic inductive effects are not specific to tobacco smoking; they can also be expected from marijuana smoking. Because inducers require the synthesis of new enzymes, several weeks are usually needed before the maximum effects of inducers are seen. Inducers' effects may take a few weeks to disappear as well. The case reports of clozapine's toxicity after smoking cessation suggest that the inductive effects of smoking take at least two to four weeks to disappear (Table 1).

The studies listed in Table 1 suggest that smoking's inductive effects may be relevant for clinicians who prescribe atypical antipsychotics. Additional pharmacologic support of the relevance of smoking's inductive effects comes from caffeine intake studies. Caffeine, a drug that is more than 90 percent dependent on CYP1A2 for its metabolism and that is widely used in the United States, can exemplify smoking's effects on drug metabolism. The C/D of caffeine appears to be threefold to fourfold as high among nonsmokers compared with smokers. This higher ratio means that smokers need three to four times the caffeine "dosage" as nonsmokers on average to get the same plasma caffeine levels. In a caffeine intake study of 147 outpatients with schizophrenia who drank caffeine, the average caffeine intake was 1.3 mg per kg a day for nonsmokers, 2.7 mg per kg a day for nonheavy smokers (less than 1.5 packs a day), and 3.4 mg per kg a day for heavy smokers (1.5 packs a day or more) (2).

A limited amount of literature has been published that suggests that atypical antipsychotics that are not dependent on CYP1A2 or UGT for their metabolism should not be influenced by smoking or caffeine intake. Thus smoking or caffeine intake should not influence the dosing of risperidone and aripiprazole (metabolized by CYP2D6 and CYP3A), quetiapine (mainly metabolized by CYP3A), and ziprasidone (mainly metabolized by an aldehyde oxidase and CYP3A). On the other hand, the metabolism of clozapine and olanzapine is mainly dependent on CYP1A2 and UGTs. Table 1 summarizes studies that describe smoking's effects on the dosing of clozapine and olanzapine. Because caffeine has the opposite effect of smoking and increases the levels of clozapine and olanzapine, studies of caffeine interactions are also reviewed in the table. The effects of caffeine on CYP1A2 are explained by competitive inhibition. The effects of inhibitors are seen sooner than those of inducers, which require CYP1A2 synthesis. The chronology of maximum inhibition and its disappearance depends on the half-life of the inhibitor—that is, caffeine.

The width of the therapeutic window determines the clinical significance of the plasma level changes associated with smoking and caffeine intake. Compared with olanzapine, clozapine has a much narrower therapeutic window. Several of clozapine's side effects are dose related: plasma levels higher than 1,000 ng per milliliter have been associated with toxicity, including seizure risk and severe sedation.

Table 1 provides an average smoking correction factor of 1.5 for clozapine. If a patient who is taking clozapine smokes, smoking cessation would probably cause an average patient's plasma clozapine level to increase by 1.5 two to four weeks later. Similarly, if a patient who is stabilized in a nonsmoking environment starts to smoke more than one pack a day, the clinician may need to consider increasing the clozapine dose by a factor of 1.5 over two to four weeks. Checking for side effects and measuring the clozapine level may then be prudent, because the 1.5 factor is a gross approximation.

Gender may also influence clozapine metabolism. The limited information available (3,4) suggests that an average female nonsmoker requires low clozapine dosages (around 300

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Table 1

Recommended correction factors for smoking or using caffeine with clozapine and olanzapine and supporting data[a]

Study	Type of study[b]	Mean correction factor	Side effects	Recommended correction factor[c]
Smoking with clozapine				1.5 (up to 2.5)
Haring et al., 1989	20 patients with, 31 without	1.7		
Haring et al., 1989	81 patients with, 67 without	1.2		
Hasewaga et al., 1993	38 patients with, 18 without	1.4		
McCarthy, 1994	1 patient on-off		Seizure	
Oyewumi, 1998	1 patient on-off		Antimuscarinic and sexual side effects	
Skogh et al., 1999	1 patient on-off	1.6	Seizure	
Dettling et al., 2000	25 patients with, 9 without	2		
Meyer, 2001	11 patients on-off	1.8, range 1.1–3.6		1 case of aspiration pneumonia
Palego et al., 2002	28 patients with, 22 without	1.5		
Zullino et al., 2002	1 patient on-off	2		
Van der Weide et al., 2003[d]	45 patients with, 35 without	2.4		
Rostami-Hodjegan et al., 2004	Mathematical model 1,118 with, 508 without	1.5		
Smoking with olanzapine				1.5
Callaghan et al., 1989	61 male patients with, 98 male patients without	1.4		
Skogh et al., 2002	69 patients with, 73 without	2.3		
Zullino et al., 2002	1 patient on-partial off		Extrapyramidal side effects	
Carrillo et al., 2003	8 patients with, 9 without	5		
Gex-Fabry et al., 2003	70 patients with, 180 without	1.1		
Using caffeine with clozapine				
Beale et al., 1994	1 patient off-on intravenous caffeine use during electroconvulsive therapy		Supraventricular tachycardia	
Vainer and Chouinard, 1994	1 patient on-off-on-off[e]		Multiple side effects	
Odom-White and de Leon, 1996	1 nonsmoking patient on-off[f]	.4	Sedation	
Carrillo et al., 1998	7 patients on-off-on[g]	.6, range .25–.7		
	5 nonsmoking patients on-off[g]	.6, range .50–.62		
	2 smoking patients on-off[g]	.4, range .25–.50		
Hagg et al., 2000	12 male nonsmoker volunteers on-off[h]	.8, lower range .5		
Using caffeine with olanzapine				
No studies[i]				.6

[a] A list with complete reference information is available from the author.

[b] On-off studies used the same patients as controls. "On" means that the individual was taking an atypical antipsychotic plus smoking or using caffeine. "Off" means that the individual was taking an atypical antipsychotic without smoking or using caffeine. With-without studies compared "with" patients who were taking an atypical antipsychotic plus smoking or using caffeine and "without" patient controls who took only the atypical antipsychotic and did not smoke or use caffeine at all.

[c] These correction factors are gross approximations that are based on the limited information available. Females may need lower doses than males.

[d] This study suggested that a CYP1A2 polymorphic variation had no effects on clozapine dosing.

[e] The patient had side effects when taking clozapine plus caffeine. The side effects disappeared when he took clozapine plus water; they reappeared when he took clozapine plus caffeinated soda, and they disappeared when he took clozapine plus decaffeinated soda.

[f] During the caffeine phase, the patient used 500 mg of caffeine a day.

[g] This controlled study examined patients who used their usual amount of caffeine, who then used no caffeine for five days and were rechallenged for 14 days with their usual amount of caffeine. Five of seven patients were nonsmokers who consumed 150 to 200 mg of caffeine a day. Two of seven patients were smokers who consumed 150 to 1,100 mg of caffeine a day.

[h] This controlled study used a single 12.5 mg clozapine dose during caffeine intake (mean, 550 mg a day; range, 400 to 1,000 mg a day) for two days, and used a 12.5 mg clozapine dose for two days with no caffeine intake.

[i] There are studies on the effects of olanzapine in urine caffeine metabolites (Carrillo et al., 2003) but no studies on caffeine's effects on olanzapine levels.

mg per day) to reach therapeutic levels, whereas an average male heavy smoker requires high dosages (around 600 mg per day). The required dosages for male nonsmokers and female smokers fall in between these numbers. Obviously, these are average results and may not apply to specific individuals. In the future, it is hoped that a better understanding of genetics may help to individualize clozapine doses. A CYP1A2 genetic variation may influence how patients respond to smoking's inductive effects. However, in a recent study this variation did not have any effects on clozapine levels in the clinical environment (5).

Table 1 shows that the average caffeine correction factor is .6 for clozapine. Assuming other variables are stable, including no changes in smoking patterns, if a patient whose clozapine dose is stabilized in a caffeine-free environment begins to regularly consume high quantities of caffeine, it may be safest to decrease the clozapine dose—for example, from 400 to 250 mg a day (400 mg a day × .6=240 mg a day). Only high quantities of caffeine seem to have significant clinical interactions with clozapine.

In the United States, brewed coffee is estimated to contain 85 mg of caffeine per 5 oz cup; instant coffee, 65 mg per 5 oz cup; decaffeinated coffee, 3 mg per 5 oz cup; tea, 40 mg per 5 oz cup; and caffeinated sodas, including caffeinated colas, 40 mg per 12 oz can. In Europe, brewed coffee is estimated to contain more caffeine (100 mg per 150 cc cup). Obviously, caffeinated over-the-counter medicines in pill form may have much more caffeine than caffeinated beverages (up to 200 mg per pill). No data are available that show what level of caffeine intake is safe for patients who are taking clozapine. Steady caffeine dosages for a patient who is stabilized and is taking clozapine should not be of concern for clinicians. However, it may be important to warn the patient to avoid "dramatic" changes—either up or down—in caffeine intake. However, no published data define "dramatic" change in caffeine intake.

Using a table from a mathematical model that was developed in a sample of volunteers without mental illness, one can grossly estimate that one cup of coffee or two cans of caffeinated soda per day provide caffeine plasma concentrations as high as 2 mg per liter among nonsmokers, whereas three cups of coffee per day or six cans of caffeinated soda per day provide concentrations lower than 2 mg per liter among smokers (6). On the basis of that volunteer study and earlier clozapine studies, caution is recommended when nonsmoking patients who take clozapine increase or decrease their daily caffeine intake by more than one cup of coffee or two cans of caffeinated soda or when smoking patients who take clozapine increase or decrease their daily caffeine intake by more than three cups of coffee or six cans of caffeinated soda. For example, when a smoker who takes clozapine increases caffeine intake by three cups of coffee—for example, from two to five cups per day—clinicians should watch for increased side effects that are caused by an increased clozapine level. When a nonsmoker who takes clozapine decreases caffeine intake by two cans of soda—for example, from four to two cans per day—clinicians should watch for a possible loss of clozapine response that results from decreased clozapine levels.

In reviewing Table 1, the reader should remember that limited information exists about olanzapine. The pharmacologic information suggests that smoking's inductive effects and caffeine's inhibiting effects may be similar for olanzapine and clozapine. However, it may not be as relevant clinically to determine the effects of smoking and caffeine intake on olanzapine, because olanzapine's therapeutic window is much wider and high olanzapine levels lack the toxicity of high clozapine levels. The clinical environment is a "dirty" world, and it may be difficult to prove pharmacologic facts that have been established in a laboratory.

Hospital restrictions on smoking and caffeine intake may have clinical importance. Smoking is banned inside hospitals in the United States. Thus, when stabilizing patients who are taking clozapine, clinicians need to carefully question them and consider the different effects of smoking for patients in the hospital, where no or limited smoking is allowed, and for patients in the community, where smoking is not restricted. The hospital may also restrict caffeinated beverages. No easy recipes or correction factors exist for patients who are stabilized in a nonsmoking and caffeine-free hospital environment when they go to other environments. The correction factors shown in the table can be used for orientation, but clinicians need to remember the pharmacologic principles of induction and inhibition as well as their timing. New studies should establish the effects of gender and smoking status on clozapine and olanzapine dosing. Real-world pharmacokinetic studies on the effects of changing smoking patterns and caffeine intake after hospital discharge need to be conducted. Until these studies are available, clinicians should be aware that important variations in smoking and caffeine intake may cause changes in the plasma levels of clozapine and olanzapine. ♦

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