

Personalized Antipsychotic Therapy Based on Smoking Status: A Review of Olanzapine and Clozapine

Thérapie antipsychotique personnalisée en fonction du statut tabagique : une revue de l'olanzapine et de la clozapine

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ABSTRACT

Smoking influences the pharmacokinetics of antipsychotic medications, particularly olanzapine and clozapine, through the induction of cytochrome P450 1A2 (CYP1A2). This narrative review explores its impact on the metabolism, efficacy, and safety of olanzapine and clozapine. Current evidence demonstrates that smokers require higher doses of these antipsychotics to achieve therapeutic serum concentrations due to accelerated drug clearance, while non-smokers and those who cease smoking are at risk of adverse effects from elevated drug levels. Genetic variations in CYP1A2 activity further complicate dose recommendations, emphasizing the importance of individualized treatment strategies. The review underlines the importance of careful monitoring and dose adjustments in smokers, non-smokers, and patients undergoing smoking cessation to prevent adverse effects and ensure therapeutic efficacy. It also highlights the need for individualized approaches, considering both smoking habits and metabolic variations.

Keywords : Olanzapine, Clozapine, Schizophrenia, Bipolar disorder, Psychosis, Smoking, Genetics, Pharmacology

RÉSUMÉ

Le tabagisme influence la pharmacocinétique des médicaments antipsychotiques, en particulier l'olanzapine et la clozapine, via l'induction du cytochrome P450 1A2 (CYP1A2). Cette revue narrative explore l'impact du tabagisme sur le métabolisme, l'efficacité et la sécurité de l'olanzapine et de la clozapine, en soulignant la nécessité d'ajustements de dose personnalisés en fonction du statut tabagique. Les données actuelles montrent que les fumeurs nécessitent des doses plus élevées de ces antipsychotiques pour atteindre des concentrations sériques thérapeutiques en raison d'une clairance accélérée du médicament, tandis que les non-fumeurs et ceux qui cessent de fumer sont exposés à un risque accru d'effets indésirables en raison de niveaux de médicaments plus élevés. Les variations génétiques dans l'activité du CYP1A2 compliquent davantage les recommandations posologiques, soulignant l'importance des stratégies de traitement individualisées. La revue insiste sur l'importance d'une surveillance attentive et d'ajustements posologiques chez les fumeurs, les non-fumeurs et les patients en sevrage tabagique pour prévenir les effets indésirables et garantir une efficacité thérapeutique. Elle met également en lumière la nécessité d'approches individualisées, tenant compte à la fois des habitudes tabagiques et des variations métaboliques.

Mots clés : Olanzapine, Clozapine, Schizophrénie, Trouble bipolaire, Psychose, Tabagisme, Génétique, Pharmacologie

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INTRODUCTION

Cigarette smoking is a common lifestyle habit, embraced by both the healthy and the sick (1,2). In the general population, it has been associated with numerous hazardous effects (3). However, in sickness, the introduction of pharmacotherapy often overturns and increases their role, as it seems to affect the efficacy and safety of many drugs, including antipsychotics (4). Olanzapine is an atypical antipsychotic agent that serves as a first-line treatment for schizophrenia. It is one of the most frequently prescribed antipsychotic medications worldwide (5). Yet, it seems that patients do not respond to this therapy equally, most probably due to significant inter-individual variation in achieved drug plasma concentrations (4,6). Olanzapine is a thienobenzodiazepine derivate, which shows potent antagonism at D1–4 dopaminergic receptors, as well as 5-HT_{2A} and 5-HT_{2C} serotonergic, α ₁-adrenergic, muscarinic and H₁ histamine receptors (7). Olanzapine is extensively metabolized in the liver, mainly via cytochrome P450 (CYP) 1A2, but also via CYP2D6, CYP3A4, flavin-containing monooxygenase (FMO), and glucuronidation. Among these enzymes, CYP1A2 accounts for approximately 50–60% of its metabolism (7).

Clozapine is the prototype atypical antipsychotic, and it belongs to the chemical class of dibenzodiazepines (8). Clozapine has much greater antagonistic activity on D₄ than D₂ dopaminergic receptors. It also shows a potent antagonism of 5-HT_{2A} and 5-HT_{2C} serotonergic, α ₁-adrenergic, muscarinic and H₁ histamine receptors (8). Clozapine is widely used because it induces relatively few extrapyramidal effects and shows therapeutic benefits for patients who have failed to respond to other agents (9). Clozapine is absorbed rapidly and undergoes extensive hepatic metabolism (10). Various lines of evidence indicate that CYP1A2 and CYP3A4 play a significant role in the N-oxidation and N-demethylation of the compound, whereas CYP2D6 plays a minor role in N-demethylation (8,10).

It is now well known that patients with schizophrenia are inclined to cigarette smoking with about 58–88% of patients with schizophrenia being current smokers (11). Compared to the general population, they initiate daily smoking earlier (12), are less prone to smoking cessation (13), and smoke considerably more (14). CYP1A2 could be induced by cigarette smoking (15), which explains their effect on olanzapine and clozapine pharmacokinetics. Yet, CYP1A2 inducibility seems to be genotype-dependent (15,16), thus the response to therapy might differ according to CYP1A2 genetic background.

Many studies about the effects of smoking on the disposition of olanzapine and clozapine have been undertaken, but no agreement regarding the dose adjustment based on the smoking status has been reached. Healthcare professionals are focused on the benefits and challenges of quitting smoking from the patient's perspective. Therefore, they may fail to consider the potential problems related to drug metabolism that can result from cessation of tobacco smoking. Whether patients are advised to quit smoking or forced to do so

upon hospital mission (as many hospitals are smoke-free), serious adverse reactions to clozapine or olanzapine are theoretically possible.

There are several reasons for the slow progress in identifying the smoking-associated dosage: (1) the sample sizes of the previous studies were small; (2) each study used different pharmacokinetic parameters (eg, plasma concentration, plasma concentration to dose (C/D) ratio, and clearance).

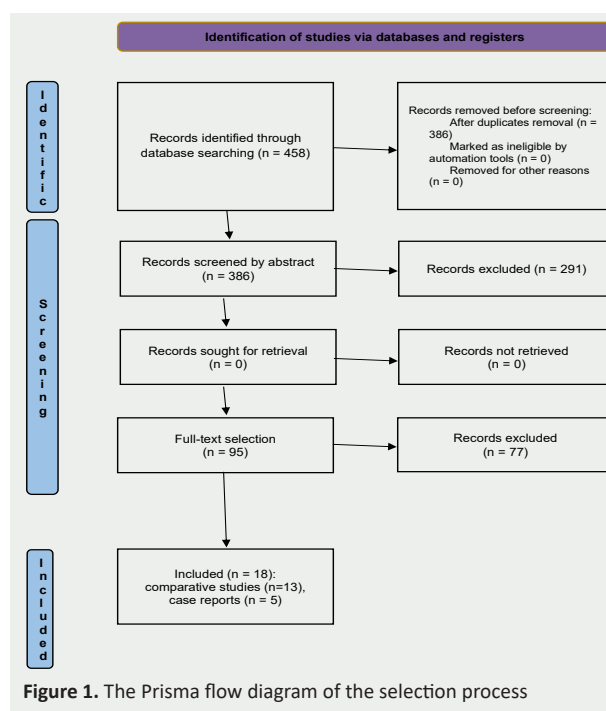
Therefore, we aimed to determine the degree of the effects of smoking on the disposition of olanzapine and clozapine, to develop standards that can be used to adjust the doses of olanzapine and clozapine based on the smoking status.

METHODS

We included cross-sectional, retrospective, and prospective comparative studies that assessed two groups of participants based on smoking status and reported serum concentrations of olanzapine and/or clozapine. Additionally, we included case reports or case series describing serum levels of olanzapine or clozapine following smoking cessation.

The literature search was conducted in PubMed using the following query: ((“Olanzapine” OR “Clozapine”) AND “smoking”). This search yielded 458 articles. After removing duplicates (n = 72), 386 articles remained for an initial screening based on abstract review. Of these, 291 were excluded. We also identified 5 commentaries, 1 editorial, 12 meta-analyses, 49 clinical trials, 13 systematic reviews, 75 narrative reviews, and 136 articles categorized under other types.

Following full-text screening, 48 case reports and 47 comparative studies were retained. Among these, 13 comparative studies and 5 case reports were ultimately included in this review. A PRISMA flow diagram illustrates the study selection process (Figure 1).



RESULTS

Smoking effects on olanzapine serum levels

The literature consistently demonstrates that smoking significantly impacts the pharmacokinetics of olanzapine by inducing CYP1A2, which accelerates the drug's metabolism. As a result, smokers typically have lower serum concentrations and a reduced concentration-dose (C/D) ratio of olanzapine compared to non-smokers, necessitating higher doses to achieve therapeutic effects. The key studies supporting these findings are summarized in Table 1.

A meta-analysis of 1094 patients (17) revealed that smokers had a lower C/D ratio of olanzapine, suggesting that non-smokers may require a 30% dose reduction to achieve equivalent serum concentrations. This finding aligns with studies by Haslemo (18), Laika (19), Citrome (20), Zang (21), Spina (22), and Skogh et al. (23) which consistently showed that smokers experience significant

reductions in olanzapine serum concentrations—ranging from 26% to 55% lower—depending on smoking frequency and genetic factors. Notably, Haslemo et al. (24) determined that smoking 7-12 cigarettes per day is sufficient to achieve maximum induction of olanzapine metabolism, while Bigos et al. (25) reported that smokers clear olanzapine 55% faster than non-smokers. Additionally, Djordjevic et al. (26) and Moschny et al. (27) found that even smoking as few as five cigarettes daily reduces olanzapine efficacy, with no significant increase in induction beyond 10 cigarettes per day. Carrillo et al. (28) observed that non-smokers experienced greater improvement compared to smokers, who had higher CYP1A2 activity and lower dose-corrected concentrations. Nozawa et al. (29) highlighted that male smokers, in particular, had significantly lower olanzapine levels than their non-smoking counterparts, underscoring the importance of personalized dosing strategies based on smoking status.

Table 1. Characteristics of the included olanzapine studies

Study	Country	Study Design	Number of Participants (Smokers)	Gender (Male/Female)	Disease	Diagnosis	Age (Mean $\pm$ SD or Range)
Haslemo et al (18)	Norway	Retrospective	129 (64)	0/129	Unknown	Unknown	18–40
Laika et al (19)	Germany	Retrospective	73 (30)	36/37	Schizophrenia, Mood disorder	ICD-10	41.7 $\pm$ 14.7
Citrome et al (20)	USA	Prospective	380 (257)	265/115	Schizophrenia, Schizoaffective disorder	DSM-IV	18–60
Zang et al (21)	China	Cross-sectional	354 (105)	239/115	Schizophrenia, Bipolar Disorder	DSM-IV	40.2 $\pm$ 15.1
Spina et al (22)	Italy	Prospective	18 (8)	10/8	Bipolar disorder, Schizoaffective disorder	DSM-IV	39.3 $\pm$ 8.6
Skogh et al (23)	Sweden	Retrospective	37 (10)	25/12	Schizophrenia, Schizoaffective disorder	DSM-IV	23–50
Haslemo et al (24)	Norway	Retrospective	40 (31)	29/11	Schizophrenia	Unknown	40–71
Bigos et al (25)	USA	Prospective	406 (267)	289/117	Schizophrenia	DSM-IV	42 $\pm$ 7.9
Nozawa et al (29)	Japan	Retrospective	51 (16)	34/17	Schizophrenia	DSM-IV	32.6 $\pm$ 9.6

Smoking effects on clozapine serum levels

The current literature suggests that smoking affects the pharmacokinetics of clozapine, primarily by inducing CYP1A2, which increases its clearance and reduces serum concentrations. Studies show that smokers have lower clozapine and norclozapine levels despite higher dosages. Smoking cessation leads to substantial increases in clozapine levels, highlighting the importance of careful dosage regulation when smoking habits change. Overall, smokers may require higher clozapine doses, while non-smokers need lower ones to achieve equivalent therapeutic effects.

Li et al. (30) applied non-linear mixed-effect modeling to Chinese patients, identifying that smokers have a 1.45-fold higher clearance of clozapine than non-smokers. A multiple regression analysis (31) of 2648 schizophrenic and schizoaffective patients showed significantly lower mean plasma clozapine and norclozapine concentrations in smokers, despite higher clozapine doses. This study used the plasma clozapine/norclozapine ratio

to indicate that metabolic capacity was significantly higher in smokers. Similarly, Palego et al. (32) evaluated steady-state plasma concentrations of clozapine and norclozapine in 50 patients and found that smokers had lower median levels of these compounds.

A study involving 44 schizophrenia inpatients (34 smokers, 10 non-smokers) demonstrated that smokers had approximately 40% lower clozapine and desmethyl clozapine concentrations compared to non-smokers (33). Dettling et al. (34) also reported that smoking significantly lowers dose-corrected serum concentrations of clozapine, primarily through the induction of CYP1A2. Weide et al. (35) found that smoking increases clozapine clearance, resulting in a C/D ratio of 2.5 times lower in smokers, necessitating higher maintenance doses. This study also noted that CYP1A2 genetic polymorphism did not significantly impact the clearance. A study from Oregon State Hospital (36) observed a mean increase of 71.9% in clozapine levels following smoking cessation in 11 patients. In a meta-analysis of clozapine (17), 196 patients (120 smokers, 76 non-smokers) from four

clinical studies were evaluated, revealing the need to carefully regulate clozapine dosage when smokers quit or reduce smoking. It was estimated that non-smokers

require about 50% lower doses than smokers to achieve equivalent clozapine concentrations.

Table 2. Characteristics of the included clozapine studies

Study	Country	Study Design	Number of Participants (Smokers)	Gender (Male/Female)	Disease	Diagnosis	Age (Mean $\pm$ SD or Range)
Dettling et al (34)	Germany	Retrospective	34 (25)	18/16	Schizophrenia	DSM-III-R	33.7 $\pm$ 10.6
Palego et al (32)	USA	Retrospective	49 (22)	25/24	Bipolar disorder, Schizophrenia, Schizoaffective disorder	DSM-IV	36.84 $\pm$ 1.96 (SE)
Weide et al (35)	The Netherlands	Retrospective	80 (45)	51/29	Schizophrenia	Unknown	18–86
Haslemo et al (24)	Norway	Retrospective	33 (28)	21/12	Schizophrenia	Unknown	28–62
Meyer et al (36)	USA	Retrospective	11 (11)	9/2	Schizophrenia, Schizoaffective disorder	DSM-IV	41.6 $\pm$ 5.0

Case reports of smoking cessation under olanzapine or clozapine

Case reports of adverse clinical outcomes following smoking cessation have been published for patients treated with olanzapine and clozapine. Some of these patients also used cannabis, but the existing literature does not suggest that cannabis has an impact on CYP1A2 metabolism (37–39).

Table 3 highlights several case reports illustrating the relationship between smoking cessation and the plasma concentrations of clozapine and olanzapine, as well as the associated clinical outcomes. When patients abruptly reduced or ceased smoking, the decreased activity of CYP1A2 led to a significant increase in the plasma concentrations of these medications, predisposing them to a range of side effects. This phenomenon is demonstrated across multiple case reports in the table. For instance, in the first case report by Zullino et al.(40), a 25-year-old patient with bipolar disorder reduced his smoking from 40 to 10 cigarettes per day while on olanzapine treatment. This was associated with extrapyramidal symptoms and Parkinson-like syndrome, likely due to elevated olanzapine levels in the absence of sufficient metabolic clearance. Similarly, patients treated with clozapine who ceased smoking altogether, such as those described by Zullino et al. (40) and Lowe et al. (41), experienced adverse effects like sedation, hypersalivation, and even seizures, all attributable to increased clozapine concentrations following smoking cessation.

The data suggests that dose adjustments of antipsychotic medications are often required following smoking cessation to mitigate these adverse effects. In each case, reductions in the dosage of clozapine or olanzapine led to the resolution or significant improvement of symptoms. This correlation between smoking cessation and increased drug levels highlights the critical role of metabolic pathways in the pharmacokinetics of antipsychotic treatments, as well as the importance of personalized dose adjustments in managing side effects.

Clinical implications of smoking cessation

As the controversy regarding high drug levels, metabolic ratios, and outcomes in terms of adverse reactions demonstrates, the interpretation of the data is challenging. Multiple factors must be taken into account, such as the patient's smoking behavior, caffeine intake, or co-medication. Whereas the effect of caffeine on metabolism via CYP enzymes is disputed—some sources state that caffeine may lead to an increase in clozapine concentrations (45,46).

A change in a patient's smoking behavior is to be expected especially before, during, and after inpatient care. For example, many patients with schizophrenic disorder have a higher use of tobacco when suffering from productive psychotic symptoms. During inpatient treatment, smoking behavior often changes, as a result of extrinsic factors such as admission to a secure unit or the use of physical restraint (if medically indicated). In addition, many hospitals pursue a "non-smoking policy" (36,47). It is important to note that patients are highly likely to return to their original smoking behavior after an inpatient stay so their medication also needs to be monitored after discharge from the hospital (47).

For patients for whom hospitalization will result in forced smoking cessation, it is important to determine both the likely duration of admission and also the patient's interest in maintaining smoking abstinence. Case reports have demonstrated symptoms from increasing olanzapine concentrations 4–10 days after smoking cessation, while those in patients taking clozapine long-term suggest a time to onset of 2–4 weeks (40,44).

In patients with an anticipated brief admission (with forced smoking cessation), clinical monitoring for adverse effects potentially due to increased serum concentrations of clozapine or olanzapine is appropriate. Specific symptoms, such as hypersalivation and sedation for clozapine and extrapyramidal symptoms, would be easily identified (48). However, symptoms such as seizures, confusion, agitation, hypotension, and/or tachycardia could be related to increasing serum concentrations of these medications and should be considered in the differential diagnosis should they arise.

For patients with a prolonged duration of admission, the possibility of increased serum concentrations resulting in adverse effects is more likely. Baseline serum clozapine concentrations and consideration of empiric dosage reductions of 30– 40% of the total daily dose may be warranted. Dosage reductions of 30– 40% for both of these agents have been observed to return patients to a pre-cessation level of functioning in approximately 1 week. Serum clozapine concentrations do not correlate well with efficacy or toxicity and, in this situation, are simply a marker to allow for adjustment of the dosage to reach a pre-cessation serum concentration. Again, psychiatric assessment and expertise would be suggested.

In outpatient settings, patients may choose to quit smoking or decrease their consumption. This may also occur in hospitalized patients who can leave the premises to smoke. Given the variation in success rates with decreasing consumption and cessation, clinical monitoring and follow-up regarding smoking consumption is likely appropriate for the first week. For successful patients, consideration should be given to dosage adjustment by their regular psychiatric healthcare professional through clear communication of this potential drug-related problem. Patients taking either olanzapine or clozapine who are attempting smoking cessation should be carefully monitored for signs of toxicity.

Table 3. General characteristics of the previously reported cases

Case report	Age	Diagnosis	Smoking History	Antipsychotic Treatment	Smoking Cessation	Symptoms Post-Cessation	Dose Adjustment	Outcome
Zullino et al. (40)	25	Bipolar disorder	40 cigarettes/day for several years	Olanzapine 30 mg/day, Lithium sulfate 1980 mg/day, Sodium valproate 3500 mg/day	Reduced from 40 to 10 cigarettes/day	Extrapyramidal effects (akathisia, akinesia, bradyphrenia), Parkinson-like syndrome (bradykinesia, stooped posture, small steps, hypomimia, cogwheel rigidity)	Reduced olanzapine to 20 mg/day (34% decrease)	Symptomatic improvement over the following week
Zullino et al. (40)	37	Paranoid schizophrenia	>20-year history, daily cannabis use	Clozapine 700 mg/day	Stopped smoking and cannabis	Increased agitation, auditory hallucinations, paranoid ideation, confusion	Reduced clozapine to 500 mg/day (30% decrease)	Psychotic symptoms disappeared, and plasma concentrations returned to pre-cessation levels within 2 weeks
Lowe et al. (41)	47	Paranoid schizophrenia	32 pack years	Clozapine 750 mg/day	Stopped smoking	Hypersalivation, extreme fatigue, daytime somnolence	Reduced clozapine to 700 mg/day, then to 650 mg/day	A modest decrease in sedation, and no significant improvement in other symptoms
Brownlowe et al. (42)	64	Schizoaffective disorder, urosepsis	Long-term 1 pack/day	Clozapine	Smoking cessation with variable success	Accumulation of clozapine, myocarditis	Clozapine discontinued, reintroduced later, dose not reported	Remission of psychosis, clozapine concentration 787 ng/mL at discharge
McCarthy et al. (43)	25	Schizophrenia	30 cigarettes/day	Clozapine 450 mg/day, Fluoxetine 20 mg/day	Stopped smoking	Myoclonus, grand mal seizure	Reduced clozapine to 350 mg/day, stopped all medications for 3 days, resumed clozapine 300 mg/day, Fluoxetine 10 mg/day	Myoclonus resolved, patient stable and not smoking
Skogh et al. (44)	38	Schizophrenia	60 cigarettes/day	Clozapine 700 mg/day	Abrupt smoking cessation	Unconscious, pulseless, excessive salivation, seizures	Reduced clozapine to 425 mg/day (40% decrease)	No further dosage adjustments were reported, and clozapine and desmethyl clozapine concentrations were stable

Factors influencing olanzapine and clozapine metabolism

The metabolism could also be genotype-dependent:

The induction of CYP1A2 is influenced by the presence of the *1F allele, which makes the enzyme more inducible (16,49). This process typically involves the ligand-dependent aryl hydrocarbon receptor (AhR) and

the aryl hydrocarbon receptor nuclear translocator (ARNT) pathway (50). The *1F allele includes a -163C>A substitution in intron 1, a regulatory element of the gene, leading to increased enzyme activity (51). As a result, the effect of inducers on olanzapine metabolism in patients may depend on their genotype, similar to findings with other CYP1A2-metabolized drugs like clozapine (52) and

carbamazepine (49).

Gender

The effect of sex on disposition and response to drugs metabolized by CYP1A2 is still a matter of debate. Numerous studies reported lower CYP1A2 activity indices (53), and higher plasma levels of both clozapine (52) and olanzapine (54,55) in women. The reason for the higher C/D ratio in women may be that CYP1A2 also metabolizes some female sex hormones (56). Therefore, there is competition between CYP1A2 substrate drugs and hormones. This observation is most pronounced in late pregnancy (56). In addition, women treated with olanzapine have been reported to experience a higher frequency of dizziness (57), but a lower frequency of weight gain (58), as compared to men.

In contrast, others failed to observe any sex-related difference in either CYP1A2 enzyme activity (59,60), or olanzapine concentration (19,20) and effects (6). According to Eli Lilly and Company (61), no apparent differences between men and women have been demonstrated in the efficacy or adverse effects of the drug although olanzapine clearance is approximately 30% lower in women than in men.

Age:

The effect of age on CYP1A2 activity yielded contradictory reports as well. While most of the studies did not detect any significant associations (53,62), several researchers reported slower CYP1A2 activity in older subjects (63). A similar discrepancy has marked olanzapine investigations too, with the lack of influence of age observed by some (6,19), opposing others, who described higher drug concentrations in older subjects (54). A study by Castberg et al. (64) which included more than 3000 patients (the oldest patient was 86 years old) showed that every five years after the age of 40, dose-adjusted concentration of olanzapine increased by 1.7% in men and 1.3% in women. It should be noted that studies examining the effect of age on olanzapine concentrations are limited due to the small number of very old patients, over 85 years of age. In elderly people, the activity of the CYP1A2 enzyme remains preserved but organ perfusion (liver and kidney) and circulation weaken so that metabolism and elimination of olanzapine can be slowed down (65). The most likely mechanism underlying the higher dose-adjusted concentrations in the elderly is a lowered hepatic clearance of the drugs caused by a decreased intrinsic hepatic metabolic function, lower liver volume, and/or reduced hepatic blood flow (64). The drug metabolism may also be altered due to kidney and liver diseases.

Race

Race is known to be associated with variability in the CYP1A2 activity. Bigos et al (25) reported that African-Americans cleared olanzapine faster than did other races (ie, Caucasians, Asians, and Native Americans). Moreover, many genetic polymorphisms were reported to affect the disposition of olanzapine and clozapine.

Comedication

Several drugs, such as fluoxetine and fluvoxamine, were reported to increase the blood concentration of olanzapine and/or clozapine through the inhibition of CYP1A2, CYP2D6, CYP3A4, and/or UDP-glucuronyltransferase 1A4 (18,66–69). Additionally, carbamazepine, phenobarbital, and trimipramine were reported to decrease the blood concentrations of olanzapine and/or clozapine through the induction of CYP1A2 or CYP3A4 (68–71).

CONCLUSION

Smoking impacts olanzapine and clozapine metabolism via CYP1A2 induction, requiring tailored dose adjustments. Smoking cessation can sharply increase drug concentrations, risking toxicity without close monitoring. Genetic factors, age, gender, and comedication add complexity to dosage decisions. Clinicians must adopt individualized dosing strategies based on smoking status and metabolic profile. Future studies should establish clear dosing guidelines to improve antipsychotic safety and efficacy in smokers and during smoking cessation.

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