A Comprehensive Review of the Effect of Vaping on the Plasma Levels of Clozapine

Abstract

Background: Clozapine is an antipsychotic medication essential for treating treatment-resistant schizophrenia. Its plasma levels are influenced by cytochrome P450 (CYP450) enzymes, particularly CYP1A2. Traditional smoking may impact clozapine metabolism.

Objective: This study aims to explore how vaping affects the plasma levels of clozapine, focusing on the pharmacokinetic interactions between clozapine and vaping constituents.

Methods: A literature review was conducted to examine the interactions between nicotine smoking, CYP450 enzymes, and clozapine metabolism. Additionally, case reports were analyzed to understand the clinical implications for patients on clozapine who switch from smoking to vaping.

Results: Unlike traditional smoking, vaping lacks combustion products like polycyclic aromatic hydrocarbons (PAHs), leading to reduced CYP1A2 induction. Case reports showed that switching from smoking to vaping often results in elevated plasma clozapine levels due to decreased CYP1A2 activity, causing adverse effects. However, some vape products containing combustible products like aldehydes and carbonyls can induce CYP450 enzymes, further complicating clozapine metabolism.

Conclusion: Vaping may affect clozapine metabolism primarily through de-induction of CYP1A2 activity in patients who switch from smoking to vaping. While switching from smoking to vaping can lower the required clozapine dose by reducing CYP1A2 induction, it also raises the risk of toxicity due to increased serum clozapine levels if the dose is not adjusted. Health professionals should carefully monitor plasma clozapine levels in patients who switch from smoking to vaping and adjust dosages as needed to maintain therapeutic efficacy and minimize adverse effects.

Keywords: Clozapine, vaping, nicotine, smoking, tobacco, cytochrome P450, CYP1A2, schizophrenia.

Introduction

Clozapine is an antipsychotic medication that has a unique place in the history of psychiatry due to its efficacy in treating schizophrenia, particularly in patients who do not respond to other treatments. Clozapine was first synthesized in 1958 by Heinz Baumann and his team at Wander AG, a Swiss pharmaceutical company (1). It was developed as part of a search for a muscarinic antagonist. Initially, clozapine did not

attract much attention until its antipsychotic properties were recognized. The drug was first marketed in Switzerland and West Germany in 1971 under the brand name Leponex (1).

Clozapine is known for its distinctive pharmacological profile, including a higher affinity for serotonin 2A and 2C receptors than for dopamine receptors, which is different from earlier typical antipsychotics that primarily targeted dopamine receptors (2). This unique mechanism helps reduce the symptoms of schizophrenia while minimizing the side effects associated with dopamine antagonism, such as extrapyramidal symptoms. Clozapine has been particularly noted for its effectiveness in treatment-resistant schizophrenia (3). It is often considered a drug of last resort due to its potential side effects, but it remains unmatched in its efficacy for certain patient populations (3).

The initial widespread use of clozapine was curtailed in the 1970s following reports of agranulocytosis, a potentially fatal blood disorder where the white blood cell count drops to a dangerously low level, leading to an increased risk of infection (4–6). As a result, clozapine was withdrawn from the market in many countries. It was reintroduced in the 1980s with strict monitoring protocols (7). Due to its potential side effects, the use of clozapine is heavily regulated. It was approved by the U.S. Food and Drug Administration (FDA) in 1989 (8), but only under a restricted program (9). This program requires regular blood monitoring to monitor white blood cell counts and is designed to ensure that the benefits of taking clozapine outweigh the risks for each patient. Despite its risks, clozapine remains a critical tool in psychiatric treatment, particularly for those with severe schizophrenia. It is also investigated for other uses, such as in treating psychotic disorders in Parkinson's disease (10) and for its potential anti-suicidal effects in patients with schizophrenia (11).

Vaping, on the other hand, is the act of inhaling and exhaling an aerosol, often referred to as vapor, which is produced by an electric cigarette (e-cigarette) or similar device (12). The term is used because e-cigarettes do not produce tobacco smoke but rather an aerosol, often mistaken for water vapor, that actually consists of fine particles. Many different substances can be vaped, including nicotine, flavorings, and other chemicals that help to make up the aerosol (13)

Types of Vaping Devices

- E-cigarettes: These are devices that look like cigarettes but use a battery to heat a liquid into an aerosol.
- Vape pens: Slightly larger than e-cigarettes, these devices offer more customization and are typically used for a variety of materials, including flavored e-liquids and sometimes cannabis products.
- Advanced personal vaporizers (Mods): These are more sophisticated devices that can be customized in many ways. Mods can have adjustable power settings and can be used with a variety of vaping liquids.

Many vapers use e-cigarettes to consume nicotine in a way that mimics smoking cigarettes. Vaping is often considered a less harmful alternative to smoking for people who are trying to quit tobacco. However, evolving science is indicating that vaping is not a safe or healthy alternative to tobacco (14). A major appeal of vaping is the wide availability of flavored vape juice, which can range from fruity to savory and beyond. However, there is ongoing debate and research regarding the safety of these flavoring agents when inhaled (15). Delta-9 tetrahydrocannabinol (THC) - the psychoactive component of cannabis and Cannabidiol (CBD) -a non-psychoactive component can also be vaped.

Cannabis oils and distillates are specially formulated for vaping and are popular for medicinal and recreational use. Less commonly, substances like synthetic cannabinoids or even psychoactive substances are vaped by some users, often leading to significant health risks.

Our rationale for studying the interaction between vaping and clozapine plasma levels is rooted in the pharmacokinetic dynamics of clozapine and the impact of substances commonly inhaled through vaping, like nicotine, on drug metabolism. This is especially relevant given the high prevalence of tobacco smoking and potentially vaping in individuals with psychiatric disorders, particularly schizophrenia, which is commonly treated with clozapine (16,17). Patients with schizophrenia are known to smoke tobacco at higher rates than the general population (16). This behavior is believed to be partly due to nicotine's neurobiological effects, which may alleviate some symptoms of schizophrenia or counteract side effects of antipsychotic medications (16). As vaping becomes more prevalent, it is important to understand if it similarly impacts these patient population.

Literature Review

Nicotine, a common component of vape juice, can induce certain liver enzymes, particularly those in the cytochrome P450 (CYP450) family such as CYP1A2. Clozapine is primarily metabolized by CYP1A2 and CYP3A4, with additional contributions from CYP2C19 and CYP2D6 (18). These enzymes are responsible for the formation of stable metabolites and chemically reactive metabolites, which may play a role in the drug's side effects (19).

Several studies have demonstrated the impact of smoking on clozapine levels. A study by Spina et al 2000 involving 100 patients with schizophrenia treated with clozapine found that smokers had significantly lower plasma clozapine concentrations compared to non-smokers. The mean clozapine concentration-to-dose ratio was approximately 50% lower in smokers (20). Similarly, a study by Haslemo et al 2006 explored the dose adjustments necessary for smokers and non-smokers and concluded that smokers need an average increase of 30-50% in their clozapine dosage to reach therapeutic levels (21). Understanding this interaction between smoking and clozapine is crucial for clinicians to optimize treatment plans for patients with schizophrenia. Key considerations may include assessing smoking status at the initiation of clozapine therapy. For smokers, higher starting doses or more frequent monitoring of plasma clozapine levels may be necessary. Secondly, regular monitoring of clozapine plasma levels may also be important to adjust doses appropriately. This is particularly important when a patient changes their smoking habits, such as reducing or quitting smoking, which can lead to a decrease in CYP1A2 activity and an increase in clozapine levels, posing a risk of toxicity. Lastly, encouraging smoking cessation is beneficial not only for overall health but also for stabilizing clozapine levels. Transitioning smokers may require careful dose reduction and monitoring to avoid adverse effects.

The interaction between vaping and plasma levels of clozapine involves complex biological regulatory pathways of the drug (22,23). Most drugs, including clozapine, are substrates of a family of membrane-bound mono-oxygenase enzymes found in the liver that make up the CYP450 system (22,24). Many isoforms of these enzymes exist naturally within the endoplasmic reticulum of hepatocytes (24). Studies have identified CYP1A2 and CYP3A4 as the major CYP isoforms catalyzing the metabolism of clozapine (18,22). Other isoforms that have also been identified include CYP2C19 and CYP2D6, although they play a minor role in clozapine metabolism (22). The main mechanism by which clozapine is metabolized is

via oxidation, a process catalyzed primarily by CYP1A2 to produce clozapine N-oxide (22). Due to its inactivity, the formation of clozapine n-oxide signals the termination of the actions of clozapine in the body (22).

Polycyclic aromatic hydrocarbons (PAHs), products of the combustion of tobacco, are inducers of the CYP1A2 enzyme (25). Consequently, they result in increased deactivation of clozapine and reduced serum levels of clozapine in patients who smoke combustible tobacco (25). Induction of CYP1A2 is typical of combustible cigarette smoking but does not occur with many vapes, owing to the lack of or reduced combustion and, therefore, an absence or reduced production of PAHs in many vapes (25). In addition to oxidation to form clozapine N-oxide, studies have identified another pathway through which clozapine may be metabolized in the liver (22,24). This pathway involves the demethylation of clozapine, resulting in the formation of N-desmethylclozapine (norclozapine), which is an active metabolite capable of effects via dopamine D2 and D3 receptors (22,24). Consequently, norclozapine has been postulated to cause some of the adverse effects associated with the use of clozapine in schizophrenia (26). For instance, norclozapine's agonistic effect on M1 receptors is responsible for the drooling associated with the use of clozapine (27).

Vapes are produced in different designs and sizes, with some containing built-in cartridges with prepackaged products and others being larger machines with interchangeable tanks allowing the user to add any product of their choice (23). Some vape models are even equipped with converters that permit the combustion of dry materials, including tobacco, marijuana, and herbs (23). The variability of vaping accounts for the variability in vape products. Examples of these vape products, especially in vapes with interchangeable tanks, include combustion products and toxins such as PAHs, carbon monoxide, toxic aldehydes (e.g., benzaldehydes, acetaldehydes, acrolein, and formaldehyde), tobacco-specific nitrosamines (TSNA), and carbonyls (28). Several of these products have been noted to influence clozapine levels via various pathways.

PAHs obtained via the combustion of tobacco are known to cause reduced clozapine levels due to their induction effects on CYP1A2 (25). On the other hand, aldehydes, which are among the most toxic constituents of tobacco products and tobacco smoke, inhibit several cytochrome enzymes (29,30). Certain carbonyl compounds can act as competitive inhibitors of cytochrome P450 enzymes, resulting in the reduced metabolism of substrates, including clozapine, broken down by the enzyme (31). Contrastingly, other carbonyl compounds found in vape are inducers of cytochrome P450 activity and hence, like PAHs, result in a decrease in serum levels of clozapine (31).

Clinical Implications

Clozapine has been found to be most effective at serum concentrations between 350-600 ng/mL, with some patients requiring levels above 600-1000 ng/mL to achieve therapeutic response if tolerated (32). Smoking has also been well-documented to decrease serum clozapine levels, which can lead to reduced efficacy of the drug. This reduction is primarily due to the PAHs in tobacco smoke that induce the activity of CYP1A2, thereby increasing the metabolism of clozapine and lowering its plasma concentration (32,33). Consequently, patients with schizophrenia who smoke may require higher doses of clozapine to maintain therapeutic serum levels, necessitating careful dose adjustments (25,32–35). In contrast, the transition from smoking to vaping has been associated with markedly increased serum clozapine levels. This increase is attributed to the

cessation of the inducing effects of PAHs on CYP1A2, leading to a reduced metabolism of clozapine and higher plasma concentrations (33,34). While this might suggest a potential for greater efficacy, it also raises significant safety concerns due to the narrow therapeutic index of clozapine. Elevated clozapine levels can precipitate severe adverse effects, such as agranulocytosis, myocarditis, and seizures, making it imperative to closely monitor patients during this transition phase (36). For those switching from combustible cigarettes to vaping, vigilant monitoring of serum clozapine levels is crucial to avoid toxicity. Regular assessments of the type of vape used and the presence of any substances that might alter CYP450 activity are essential to prevent fluctuations in clozapine levels that could compromise treatment efficacy and safety (25,35,36). Given the relationship between vaping and clozapine therapy, with some vapes having little to no effect on clozapine levels and others containing tobacco products capable of either inhibiting or inducing cytochrome levels and hence influencing clozapine levels, it is important that clinicians take proactive measures in monitoring and managing patients on clozapine who also vape (23). In order to manage the patient appropriately, the clinicians should educate patients on the potential interactions between vaping and clozapine. Informing patients about the risks associated with abrupt changes in smoking habits can facilitate better adherence to treatment protocols and ensure a collaborative approach to managing their condition (23,25).

Case Reports Review

Of the four cases reviewed as shown in Table 1, 75% were male, and the majority (75%) were young adults aged 18 to 28 years. Three patients had a diagnosis of schizophrenia, while one was diagnosed with schizoaffective disorder. All patients were being treated with clozapine. Three out of the four cases reported a significant increase in serum clozapine levels after switching from traditional cigarette smoking to electronic nicotine delivery systems/vapes (ENDS). One case did not measure clozapine blood concentration at the time of conversion to vaping. All four cases reported worsening adverse effects following the use of ENDS. Despite these adverse effects, none of the patients experienced worsening psychotic symptoms after switching to ENDS. In two cases, the severity of adverse effects from high clozapine serum levels necessitated a reduction in clozapine dosage, leading to an improvement in side effects and a decline in serum clozapine concentrations. In one case, switching back to cigarette smoking and adding haloperidol to the medication regimen resulted in lowered serum clozapine levels and reduced adverse effects. For another patient, reducing daily nicotine content resolved the side effects.

The case report by Montville et al. (2021) highlights a patient who experienced increased medication side effects, specifically constipation, after switching from tobacco smoking to ENDS (35). This switch resulted in higher serum concentrations of Clozapine and Norclozapine, attributed to the de-induction of CYP1A2. Interestingly, the patient did not exhibit worsening psychotic symptoms while vaping, unlike with tobacco smoking, which led to a relapse in their mental illness. These findings are consistent with Blacker's case report, where a patient experienced hypersalivation, anxiety, palpitations, and shortness of breath, along with elevated clozapine levels while using ENDS. The patient's anxiety symptoms resolved, and clozapine levels decreased after reducing ENDS nicotine intake (23). Similarly, a letter by Thomas Kocar et al. reported a patient whose plasma clozapine levels rose to 1290 ng/mL after switching to vaping, unlike tobacco, which induces this enzyme system to result in decrease clozapine plasma levels. This patient also experienced exacerbated side effects, including blurred vision, drowsiness, and binge eating behaviors, which diminished after reducing the clozapine dose from 550 mg/day to 250 mg/day. Khorassani et al. (2018) described a patient who experienced

increased adverse effects, such as anergia and hypersomnia, after switching from smoking to e-cigarettes, with a notable rise in blood clozapine concentration up to 1580 ng/mL (32).

Table 1: Case reports/Letter to Editor reviewed

S/N	Author(s), Year	Type of Study	Patient Profile	Effect of Vaping on Clozapine	Side Effects Profile	Intervention
1	Montville et al. 2021 (35)	Case report	28-year-old male with diagnosis of schizophrenia	Clozapine and Norclozapine serum concentration increased considerably after the patient switched to vaping.	worsening constipation which warranted medical intervention.	Switching back to cigarette smoking and the addition of Haloperidol 5 mg led to reduced serum levels of Clozapine and Norclozapine. Patient also reported resolution of his constipation.
2	Blacker 2020 (23)	Case report	18-year-old Caucasian male with diagnoses of schizophrenia and substance use disorder-marijuana, alcohol and nicotine.	Improvement in the patient's psychotic symptoms- auditory hallucinations and paranoia within 3 weeks of switching to vaping.	Return of side effects-hypersalivation once he switched to vaping. Also reports palpitations, shortness of breath and anxiety.	Patient reported Complete resolution of palpitations, shortness of breath and anxiety once he reduced his vaping-nicotine exposure from 240mg/day to 90mg/day.
3	Thomas Kocar et al. 2018 (25)	Letter to the editors-case report	23-year-old white female patient with diagnosis of paranoid schizophrenia	There was significant increase in plasma Clozapine levels up to 1290 ng/mL once the patient started vaping	The patient reported binge eating, drowsiness and blurred vision following her switch to ENDS	The patient's Clozapine dose was reduced from 550 mg/day to 250 mg/day, and this led to resolution of adverse effects. There were also a return of the Clozapine plasma levels to therapeutic ranges.
4	Khorassani et al 2018 (32)	Case report	52-year-old man with diagnoses schizoaffective disorder, bipolar disorder,	Increase in serum clozapine levels to 1580 ng/mL from a	Anergia, hypersomnia.	Patient had a rehospitalization where his Clozapine dose was lowered to 500 mg/day. This abated the

			stage 2 chronic kidney disease (CKD), macular degeneration, and ventricular tachycardia	dose of 600 mg/day once he changed from traditional smoking to electronic cigarettes.		toxicity symptoms and reduced serum clozapine levels to 889 ng/mL.

Research Gaps and Future Directions

The current body of literature highlights several significant gaps and areas for future research concerning the pharmacokinetic variability of clozapine and the impact of vaping on its plasma levels. Despite a general consensus on the association between vaping and altered clozapine plasma levels, the exact nature of this relationship remains inadequately characterized due to a lack of comprehensive clinical data and limited studies on the topic. A significant portion of the pharmacokinetic variability of clozapine remains unexplained, necessitating further investigation to identify additional contributing factors. Understanding these factors is crucial for optimizing clozapine therapy and ensuring consistent therapeutic outcomes. Although there is an acknowledged relationship between vaping and clozapine plasma levels, a detailed characterization of this interaction is still lacking. Future studies should focus on conducting robust prospective clinical trials to gather comprehensive data on how vaping influences clozapine metabolism and plasma levels and investigate the specific dosing adjustments required for patients who vape and exhibit changes in serum clozapine levels. Clozapine is metabolized into its active metabolite, norclozapine (N-desmethylclozapine), and the ratio of clozapine to norclozapine (CLZ: NDMC) is influenced by external factors like vaping. This ratio has been linked to the efficacy and side effects of clozapine, necessitating detailed pharmacokinetic and genetic studies to elucidate the impact of vaping on the CLZ:NDMC ratio and its correlation with the psychopathologic, cognitive, cardiac, and metabolic effects of clozapine. The potential clinical utility of the CLZ:NDMC ratio in plasma clozapine monitoring needs further exploration. If future studies confirm the hypothesized benefits, this ratio could serve as a valuable tool in optimizing clozapine therapy. Additionally, research should evaluate the efficacy of treatment adjuncts and medications that can alter the CLZ:NDMC ratio to enhance clozapine's clinical benefits while minimizing its side effects. Addressing these research gaps is vital for improving the therapeutic management of patients with schizophrenia on clozapine therapy, leading to better individualized treatment strategies and enhanced patient outcomes.

Conclusion

The findings from the reviewed literature suggest that vaping may or may not alter the plasma concentration of clozapine, depending on the content, particularly combustible products. Unlike traditional smoking, which induces the metabolism of clozapine through the induction of cytochrome P450 enzymes by its combustible contents (primarily CYP1A2 and CYP3A4), and results in decreased plasma levels of clozapine, vaping (without combustible contents) is shown to result in de-induction of the CYP system, hence resulting in elevated plasma levels of

clozapine, increasing the risk of toxicity and associated adverse effects such as agranulocytosis, myocarditis, seizures, hypersalivation, constipation, palpitations, and other systemic reactions.

For patients with schizophrenia on clozapine therapy who smoke and experience significant side effects from high doses of clozapine, switching to vaping might be an alternative option. This change may potentially reduce the required clozapine dose needed to manage their schizophrenia, thereby decreasing the side effects associated with higher doses necessitated by their smoking habits.

The clinical implications of these findings are profound, highlighting the need for healthcare providers to closely monitor patients with schizophrenia who are on clozapine therapy and switch from traditional smoking to using vaping products. It is essential for clinicians to take comprehensive smoking and vaping histories before initiating clozapine therapy and to conduct regular monitoring of plasma clozapine levels and frequent habit reviews throughout treatment. Adjustments in clozapine dosage may be required based on the patient's smoking and vaping habits to avoid subtherapeutic or supratherapeutic drug levels, ensuring optimal therapeutic outcomes while minimizing the risk of severe side effects.

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