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Review

Distinguishing psychopathology from medication-induced tachycardia in patients treated with clozapine: is it anxiety or a medication side effect?

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SUMMARY

Objectives

The purpose of this paper is to review the characteristics and mechanisms of clozapine-induced tachycardia and anxiety-induced tachycardia. The paper aims to provide a comprehensive understanding of the prevalence, risk factors, underlying causes, and clinical features of each condition to assist the clinician in distinguishing between the various causes and mechanisms that may contribute to tachycardia.

Methods

A comprehensive literature search was conducted using the MEDLINE and Scopus databases with keywords including "clozapine", "tachycardia", "anxiety", "cardiac effects", and "adverse effects". The selection process included screening of titles and abstracts, followed by full-text review of relevant studies. Data on study design, sample size, patient demographics, incidence of tachycardia, and proposed mechanisms were extracted and synthesized to highlight key findings, identify knowledge gaps, and suggest areas for future research.

Results

Clozapine-induced tachycardia has been reported in approximately 25-50% of patients, particularly during the early stages of treatment. Proposed mechanisms include alpha-adrenergic receptor antagonism, interactions with muscarinic receptors, effects on plasma norepinephrine levels, and inflammatory pathways. Risk factors include advanced age, high dose, rapid dose titration, and comorbid conditions such as thyroid dysfunction and metabolic disorders. Anxiety-induced tachycardia results from activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased heart rate and cardiovascular stress.

Conclusions

Clozapine is effective in treating resistant schizophrenia but carries significant cardiovascular risks, including tachycardia. Differentiation between clozapine-induced and anxiety-induced tachycardia is critical for appropriate management. Regular cardiovascular monitoring, dose adjustment, and lifestyle modifications are essential to reduce these risks. Further research is needed to clarify the exact incidence of clozapine-induced tachycardia, explore specific mechanisms, and develop effective management strategies. Understanding the interaction between clozapine and tachycardia, as well as the impact of comorbid anxiety, is critical to optimizing patient care and ensuring safe long-term use of clozapine.

Key words: clozapine, tachycardia, anxiety, heart rate, anticholinergic

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Introduction

Tachycardia is a common physical symptom in patients with mental illness. Both anxiety disorders and certain antipsychotic medications, such as clozapine, can cause tachycardia, which can lead to diagnostic uncertainty. Differentiating the cause of tachycardia is critical for effective treatment and patient safety.

Anxiety disorders are among the most common psychiatric conditions, affecting approximately 18% of the adult population in the United States each year[1]. Tachycardia is a frequent symptom in these patients, with studies indicating that up to 60-70% of individuals with anxiety disorders experience increased heart rates during anxiety episodes[2]. The prevalence of tachycardia is higher in patients with panic disorder, generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD), where autonomic dysregulation is more pronounced[3]. In patients with schizophrenia, the prevalence of anxiety is significantly higher than in the general population[4,5]. Studies indicate that up to 38-60% of patients with schizophrenia experience clinically significant anxiety symptoms or meet the criteria for an anxiety disorder[6,7].

Tachycardia is one of the most common cardiovascular side effects associated with clozapine treatment. Studies report that approximately 25-50% of patients on clozapine experience tachycardia, particularly during the initial stages of treatment. Clozapine-induced tachycardia can be symptomatic, causing palpitations, dizziness, and in severe cases, syncope. Chronic tachycardia increases the risk of developing other cardiovascular conditions, including hypertension, cardiomyopathy, and heart failure, and it is crucial to monitor heart rate and other cardiovascular parameters regularly in patients receiving clozapine[8-10]

This article reviews the characteristics of anxiety-induced tachycardia and clozapine-induced tachycardia, with special emphasis on the mechanisms, clinical features, diagnostic approach, and management of this condition.

Methods

Studies examining the association between anxiety and tachycardia and between clozapine and tachycardia were selected. MEDLINE and Scopus databases were searched using the following keywords: “clozapine”, “tachycardia”, “anxiety”, “cardiac effects”, “side effects”.

After an initial screening of titles and abstracts to identify potentially relevant studies, a full-text review of selected articles was conducted to evaluate the clinical characteristics and mechanisms of anxiety-induced tachycardia and clozapine-induced tachycardia.

Anxiety-induced tachycardia

Clinical features of anxiety-induced tachycardia

Tachycardia in patients with anxiety often presents with a heart rate that typically exceeds 100 beats per minute (bpm) at rest. This symptom is usually accompanied by other physical and psychological signs of anxiety[11], including:

1. Palpitations: patients may report a feeling of the heart racing or pounding.

2. Shortness of breath: difficulty breathing or hyperventilation often accompanies tachycardia.

3. Chest Pain: although typically non-cardiac in origin, chest pain can be alarming and distressing.

4. Sweating: excessive sweating is a common autonomic response to anxiety.

5. Tremors and shaking: fine motor tremors and shaking can occur during episodes of intense anxiety.

6. Dizziness and lightheadedness: these symptoms may result from hyperventilation and associated changes in blood gases.

Tachycardia in patients with anxiety results from complex interactions between the sympathetic nervous system (SNS), the hypothalamic-pituitary-adrenal axis (HPA) axis, and other physiological factors. The primary mechanism driving tachycardia in anxiety is activation of the SNS. Anxiety triggers the body’s “fight or flight” response, which is mediated by the hypothalamus[12]. The hypothalamus sends signals through the autonomic nervous system, specifically the SNS, to the adrenal medulla[12].

During this fight-or-flight response[13], the body releases epinephrine, norepinephrine, and other stress hormones, resulting in increased heart rate, elevated blood pressure, and rapid breathing[13]. These physiological changes prepare the body to respond to perceived threats by increasing blood flow to essential muscles and organs[13]. Once released, epinephrine and norepinephrine bind to beta-adrenergic receptors on heart muscle cells. This binding increases heart rate by increasing the activity of the sinoatrial (SA) node, the heart’s natural[1]. Binding of catecholamines to beta-1 adrenergic receptors also increases the force of myocardial contractions, contributing to increased cardiac output[14]. The HPA axis is another critical pathway in the stress response. Anxiety activates the HPA axis, resulting in the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal cortex to produce cortisol[15,16]. Cortisol increases the cardiovascular system’s sensitivity to catecholamines, further enhancing the tachycardic response[17].

In addition, cortisol itself enhances the tachycardic response by acting on mineralcorticoid receptors in the cardiovascular system[17]. Anxiety can also cause vagal withdrawal, which reduces the inhibitory effects of the parasympathetic nervous system on the heart. This leads to unopposed sympathetic influence, resulting in tachycardia[18,19]. In addition, anxiety often leads to

hyperventilation, which decreases the level of carbon dioxide in the blood. This respiratory alkalosis can increase heart rate and cause palpitations, further contributing to tachycardia[20].

Anxiety-induced tachycardia typically presents with a constellation of psychological symptoms, including feelings of anxiety, nervousness, or panic, being temporally associated with the peak of anxious symptoms[21]. Chronic anxiety can lead to persistently elevated heart rates (tachycardia), which can stress the cardiovascular system over time. This sustained activation of the stress response can lead to long-term cardiovascular problems, including hypertension, heart disease, and arrhythmias[22].

The potential link between anxiety and tachycardia may be highlighted by the fact that some studies show how benzodiazepines, commonly prescribed for anxiety, can have a calming effect on the central nervous system and effectively reduce heart rate. For example, it has been observed that the administration of alprazolam and lorazepam to hypertensive patients reduced heart rate along with blood pressure[23]. In addition, bromazepam reduced heart rate in patients with mild hypertension[24].

Clozapine induced tachycardia

Clozapine exhibits high-affinity binding to adrenergic receptors, particularly $\alpha 1$ and $\alpha 2$[25]. This binding is significant as it plays a role in the modulation of the sympathetic nervous system, influencing cardiovascular and stress responses[26]. The drug also targets dopamine receptors D1, D2, and D4, which are critical in the regulation of psychotic symptoms, mood, cognition, and reward[25,27-30]. Clozapine interacts with several serotonin receptors, including 5-HT2A/5HT2C, 5HT2B 5-HT6 and 5-HT7: these interactions are believed to contribute to its effects on mood and anxiety, as well as psychotic symptoms and cognitive functions[31-35]. The binding to muscarinic receptors, specifically M1, M2, M3, M4 and M5, has been linked to its anticholinergic effects, which can impact cognitive and gastrointestinal functions[36-38]. In addition, clozapine has a notable affinity for histaminergic receptors H1 and H3, influencing sedation and weight gain, common side effects associated with its use[36,39].

Proper management of clozapine dosing is crucial to ensure its effectiveness and minimize the risk of adverse effects[40]. One study highlighted the importance of monitoring clozapine plasma concentrations to achieve optimal treatment responses in patients with treatment-resistant schizoaffective disorder[41].

While clozapine is effective in managing psychiatric symptoms, its use is associated with a range of adverse effects that require careful monitoring and management[42-44]. For instance, the ClozaGene Study[45], a nationwide cohort of adults treated with clozapine, identified various side effects based on self-report questionnaires from 1021 participants recruited via mail-out based on clozapine prescriptions. The study found the following side effects: sialorrhea (80.3%), weight gain (71.0%), constipation (56.9%), and sleeping 10 hours or more a night (52.8%). Additionally, 24.3% reported experiencing heart problems, about 20% reported type II diabetes or high blood sugar levels, 8.2% experienced neutropenia, and 6.5% had seizures. In particular, one notable adverse effect of clozapine is tachycardia, a condition characterized by an abnormally rapid heart rate (HR), defined as a HR > 100 beats per minute (bpm)[46]. Tachycardia is a significant concern in patients taking clozapine, as it can have serious implications for cardiovascular health and overall well-being. The occurrence of tachycardia as an adverse effect of clozapine underscores the importance of closely monitoring patients for cardiovascular side effects during treatment[42,45,47,48].

Studies have shown that clozapine can lead to changes in heart rate and rhythm, necessitating regular monitoring of cardiac function during treatment[42,47,48]. The potential for clozapine to cause cardiovascular side effects, including tachycardia, underscores the need for individualized treatment approaches that consider both the therapeutic benefits and potential risks associated with this medication.

Incidence

The incidence of clozapine-induced tachycardia varies across different patient populations and settings. Research has indicated that a benign, sustained tachycardia, characterized by an average heart rate elevation of 10 to 15 beats per minute, can manifest in approximately 25% of patients treated with clozapine[49]. A review by Safferman[9] has shown as well an incidence of tachycardia around 25% in patients treated with clozapine, stressing that tachycardia can occur even when the patient is resting in a supine position, indicating that it is not solely due to orthostatic changes. Another study involving patients previously treated with two to four other neuroleptics showed a prevalence of tachycardia of 3%. Another study of clozapine-treated patients found a prevalence of tachycardia of only 3%. However, this was a retrospective study based on chart review and it is likely that the majority of cases of tachycardia were not recorded in the chart[50].

Several other studies have documented varying incidences of tachycardia among patients treated with clozapine. One study reported an incidence of approximately 30%[51], another observed a higher rate at 58%[52], and a third found a lower incidence of 14%[53]. Additionally, research comparing clozapine with long-acting antipsychotics identified that 33% of patients on long-

term clozapine therapy experienced tachycardia[54]. Another observational study highlighted gender differences, showing a prevalence of tachycardia in males of 70.83% versus a prevalence in females of 51.16%[55]. A 2020 study based on 101 individuals with psychotic disorders attending a clozapine community clinic revealed a tachycardia prevalence of 51%[56].
Tolerance to clozapine-induced tachycardia generally develops within 4 to 6 weeks[57]. Sinus tachycardia is the most common electrocardiogram (ECG) abnormality observed with clozapine-induced tachycardia[58-60].

Mechanisms of clozapine-induced tachycardia

Clozapine may cause tachycardia by several mechanisms, including alpha-adrenergic antagonism, cholinergic antagonism, fever, and inflammatory conditions such as myocarditis and pericarditis.

Alpha-adrenergic antagonism

One significant mechanism believed to contribute to clozapine-induced tachycardia involves the drug's antagonistic impact on alpha-adrenergic receptors[61] The blockade of alpha-adrenergic receptors can cause tachycardia through mechanisms involving reflex responses and increased norepinephrine release. Alpha-1 adrenergic receptors, when activated, induce vasoconstriction. Blocking these receptors leads to vasodilation and a consequent drop in blood pressure. To compensate for this drop, the body increases the heart rate through a reflex mechanism[62-65]. The potent antagonist properties of clozapine on alpha-1 adrenergic receptors may underlie the association between clozapine and hypotension, and thus to reflex tachycardia[66].
Clozapine might be associated with a 'first-dose effect,' resulting in significant hypotensive effects when the treatment is started or during dose increases, particularly with rapid titration[67]. However, desensitization of the α1-adrenergic receptors occurs with repeated exposure to α1-adrenergic antagonists, potentially leading to the development of tolerance over several weeks of treatment[68,69]. A 2021 meta-analysis indicated no correlation between orthostatic hypotension and clozapine/norclozapine plasma levels at steady state[70]. Nevertheless, other studies have observed a dose-related relationship: for instance, patients in clinical trials receiving 150-300 mg of clozapine per day experienced less dizziness compared to those taking 300-600 mg per day[71].
A study by Breier has shown that clozapine significantly increases plasma norepinephrine (NE) levels compared to conventional antipsychotics[72]. This effect may be due to the inhibition of NE reuptake into postganglionic terminals, enhanced NE vesicular fusion, downregulation of β-adrenoceptors, and/or inhibition of the norepinephrine transporter (NET)[72,73]. Increased plasma NE levels can contribute to tachycardia by stimulating beta-adrenergic receptors on the heart, which enhances heart rate and myocardial contractility[74-76].
Clozapine can cause tachycardia by blocking specific potassium channels in the heart, particularly the hERG (human Ether-à-go-go-Related Gene)/Kv11.1 channels[77,78]. This blockade interferes with the repolarization phase of the cardiac action potential, leading to prolonged QT intervals and increased susceptibility to arrhythmias such as Torsades de Pointes[77,78]. Additionally, clozapine's inhibition of Kv7.1 channels further disrupts cardiac electrical stability, contributing to the risk of tachycardia and other arrhythmias[77].

Cholinergic antagonism

Clozapine-induced tachycardia may arise also from anti-muscarinic effects. Clozapine indeed exhibits a range of anticholinergic effects that can impact various physiological systems. These effects include hypersalivation, constipation, loss of accommodation, urinary retention, and tachycardia[36-38,43,79,80]. The anticholinergic properties of clozapine primarily stem from its interaction with muscarinic receptors, in particular to M1 and M3 antagonism, leading to disturbances in cholinergic signaling pathways[16-18, 65].
Under normal resting conditions, the parasympathetic nervous system significantly influences the heart by activating muscarinic receptors[81]. This activation reduces the intrinsic firing rate of pacemaker cells, thereby decreasing the heart rate[82]. Additionally, parasympathetic input slows atrioventricular (AV) conduction[83]. Pharmacologically, this is important because muscarinic receptor antagonists, particularly M2 antagonists, can increase the intrinsic heart rate and enhance AV conduction by counteracting the parasympathetic effects[81].
As for the action of clozapine on muscarinic receptors, some in vitro studies have shown that clozapine has agonist activity at M4 receptors, while clozapine was an antagonist at M1, M2, M3, and M5 receptors[38,84]. Others have shown an action attributable to that of a partial agonist of clozapine on M2 and M4[37]. In vivo studies, however, have shown the presence of anticholinergic effects, hypothesizing an antagonistic activity of clozapine towards M2 receptors, although its action on these receptors in vivo remains not entirely clarified[18]. Nonetheless, the complex range of actions on muscarinic receptors, generally showing antagonist properties[9,61,84], could further explain the onset of tachycardia.
Furthermore, an interaction between the cholinergic and noradrenergic systems is also known: agonism at muscarinic receptors located on the postganglionic sympathetic nerve endings in the heart inhibits the release of NE during sympathetic neural activity[86].
Additionally, studies have demonstrated the presence

of other muscarinic receptors at the cardiac level, including M3[87] and M1[88].
Consequently, by interacting in a complex manner with the cholinergic system and exhibiting predominantly antagonistic action, clozapine may induce tachycardia[54,89].

Fever and inflammation

Clozapine-induced fever is a common occurrence, typically manifesting within the first four weeks of treatment. Studies report its prevalence varies widely, from 0.5% to 55%[90,91].This febrile response can activate the sympathetic nervous system, resulting in an increased heart rate as the body attempts to regulate its temperature[92].
The exact cause of clozapine-induced fever remains elusive. Hypotheses include a mild form of neuroleptic malignant syndrome (NMS), infection due to neutropenia, allergic reactions, or the immunomodulatory effects of clozapine[90,91]. The absence of typical NMS symptoms often rules out this condition as the cause. While some patients exhibit mild leukocytosis, the lack of other infection signs suggests infection secondary to agranulocytosis is not the primary cause clozapin[90,91]. The theory of an allergic reaction is also debated, as fever does not always recur upon resuming clozapine[90,91].
Clozapine's impact on inflammation has also been noted. It can modulate immune responses by affecting cytokine levels, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2), and interferon-gamma (INF-γ)[93]. Its immune-modulatory activity resembles that of cyclosporin A, enhancing sIL-2R release and inhibiting IL-2 production by activated T cells[94]. Another study found that clozapine increased plasma levels of TNF-alpha, soluble TNF receptors p55 and p75, and sIL-2r[93,95].
Although there are insufficient studies directly linking clozapine's inflammatory impact to fever, it is plausible that clozapine-induced fever could result from elevated levels of these inflammatory cytokines[96].
Clozapine is associated with other significant cardiac adverse effects, including myocarditis, pericarditis, and cardiomyopathy[80]. Myocarditis is an inflammation of the myocardium, which can impair the heart's ability to pump blood effectively and lead to rapid or irregular heart rhythms[97]. Common symptoms include chest pain, fatigue, shortness of breath, and palpitations[97]. Although rare, myocarditis occurs in approximately 3 per 1000 patients[98], typically within the first month of treatment, and is characterized by symptoms such as fever, chest pain, palpitations, and fatigue[97,98]. Diagnosis is supported by elevated cardiac biomarkers like troponin and C-reactive protein (CRP) and echocardiographic findings[99].
Pericarditis, an inflammation of the pericardium, is also linked to clozapine. It presents with chest pain and dyspnea and is often accompanied by pericardial effusion detectable via echocardiography[100]. Cases of pericarditis have been reported in patients undergoing clozapine therapy[101]. Management involves discontinuing clozapine and providing anti-inflammatory treatments, with documented symptom resolution following these interventions[101].
Dilative cardiomyopathy (DCM) is a clozapine adverse effect that may be related to direct cardiotoxic effects, immune-mediated reactions, or a combination of both. Immune-mediated myocarditis can lead to chronic inflammation and fibrosis, which may progress to DCM over time. DCM is often accompanied by tachycardia and typically presents with symptoms of fatigue, shortness of breath, and peripheral edema due to the heart's reduced ability to pump blood effectively[102]. This condition can lead to progressive heart failure and requires prompt diagnosis and treatment. The mechanisms linking tachycardia and DCM include**:**

1. Compensatory Mechanism:

o **Reduced Cardiac Output:** In DCM, the heart›s reduced ability to pump blood effectively triggers compensatory mechanisms to maintain adequate blood flow to vital organs. One such mechanism is an increased heart rate (tachycardia). The body attempts to compensate for the decreased stroke volume by increasing the heart rate to maintain cardiac output[103].

o **Neurohormonal Activation:** The sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) are activated in response to reduced cardiac output. This leads to increased levels of catecholamines (e.g., adrenaline) that stimulate the heart to beat faster[104].

Direct Cardiac Effects

Clozapine can have direct effects on cardiac tissue. It can cause alterations in myocardial ion channels, potentially leading to arrhythmias and tachycardia[77]. Additionally, clozapine's antagonistic effects on muscarinic receptors reduce vagal tone, contributing to an elevated heart rate[61].

Increased Metabolic Demand

The metabolic side effects of clozapine, such as weight gain, insulin resistance, and hyperlipidemia, can increase cardiovascular workload and contribute to tachycardia. These metabolic changes place additional strain on the cardiovascular system[105].

2. Arrhythmias:

o **Electrical Instability:** DCM can cause structural changes in the heart, such as fibrosis and remodeling, leading to electrical instability. This can result in various arrhythmias, including tachycardia (Dec, G. W., & Fuster, V. (1994). Idiopathic dilated cardiomyopathy. *New England Journal of Medicine*, 331(23), 1564-1575)

o **Atrial and Ventricular Tachycardia:** Patients with DCM are at increased risk of developing both atrial and ventricular tachycardia. These arrhythmias can further decrease cardiac efficiency and exacerbate symptoms of heart failure[106]

Risk factors

Several factors have been implicated in predisposing patients to clozapine-induced heart problems such as myocarditis, including age, dosage, comorbidities, and individual patient characteristics[107].

Age is a significant ++factor, as older patients often have reduced cardiovascular reserve and may be more susceptible to the cardiac side effects of clozapine[107]. There is conflicting evidence regarding age as a risk factor, with some studies suggesting that older age increases the risk of myocarditis. Higher cumulative doses of clozapine and rapid dose titration are potential risk factors, with the odds of myocarditis increasing with higher clozapine doses and rapid titration[107-109].

It is also important to consider comorbidities, which could predispose patients to tachycardia. Conditions such as hypertension, ischemic heart disease, or arrhythmias increase the risk of developing tachycardia[110]. Additionally, metabolic disorders such as diabetes and obesity, prevalent among patients with schizophrenia, can exacerbate cardiovascular stress and increase the propensity for tachycardia[110].

In particular, thyroid dysfunctions must be considered; indeed, several drugs commonly used in psychiatry can impact thyroid function[111], including lithium[111,112], phenothiazine antipsychotics, tricyclic antidepressants, some atypical antipsychotics, and carbamazepine[111]. It is well known that the thyroid has a close relationship with cardiac function and heart rate[113].

Moreover, patients taking clozapine might also be prescribed other psychotropic medications that can directly promote the onset of tachycardia, particularly those belonging to the class of antipsychotics[114].

Dosage of clozapine is another crucial factor. Studies have shown that both the dosage and the type of titration are correlated with the risk of cardiac issues such as myocarditis[107]. Furthermore, one study found a positive correlation between heart rate and plasma levels of clozapine and norclozapine[56]. The clozapine to norclozapine ratio was also significantly associated with heart rate, suggesting that serum clozapine levels might have a more potent effect on heart rate than norclozapine[56].

This concept suggests that variables influencing the plasma levels of clozapine and norclozapine also impact the likelihood of tachycardia[115,116].These variables include genetic polymorphisms in enzymes such as CYP1A2, CYP2D6, and CYP3A4, leading to different metabolic rates among individuals[115,116]. Smoking, which induces CYP1A2, can reduce clozapine levels, while smoking cessation can increase them[115,117]. Drug interactions are pivotal as well; for instance, medications that inhibit CYP450 enzymes, such as fluvoxamine, can elevate clozapine levels[115,118]. Dietary factors like caffeine, an inhibitor of CYP1A2, can also increase clozapine levels[115,119]. Furthermore, age and gender differences affect metabolism, with older patients and women generally showing higher plasma levels.

Management strategies

Dose adjustment

Gradual titration of clozapine can help minimize the risk of tachycardia. Starting at a low dose and slowly increasing it allows the body to adapt to the medication's cardiovascular effects[120].

Beta-blockers

Beta-blockers, such as propranolol and metoprolol, are often used to manage clozapine-induced tachycardia. These medications reduce heart rate by blocking the effects of catecholamines on beta-adrenergic receptors[121].

Lifestyle modifications

Encouraging patients to adopt healthy lifestyle practices, such as regular exercise, a balanced diet, and smoking cessation, can mitigate some cardiovascular risks associated with clozapine therapy[122].

Monitoring and regular assessments

Regular cardiovascular assessments, including ECG monitoring and measurement of heart rate and blood pressure, are essential for early detection and management of tachycardia in clozapine-treated patients. Holter monitoring can be useful for capturing intermittent arrhythmias[123].

Adjunctive medications

In some cases, adjunctive medications like clonidine or ivabradine may be considered. Clonidine, an alpha-2 adrenergic agonist, can reduce sympathetic outflow, thereby decreasing heart rate[121]. Ivabradine specifically inhibits the If current in the sinoatrial node, leading to heart rate reduction without affecting myocardial contractility[121,124].

Clozapine discontinuation

In cases of serious or potentially dangerous conditions such as mycarditis, pericarditis, or dilative cardiomyopathy, a cardiologist should be consulted immediately to evaluate the need for discontinuation of medication and initiation of specific treatment for the above conditions.

Discussion

Clozapine is considered one of the cornerstone treatments for schizophrenia, especially treatment-resistant schizophrenia[125-127]. However, its use requires careful consideration of its tolerability profile and potential adverse effects, including cardiac side effects[43,44]. The most frequently encountered cardiac issues include tachycardia, orthostatic hypotension, myocarditis, and cardiomyopathy[25,61]. Tachycardia, characterized by an increased heart rate exceeding 100 beats per minute, occurs in 10-58% of patients treated with clozapine[9,52,56].

In a patient with tachycardia, it is important to consider the presence of certain comorbidities, such as anxiety disorders, which are known to be associated with tachycardia. Anxiety-induced tachycardia is characterized by its episodic nature, being associated with the exacerbation of both psychological and somatic symptoms, and tends to subside with the treatment of the underlying anxiety[2,128]. Anxiety triggers the body's "fight or flight" response, leading to the release of epinephrine and norepinephrine, which increase heart rate by acting on beta-adrenergic receptors in the heart[12,129]. Chronic anxiety can lead to sustained elevated heart rates, which can stress the cardiovascular system over time, potentially leading to hypertension, heart disease, and arrhythmias[17].

In addition to the role of comorbid anxiety, clozapine itself is a very common and direct cause of tachycardia through a variety of mechanisms. Myocarditis and pericarditis, are among the most serious conditions associated with clozapine use that can cause tachycardia[8,99,101]. Myocarditis has an incidence of 0.1% to 1.0% within the first two months of treatment and a fatality rate of approximately 25%, while cardiomyopathy occurs less frequently but is still a concern[8,99,101]. Genetic factors, such as polymorphisms in cytochromes responsible for drug metabolism, can affect clozapine levels and contribute to several cardiovascular side effects[115,116].

Management strategies for clozapine-induced tachycardia include dose adjustment, the use of beta-blockers, and regular cardiovascular monitoring[120,122]. In cases of severe tachycardia, adjunctive medications like clonidine or ivabradine may be considered. Additionally, lifestyle modifications such as regular exercise and smoking cessation can mitigate cardiovascular risks[123].

The paper, has several limitations that should be acknowledged:

1. The paper predominantly focuses on studies that highlight the adverse effects of clozapine, particularly tachycardia, but may not comprehensively cover all potential mechanisms or newer therapeutic strategies that mitigate these effects. The literature search might have missed some recent studies due to publication lags or access limitations.
2. The studies reviewed have considerable variability in their design, sample size, and methodologies, which can lead to heterogeneity in the findings. This variability makes it challenging to draw definitive conclusions about the incidence and mechanisms of clozapine-induced tachycardia and the differences from anxiety induced tachycardia.
3. The paper does not adequately address the impacts of age, gender, ethnicity, comorbid conditions, and genetic backgrounds. These factors can significantly influence the incidence and severity of tachycardia in anxiety patients as well as tachycardia in clozapine-treated patients.
4. While the paper discusses anxiety as a comorbid condition that can influence tachycardia, other psychiatric and medical comorbidities are not explored in sufficient detail. Conditions like metabolic syndrome, diabetes, and thyroid disorders, which are common in schizophrenia patients, can also affect heart rate and complicate the clinical picture.
5. There is a lack of longitudinal data in the reviewed studies. Most studies provide cross-sectional data, which do not capture the long-term cardiovascular risks associated with chronic clozapine use. Longitudinal studies are needed to understand the progression and management of tachycardia over time.
6. The paper offers limited and not comprehensive practical guidance on managing clozapine-induced tachycardia in clinical settings. While it discusses potential management strategies, more detailed protocols and evidence-based recommendations would benefit clinicians.
7. Although genetic polymorphisms affecting clozapine metabolism are mentioned, the paper does not delve deeply into pharmacogenomics, which could provide insights into personalized treatment approaches to minimize adverse effects.
8. The impact of psychosocial factors, such as stress, lifestyle, and adherence to treatment, on the development of tachycardia is not adequately covered. These factors can play a significant role in the overall health and treatment outcomes of schizophrenia patients.
9. There is a lack of comparative analysis with other antipsychotics regarding their cardiovascular side effect profiles. Such comparisons could help place the risks associated with clozapine in a broader context and guide clinicians in choosing the most appropriate treatment.
10. While several risk factors for clozapine-induced tachycardia are mentioned, the paper lacks a thorough quantitative analysis of these factors. Future studies should aim to quantify the risk associated with each factor to better inform clinical decision-making.

11. There is a paucity of intervention studies exploring how different treatment strategies (e.g., use of beta-blockers, lifestyle modifications) can effectively manage clozapine-induced tachycardia. Research in this area could provide actionable insights for improving patient care.

Despite these limitations, we have provided a comprehensive and clinically relevant review that warrants further research and may provide a practical aid to clinicians in the diagnosis and management of clozapine-induced tachycardia. In conclusion, when considering tachycardia in patients treated with clozapine, it is important to evaluate for comorbid conditions, such as anxiety, that may independently cause tachycardia. However, it is important to consider that clozapine itself has multiple mechanisms that can induce tachycardia, requiring careful monitoring and management to mitigate these risks. Further research is needed to better understand the interactions between anxiety, clozapine treatment, and tachycardia and to develop more effective management strategies.

Conflict of interest statement

Andrea Fagiolini has received research grants and/or has been a consultant for, and/or has been a speaker for: Allergan, Angelini, Apsend, Generici DOC, Lundbeck, Italfar-maco, Janssen, Otsuka, Pfizer, Recordati, Roche, Sanofi Aventis, Sunovion; Alessandro Cuomo is/has been a consultant and/or a speaker for Angelini, Glaxo Smith Kline, Lundbeck, Janssen, Otsuka, Pfizer, Recordati.

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Authors contribution

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Ethical consideration

Not applicable

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