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Highlights

- Hypersalivation and weight gain were the two most common adverse drug reactions.
- Younger participants were more prone to experiencing common adverse drug reactions.
- Lower BMI prior to treatment was associated with higher significant weight gain.
- Higher clozapine blood levels were linked to the occurrence of constipation.
- Antipsychotic polypharmacy was not associated with more adverse drug reactions.

Comprehensive dissection of prevalence rates, sex differences, and blood level-dependencies of clozapine-associated adverse drug reactions

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Abstract

Clozapine is often underused due to concerns about adverse drug reactions (ADRs) but studies into their prevalences are inconclusive. We therefore comprehensively examined prevalences of clozapine-associated ADRs in individuals with schizophrenia and demographic and clinical factors associated with their occurrence. Data from a multi-center study (*n*=698 participants) were collected. The mean number of ADRs during clozapine treatment was 4.8, with 2.4% of participants reporting no ADRs. The most common ADRs were hypersalivation (74.6%), weight gain (69.3%), and increased sleep necessity (65.9%), all of which were more common in younger participants. Participants with lower BMI prior to treatment were more likely to experience significant weight gain (>10%). Constipation occurred more frequently with higher clozapine blood levels and doses. There were no differences in ADR prevalence rates between participants receiving clozapine monotherapy and polytherapy. These findings emphasize the high prevalence of clozapine-associated ADRs and highlight several demographic and clinical factors contributing to their occurrence. By understanding these factors, clinicians can better anticipate and manage clozapine-associated ADRs, leading to improved treatment outcomes and patient well-being.

Key words: Schizophrenia, treatment-resistant schizophrenia, antipsychotics, side-effects.

1. Introduction

One-quarter to one-third of people diagnosed with schizophrenia experience treatment-resistant symptoms, leading to poor outcomes and a high social and economic burden (Howes et al., 2017; Kennedy et al., 2014). Clozapine is the most effective antipsychotic in reducing positive symptoms and hospitalizations among people diagnosed with treatment-resistant schizophrenia (TRS), with approximately 40% of people diagnosed with TRS responding to clozapine treatment (Land et al., 2017; Siskind et al., 2016, 2017). Despite its effectiveness, clozapine is substantially underused in most countries (Bachmann et al., 2017). Several barriers, including patient and clinician-related factors, can impede or delay the initiation of clozapine treatment. Besides the need for routine blood monitoring, important obstacles include the fear of adverse drugs reactions (ADRs) and insecurities and challenges in managing them (Baig et al., 2021; Farooq et al., 2019).

ADRs associated with clozapine range from potentially fatal conditions , such as agranulocytosis, ileus, pneumonia, and myocarditis, to more common and disabling side effects such as weight gain, hypersalivation, and sedation.

To the best of our knowledge, the largest study on clozapine-associated ADRs, conducted by Iqbal et al. in 2020, analyzed electronic health care data from N=2,835 clozapine users, identifying agitation, fatigue, and sedation as the most common ADRs (Iqbal et al., 2020). However, ADRs are often underreported in medical files due to inaccurate, incomplete, and non-standardized documentation (McLachlan et al., 2021). Several other studies have also examined the prevalence of clozapine-associated ADRs, but these studies had small sample sizes and used different methods for eliciting and quantifying ADRs, leading to widely varying prevalence numbers (De las Cuevas et al., 2023; Tuunainen et al., 2000; Yusufi et al., 2007).

Regarding factors associated with ADRs, the findings in the systematic review by Gurrera et al. hint that higher clozapine blood levels increase seizure risk and higher clozapine doses may lead to sedation, delirium, and seizures (Gurrera et al., 2022). However, the authors concluded that most studies were case reports, studies with small sample sizes, or analyses of administrative databases, which are known to be affected by selection bias, low power, and poor reproducibility (Gurrera et al., 2022). A meta-analysis by Shirazi et al. found no association between constipation on the one hand and age, clozapine dose, duration of treatment, clozapine blood level, or norclozapine blood levels on the other (Shirazi et al., 2016). Again, sample sizes in the included studies were low (mean N=64 participants per study).

In sum, the literature on the prevalence and risk factors of clozapine-associated ADRs is inconclusive. To overcome limitations of previous studies, we conducted a comprehensive analysis of clozapine-associated ADRs using an extensive, international dataset, based on homogeneous and structured data collection. Our aim was to inform patients and clinicians about prevalence rates of common clozapine-associated ADRs. We therefore collected and analyzed detailed ADR data from patients representative of the real-world population of clozapine using patients with schizophrenia. We refrain from inferring hazard ratios for these ADRs relative to control groups as this was not a (placebo-)controlled study. We highlight several actionable findings for clinical practice and guidelines, thus aiming to contribute to improved outcomes for these patients.

2. Methods

2.1 Study design, setting and participants

A cross-sectional analysis was conducted using data recruited by the the CLOZapine INternational (CLOZIN) consortium between 2016 and 2022. This multi-center study (www.clozinstudy.com) aims to detect associations of clozapine response and clozapine-associated ADRs using extensive phenotypic and genetic data. Details of the study set-up and inclusion criteria can be found elsewhere (Okhuijsen-Pfeifer et al., 2022). In brief, participants of the CLOZIN study were enrolled via community and academic psychiatric hospitals in The Netherlands, Germany, Austria, Finland, Italy, Spain, Turkey, and Serbia (Supplementary Methods). Participants were included if they: (1) were aged 18 years or older, (2) had had been diagnosed with a schizophrenia spectrum disorder according to the fourth or fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), and (3) were using clozapine (without minimum duration of treatment). The eligibility criteria were intentionally non-restrictive to represent real-world patients, as this enhances clinical value and applicability. All participants provided written informed consent prior to participation. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by METC NedMec, 15-306/M.

2.2 Variables

2.2.1 Outcome measurement

The dependent variables in this study were the occurrence of specific clozapine-associated ADRs anytime during clozapine therapy; the occurrence of any serious adverse event (SAE)(OHRP, 2007); and the total number of ADRs (i.e., the sum of all ADRs and SAEs reported by a participant).

To determine the prevalence of clozapine-associated ADRs, a standardized questionnaire (Supplementary Figure 1) was used to query participants during the single study visit. Participants were asked to report if they experienced any of the following common ADRs during clozapine treatment (past or present): drowsiness, dizziness, hypersalivation, increased sleep necessity, nausea, urinary incontinence, heart palpitations, weight gain, decreased libido, and constipation (Hynes et al., 2015). Furthermore, participants were asked how many kilograms of weight change they had experienced since starting clozapine treatment. If there was uncertainty or ambiguity concerning the experience of ADRs, the treating physician was consulted. We then calculated for each participant whether they experienced >10% of weight gain since starting clozapine treatment (measured as binary outcome; see Supplementary

Methods for different cut-offs that we also used to corroborate the robustness of our results)(Wilding et al., 2021). The occurrence of metabolic syndrome at the time of the study visit was assessed based on the National Cholesterol Education Program Adult Treatment Panel III criteria (Rezaianzadeh et al., 2012). For the assessment of SAEs, participants and their treating physicians were asked if the participant had ever experienced one of the following ADRs during clozapine treatment: agranulocytosis, neutropenia (local cutoff values, which may slightly differ by country, were used), diabetic keto-acidosis, neuroleptic malignant syndrome, ileus, or myocarditis. Whenever either a participant or a physician reported one of these during clozapine treatment this outcome was rated affirmatively.

2.2.2 Independent variables

The following independent variables were examined for their associations with ADRs: age, sex, body mass index (BMI) before start of clozapine treatment, clozapine blood levels, clozapine dose, and duration of clozapine treatment. All were continuous measures, except sex. Age was additionally categorized into 10-years increments to allow for clinical interpretation. To calculate BMI before the start of clozapine treatment, we subtracted the number of kilograms of weight change since the start of clozapine treatment (based on self-report) from the body weight measured during the study visit. This allowed us to classify participants into three categories: those with a BMI in the normal range (<25 kg/m^2), those with a BMI in the overweight range (25 to 30 kg/m^2), and those with a BMI in the obesity range (≥30 kg/m^2). Additionally, we categorized BMI into six categories according to the World Health Organization guidelines, ranging from 'underweight' to 'obesity class 3' (Supplementary Figure 2)(WHO, 2010).

Steady-state clozapine blood levels were assessed either as a routine practice or, whenever not performed as such, as part of the study protocol. Specifically, accredited clinical laboratories at each center measured clozapine blood levels using liquid chromatography tandem mass spectrometry 11-14 hours after the last dose of clozapine (LC-MS/MS)(assay and further details can be found in(Okhuijsen-Pfeifer et al., 2022). Clozapine blood levels were divided into three categories based on therapeutic efficacy: sub-therapeutic (<250 ug/L), therapeutic (250-550 ug/L), and supra-therapeutic (>550 ug/L)(Northwood et al., 2023). Additionnaly, clozapine blood levels and clozapine dose were subdivided in quintiles to allow for unbiased statistical confirmation of any ADR blood-level dependency findings. The quintiles for clozapine blood levels were: Q1 (<196 µg/L), Q2 (197-316 µg/L), Q3 (317-415 µg/L), Q4 (416-600 µg/L), and Q5 (>600 µg/L). The quintiles for clozapine dose were: Q1 (<150 mg), Q2 (151-250 mg), Q3 (251-325 mg), Q4 (326-450 mg), and Q5 (>450 mg). Duration of clozapine treatment was assessed as the

number of years since clozapine initiation, which was determined by self-report or physician assessment in case of uncertainty.

2.3 Statistical analyses

The Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 26.0) was used for data analysis. For descriptive statistics, categorial variables were described using frequencies and percentages and continuous variables were described using means and standard deviation (SD). Participants were excluded from data analysis if age, sex, or data on the occurrence of *all* ADRs was missing. If data on other independent variables or the occurrence of a specific ADR was missing, participants were excluded from these specific analyses.

We checked that the assumptions of normality, homoscedasticity, linearity, and multicollinearity were not violated. Multiple linear regression analyses were then conducted to examine the associations between the independent variables and the total number of ADRs per participant. We report the unstandardized coefficient beta (B) as our main test statistic, representing the change in the dependent variable for a one-unit change in the independent variable, with 95% confidence intervals (CIs). Furthermore, multiple logistic regression analyses were performed to assess the associations between the independent variables and the occurrence of specific ADRs and any SAE. The odds ratio (OR) is interpreted as the ratio of the odds of the dependent variable occurring in the group with the independent variable compared to the odds of the dependent variable occurring in the group without the independent variable. 95% CIs were provided for each outcome. In both the linear and logistic regression analyses, we included one independent variable along with age and sex. If age was the variable of interest, only sex was included, and vice versa.

To account for multiple testing, we applied Bonferroni correction: α=0.05 was thus divided by the total number of tests performed (13; i.e., one test for associations with the total number of ADRs; eleven tests for each specific ADR; and one test for experiencing any SAE), resulting in a corrected significance level of $p<0.05/13=3.8x10^{-3}$.

To assess the robustness of our models, we conducted sensitivity analyses by adjusting for potential confounders. Based on previous literature and considering variables that may interact with clozapine metabolism, we identified several potential confounders. These included the participant's diagnosis, ethnicity, country of residence, illness duration, clinical global impression (CGI) score, smoking status, use of cannabis, consumption of coffee exceeding 5 cups or 1 L per day, use of an antipsychotic drug in addition to clozapine (clozapine monotherapy vs. polypharmacy), use of a drug with

anticholinergic activity (Supplementary Table 1), and use of a CYP1A2 inhibitor (Supplementary Table 2). To measure the relationship between variables, we used Spearman's correlation coefficients for continuous variables, Point-Biserial correlation coefficients for the relationship between a continuous variable and a dichotomous or categorical variable, and Phi coefficient to measure the degree of agreement between two dichotomous variables. For each outcome measure, we included the variables that were found to be correlated with that outcome measure ($p<3.8x10^{-3}$) in the analyses (see Results section for the number of sensitivity analyses conducted).

3. Results

3.1 Clinical characteristics

698 patients were included in this study (Table 1 and Supplementary Table 3). Their mean age was 43.6 ±11.9 years and 31.5% were female. The mean clozapine blood level was 405.4 ±274.8 µg/L and the mean daily clozapine dose was 310.4 ±185.9 mg. The mean duration of clozapine treatment was 7.6 ±7.8 years. The percentage of missing values ranged from 10.7% for hypersalivation to 26.2% for drowsiness, with an average of 13.8% per ADR.

3.2 Prevalence of adverse drug reactions

Participants reported a mean of 4.8 (±2.3) ADRs during clozapine treatment (Figure 1). While any ADR occurred in ≥ 20% of participants, 2.4% of participants reported no ADR at all. The most common ADRs were hypersalivation (74.6%; *n*=465/623), weight gain (69.3%; *n*=422/609), and increased sleep necessity (65.9%; *n*=406/616). Before initiation of clozapine treatment, 56.6% of participants had a BMI within the normal range (BMI <25 kg/m^2), compared to 29.1% during the study visit. The group of people with a BMI in the obesity range (BMI >30kg/m^2) more than doubled after starting clozapine treatment (15.1% vs. 31.6%). 9.2% of the participants had reported an SAE (*n*=64), most commonly ileus (4.9%; *n*=30/607). Prevalence rates of ADRs stratified by sex, ethnicity, smoking status, and clozapine monotherapy vs. polytherapy can be found in Supplementary Table 4.

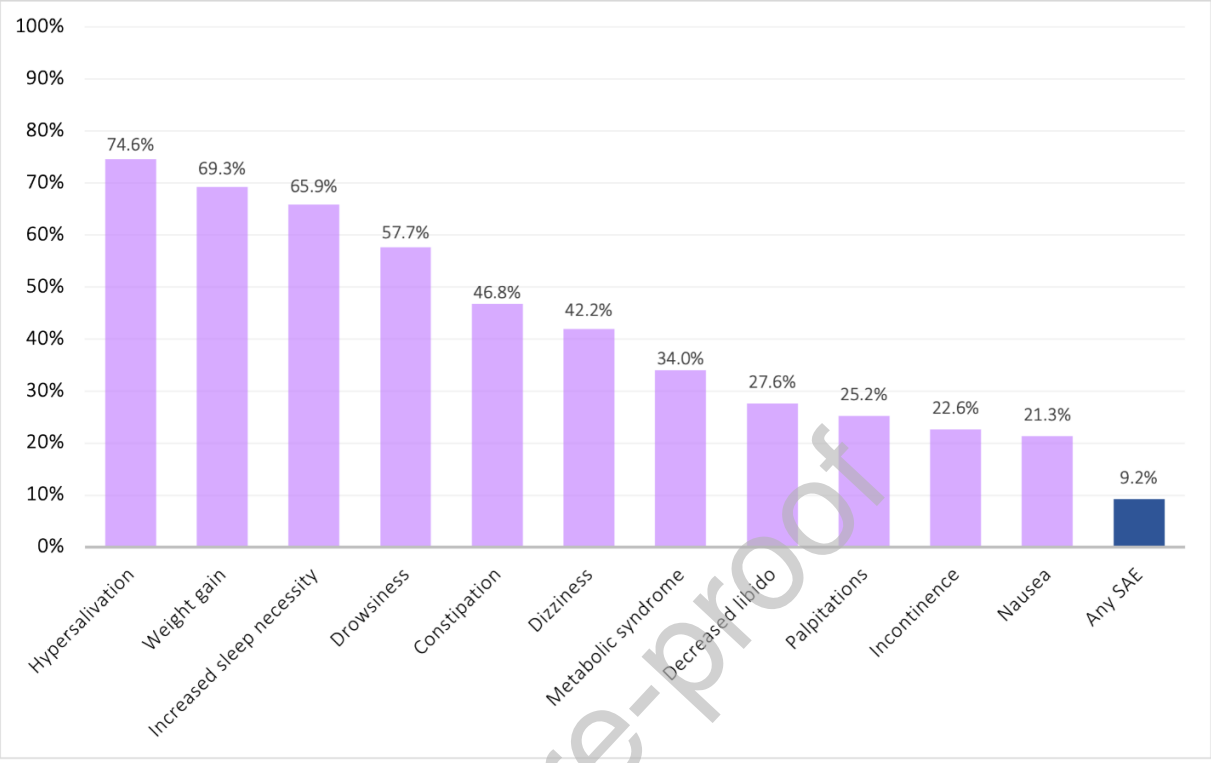


Figure 1. The prevalence of adverse drug reactions (ADRs) and serious adverse events (SAEs) occurring at any time during clozapine treatment. The prevalence of ADRs is presented on the y-axis as a percentage of participants who reported experiencing the specific ADR during clozapine treatment. The number of participants (N) who reported each ADR is displayed above the bars. Pink bars represent common ADRs, while the blue bar represents the occurrence of any SAE during clozapine treatment. The ADRs are listed in descending order of frequency, with the most commonly reported ADR appearing first and the least commonly reported ADR appearing last.

Table 1. Demographic and clinical characteristics assessed during the participant visit

	Total (*n*=698)	Mean (SD)	Median (min, max)
Age in years		43.6 (11.9)	44 (19, 76)
Sex			
Male	478 (68.5%)		
Female	220 (31.5%)		
Diagnosis			
Schizophrenia	526 (78.4%)		
Schizophreniform disorder	4 (0.6%)		
Schizoaffective disorder	96 (14.3%)		
Psychotic disorder NOS	45 (6.7%)		
Weight (kg) before start of clozapine treatment		78.7 (16.0)	76 (45, 147)
Weight (kg) during study visit		88.6 (19.1)	86 (48, 200)
BMI (kg/m^2) before start of clozapine treatment		25.4 (5.0)	24.3 (14.6, 48.9)
<25 kg/m^2	244 (56.6%)		
25-30 kg/m^2	122 (28.3%)		
> 30 kg/m^2	65 (15.1%)		
BMI (kg/m^2) during study visit		28.5 (5.8)	27.6 (18.8, 56.6)
<25 kg/m^2	175 (29.1%)		
25-30 kg/m^2	236 (39.3%)		
> 30 kg/m^2	190 (31.6%)		
Clozapine level (µg/L)		421.6 (278.3)	365.5 (5, 1850)
Clozapine dose (mg/day)		310.4 (185.9)	300 (12.5, 1200)
Duration of clozapine treatment (years)		7.6 (7.8)	5 (0, 50)
Illness duration (years)*		17.8 (10.6)	17 (0, 52)
Clozapine monotherapy vs. polytherapy			
Clozapine monotherapy	329 (55.6%)		
Polytherapy	263 (44.4%)		
Clozapine + 1 antipsychotic	191 (32.3%)		
Clozapine + 2 antipsychotics	58 (9.8%)		
Clozapine + 3 antipsychotics	12 (2.0%)		
Clozapine + 4 antipsychotics	2 (0.3%)		

Abbreviations: SD=standard deviation; min=minimum; max=maximum; NOS=not otherwise specified; BMI=body mass index.

*Number of years since the first episode of psychosis, which was determined by self-report or physician assessment in case of uncertainty.

3.3 Total number of adverse drug reactions

The total number of ADRs was significantly associated with sex (B=0.59, 95% CI 0.20-0.97, $p=3.3x10^{-3}$), with women experiencing an average of 5.1 ADRs compared to men experiencing 4.6 ADRs on average (i.e., 11% more ADRs than men). No association between the total number of ADRs and any other independent variable was found.

3.4 Specific adverse drug reactions

The prevalence of hypersalivation, increased sleep necessity, and weight gain was significantly associated with age, with every 10-year *increase* in age being associated with a 21% *decrease* in the odds of experiencing hypersalivation (OR=0.79, 95% CI 0.67-0.92, $p=1.0x10^{-3}$); a 25% *decrease* in the odds of experiencing increased sleep necessity (OR=0.75, 95% CI 0.64-0.87, $p=1.6x10^{-4}$); and a 28% *decrease* in the odds of experiencing weight gain (OR=0.72, 95% CI 0.62-0.85, $p=2.0x10^{-5}$; Supplementary Figure 3A-C).

Furthermore, people with an initial BMI <25 kg/m^2 were 3.3 times more likely to gain >10% weight than those with an initial BMI >30 kg/m^2 (OR=3.29, 95% CI 1.58-6.84, $p=1.5x10^{-3}$, Figure 2). The results of additional analyses, which examined the correlation between BMI and weight gain using various measurement approaches and BMI categories, are consistent with the aforementioned findings (Supplementary Figures 4-6). In addition, people with an initial BMI>30 kg/m^2 were 5.5 times more likely to experience metabolic syndrome compared to people with an initial BMI<25 kg/m^2 (OR=5.54, 95% CI 2.93-10.48, $p=1.4x10^{-7}$, Supplementary Figure 7A&B).

The likelihood of constipation increased as clozapine blood levels and dose increased: compared to people in a sub-therapeutic clozapine blood level range, those in a therapeutic blood level range had a 2.05 (95% CI 1.30-3.23, $p=2.0x10^{-3}$) times and those in a supra-therapeutic range had a 2.94 (95% CI 1.66-5.20, $p=2.2x10^{-4}$) times greater odds of reporting constipation (Figure 3A). Results were similar for clozapine blood levels divided into quintiles (Figure 3B) and clozapine dose (Supplementary Table 5)(Northwood et al., 2023). No other ADRs were associated with either clozapine blood levels or dose.

Lastly, urinary incontinence was associated with sex (OR=1.87, 95% CI 1.26-2.77, $p=2.0x10^{-3}$), with 19% of men experiencing urinary incontinence vs. 31% of women. There was no association between dizziness, nausea, drowsiness, palpitations, or decreased libido and any of the independent variables.

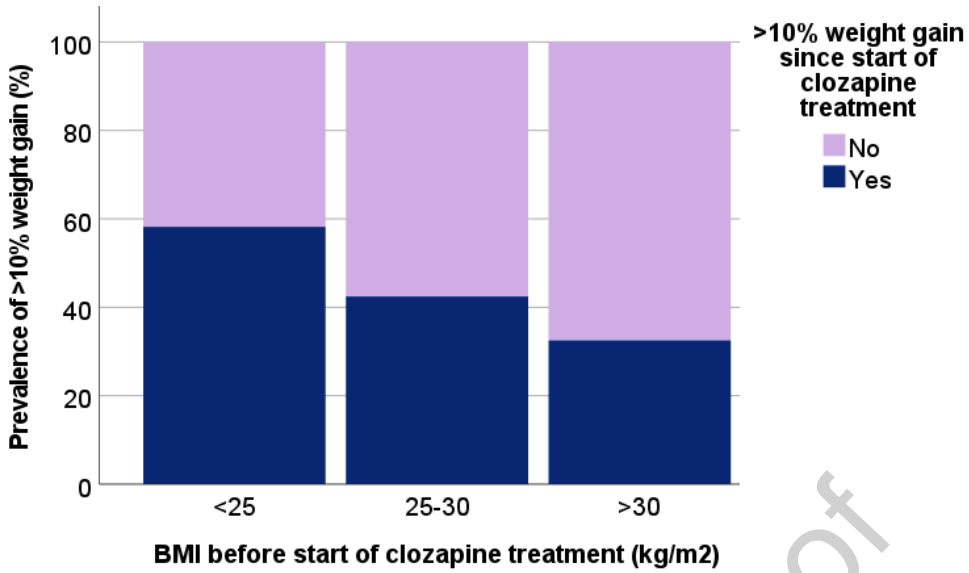
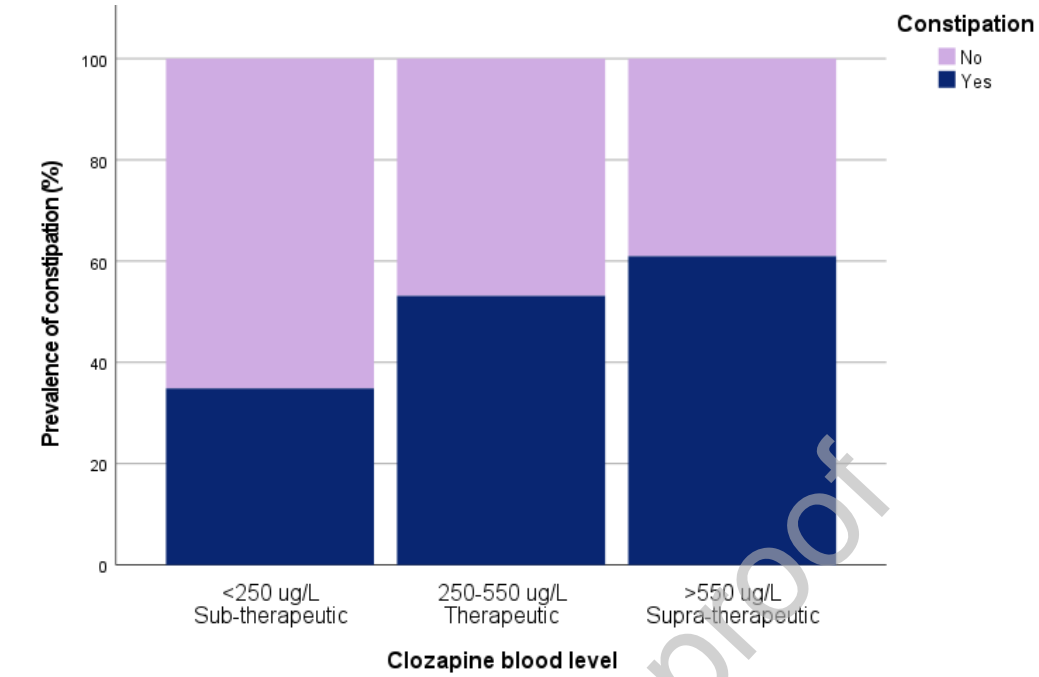
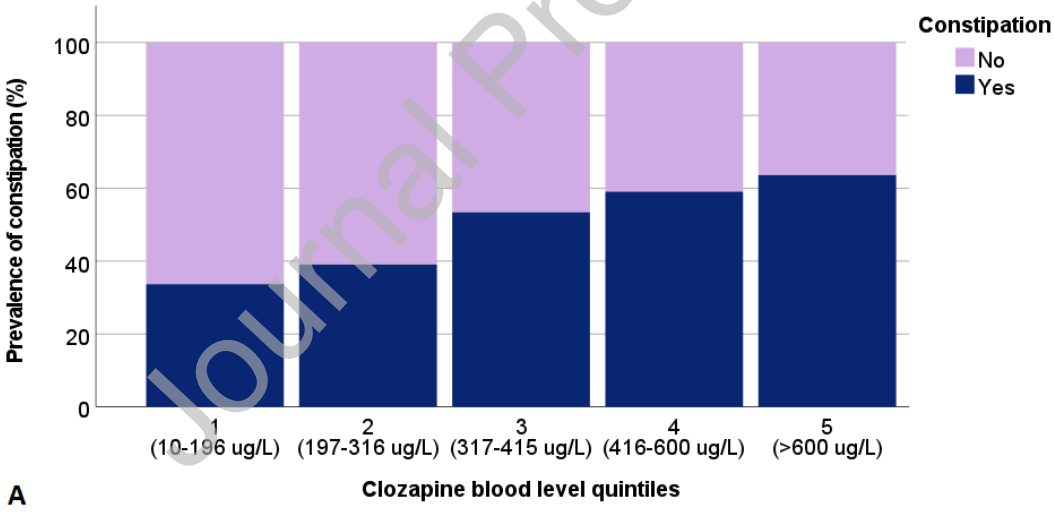


Figure 2. Prevalence of >10% weight gain in relation to BMI before start of clozapine treatment. Individuals with a BMI <25 kg/m^2 had a 10% weight increase prevalence rate of 58.2%, while those with BMI 25-30 kg/m^2 and BMI >30 kg/m^2 had rates of 42.5% and 32.6%, respectively.

A



B



A

Figure 3. Prevalence of constipation among participants within sub-therapeutic (34.8%), therapeutic (53.1%), and supra-therapuetic (61.0%) clozapine blood level ranges (A) and those according to clozapine blood level quintiles (33.7%, 39.1%, 53.4%, 59.1%, and 63.6%, respectively)(B).

3.5 Serious adverse events

No associations were found between the occurrence of an SAE and any of the independent variables.

3.6 Sensitivity analyses

The sensitivity analyses showed that all directions of effect and most significant levels of the associations remained robust when controlling for potential confounders (Supplementary Table 6; with only the associations between increased sleep necessity and age and between constipation and clozapine dose decreasing in signifance when controlling for illness duration and clozapine blood levels, respectively). Notably, we found no differences in the prevalence of ADRs between participants who were on clozapine monotherapy and those who received it in combination with other antipsychotics or drugs with high anticholinergic activity.

4. Discussion

We present results of a comprehensive analysis of clozapine-associated ADRs using an extensive international dataset comprising 698 individuals diagnosed with schizophrenia spectrum disorders. We found that participants reported a mean of 4.8 ADRs. Nearly, one in 10 (9.2%) of participants reported an SAE and only 2.4% of participants reported no ADR at all. The most commonly reported ADRs were hypersalivation (74.6%), weight gain (69.3%), and increased sleep necessity (65.9%), all of which were more common among younger participants. Furthermore, participants with a lower BMI prior to starting clozapine treatment were more likely to experience weight gain during clozapine treatment: 58% of participants with a BMI <25 kg/m^2 reported >10% weight gain during clozapine treatment. Constipation was the only ADR that occurred more frequently with increasing clozapine blood levels and dose. Finally, we found evidence that clozapine polytherapy does not increase risks of ADRs relative to clozapine monotherapy.

4.1 Main findings

To the best of our knowledge, the largest study to date on a broad range of clozapine-associated ADRs was conducted by Iqbal et al. in 2020. They analysed electronic healthcare data from 2,835 individuals who were prescribed clozapine, evaluating the prevalence of 33 clozapine-associated ADRs (Iqbal et al., 2020). The authors reported that the most prevalent ADRs occurred in around 40% of all participants, and only 14% of the participants experienced hypersalivation (Iqbal et al., 2020). We found that the prevalence of ADRs was much higher, with six ADRs occurring in over 40% of the participants, and hypersalivation occurring in 75% of participants. Prevalence rates reported in different studies vary widely (Yusufi et al., 2007). These inconsistencies may result from the underreporting of ADRs, which could be attributed to incomplete and imprecise documentation in medical records, as well as the tendency for ADRs to remain undetected unless patients are explicitly asked about them (McLachlan et al., 2021).

A meta-analysis of 32 studies comprising 2,013 participants reported a pooled prevalence of 31.2% for clozapine-associated constipation (Shirazi et al., 2016), an ADR that sometimes leads to life-threatening ileus (Handley et al., 2022). We found a higher prevalence (46.8%). This difference could be explained by the finding of Shirazi et al. that constipation rates tend to be higher in studies that measure constipation as a primary or secondary outcome compared to studies in which constipation was not a specified outcome measure (Shirazi et al., 2016). Moreover, it is known that prevalence rates of gastrointestinal hypomotility are often underreported (Cohen, 2017).

Our study confirms the findings of Iqbal et al. that women experience more clozapine-associated ADRs than men (Iqbal et al., 2020). Of note, our finding that women were more likely to experience urinary incontinence than men had to our knowledge not been reported before. Furthermore, we found that people with lower BMI prior to starting *clozapine* treatment were more susceptible to substantial weight gain after starting clozapine. A similar association was previously described for *antipsychotic*-induced weight gain (Correll et al., 2011). Other than metabolic syndrome, we found no indications that ADRs are experienced more by participants with higher BMI, as was suggested in a previous study (Modesto et al., 2020).

We show that constipation is associated with higher clozapine blood levels and dose. This finding is consistent with a prior study concluding that higher clozapine levels are positively associated with gastrointestinal hypomotility (Every-Palmer et al., 2016). However, the meta-analysis by Shirazi et al. showed no association between constipation and clozapine blood levels or dose (Handley et al., 2022). This may be explained by the low number of participants in the original studies, with only one study with more than 100 participants (*n*=202)(Shirazi et al., 2016). The finding of high prevalence rates of increased sleep necessity is aligned with previous research. Clozapine is well known to improve overall sleep quality and continuity in patients diagnosed with schizophrenia who experience insomnia (Kluge et al., 2014). However, most patients will experience sedation during clozapine titration, many of whom will complain of excess sleep for the whole duration of treatment. Indeed, sedation is the most frequently reported cause of clozapine discontinuation by patients and the second most reported cause by clinicians, after neutropenia (Legge et al., 2016). Further research is needed to elucidate the potential impact of co-morbid sleep disorders, such as obstructive sleep apnea syndrome, which is prevalent among individuals with increased BMI, as well as co-medication, on the occurrence of this ADR. In contrast to a previous study, we did not find an association between hypersalivation and clozapine blood levels or dose (Schoretsanitis et al., 2021).Other studies have also found associations between clozapine blood levels and/or dose and other ADRs, such as seizures, electroencephalogram (EEG) changes, and increased liver enzyme activity, but data on these ADRs were not available in our cohort (Gurrera et al., 2022; McLachlan et al., 2021). Finally, we have found no evidence indicating an increased risk of ADRs associated with the concomitant use of other antipsychotic medications during clozapine therapy, or the concomitant use of drugs with anticholinergic activity or CYP1A2. Nonetheless, it is important to acknowledge that the number of participants taking the latter was low, which limited our power to detect any potential impact on ADRs.

4.2 Strengths and limitations

A strength of our study is the large sample size with extensive phenotypic data, as this is the first study that assessed a broad spectrum of clozapine-associated ADRs by interviewing nearly 700 participants. Moreover, several sensitivity analyses were performed, confirming the robustness of the results. Our approach also had some limitations. First, our study population consists of individuals with sustained use of clozapine, and as such, may not be representative of those who have just initiated treatment or suspended treatment due to inefficacy, ADRs, or death. Consequently, the reported prevalence numbers in this study are likely to underestimate the true rates, i.e. as reported by all people who start a clozapine trial. Second, the cross-sectional design of the study limits our ability to establish causal relationships. Third, the occurrence of ADRs relies on participants subjectively reporting side effects, potentially introducing unquantifiable recall bias, particularly in the context of factors like weight gain. Nevertheless, this risk may be minimal for the majority of clozapine-associated ADRs since many clozapine users experience ADRs on a (almost) daily basis. Fourth, participants may not be inclined to report certain, potentially embarassing ADRs, such as urinary incontinence and decreased libido, possibly resulting in underreporting. Fifth, the relative rarity of clozapine-associated SAEs, such as agranulocytosis, ileus, pneumonia, and myocarditis, diminishes the reliability of prevalence estimates and curtails our ability to identify associations with demographic and clinical factors. Nevertheless, it is important to recognize that these specific ADRs can result in clozapine discontinuation. Studies with even larger study samples are required to examine associations between clozapine and with these rare but hazardous ADRs. Lastly, we focused on eleven possible clozapine-associated ADRs and did not analyze other potential ADRs such as seizures, obsessive-compulsive disorder symptoms, pneumonia, and orthostatic hypotension.

4.3 Conclusion and recommendations

The results of our study highlight the high prevalence of clozapine-associated ADRs and suggest that several clinical and demographic characteristics are associated with experiencing these ADRs. Hypersalivation and constipation were among the most common ADRs and can significantly impair quality of life and health. Effective and generally well tolerated treatment options exist for these ADRs, underscoring the importance of clinicians systematically and routinely querying for them to enable early detection and management. Additionally, based on our findings, we recommend clinicians to be aware of patient characteristics that might increase the risk of experiencing ADRs, such as younger age (for hypersalivation, increased sleep necessity, and weight gain), BMI <25 kg/m^2 (for weight gain), female sex (for urinary incontinence), and high clozapine blood levels (for constipation). On the other hand,

antipsychotic polypharmacy was not associated with increased prevalence rates of ADRs in our study. Guidelines may include these considerations to ensure more personalized clozapine prescribing. Follow-up research into an even broader array of ADRs and including other factors, such as medical history and genetic factors, is expected to further increase the understanding of clozapine's complex ADR profile. Additionally, more randomized controlled trials focusing on the management of clozapine ADRs are needed to improve treatment outcomes and quality of life.

Declarations of Interest

None.

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Author Contributions

Marte van der Horst: conceptualization, methodology, formal analysis, investigation, writing – original draft, visualization. **Yoeki Meijer:** formal analysis, investigation, writing – original draft, visualization. **Nini de Boer:** methodology, writing – review & editing. **Sinan Guloksuz:** methodology, writing – review & editing. **Alkomiet Hasan:** methodology, writing – review & editing. **Dan Siskind:** methodology, writing – review & editing. **Elias wagner:** methodology, writing – review & editing. **CLOZIN consortium:** investigation, resources, writing – review & editing. **Cynthia Okhuijsen-Pfeifer:** investigation, methodology, writing – review & editing. **Jurjen Luykx:** conceptualization, methodology, writing – review & editing, supervision.

Data availability

The data that support the findings of this study are available from the corresponding author, MH, upon reasonable request.

Supplementary Material

Supplementary material is available online.

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Declaration of Conflict of Interest:

None.