Vaccination and clozapine use: a systematic review and an analysis of the VAERS database

Aslihan Aksar[1] · Justina Lutz[1] · Elias Wagner[1,2] · Wolfgang Strube[1] · Jurjen J. Luykx[3,4,5] · Alkomiet Hasan[1,6]

Abstract
In the context of COVID-19 concerns related to the potential interactions between clozapine and vaccination arose. With the ultimate goal of deriving recommendations for clinical practice, we systematically reviewed the current evidence regarding altered vaccine effectiveness in clozapine-treated patients and safety aspects of vaccination, such as haematological changes and the impact of vaccines on clozapine blood levels, in clozapine-treated patients. A systematic PRISMA-conform literature search of four databases (PubMed, PsycINFO, EMBASE and Cochrane Library) complemented by a case-by-case analysis of the Vaccine Adverse Event Reporting System (VAERS) database was performed. We then systematically appraised the joint evidence and tried to derive recommendations for clinical practice. 14 records were included in this analysis. These records consisted of 5 original articles and 9 case reports. Among the original articles, two studies provided data on the association between clozapine use and antibody responses to vaccination, both indicating that clozapine use in schizophrenia may be associated with reduced levels of immunoglobulins. Additionally, three studies examined vaccine safety in clozapine-treated patients, with no clinically significant adverse effects directly attributable to the interplay between vaccinations and clozapine. VAERS Analysis encompassed 137 reports and showed no consistent evidence of an increased risk for clozapine blood level increases or adverse events. We found no evidence indicating that clozapine impairs the effectiveness of vaccines. Moreover, no serious safety concerns seem to apply when patients on clozapine are receiving vaccines. However, it is crucial to acknowledge that data on the interaction between clozapine and vaccines remain limited.

Keywords Clozapine · Vaccination · Immunization · Blood levels · Safety · Therapeutic drug monitoring (TDM)

Introduction

Clozapine (CLZ) is the only licensed antipsychotic monotherapy for treatment-resistant schizophrenia (TRS), which affects approximately 30% of individuals with schizophrenia [1]. Due to its unique side effect profile with rare, but potentially life-threatening complications, such as agranulocytosis or myocarditis, clozapine remains a third-line antipsychotic treatment and its use warrants regular haematological monitoring. Furthermore, therapeutic drug monitoring of clozapine blood levels is recommended in clinical practice, not only since adequate blood levels are associated with higher response rates [2] but also because blood levels above the therapeutic threshold may bring a higher risk for potentially severe side effects, such as epileptic seizures [3]. This is particularly relevant in clinical practice, given that numerous factors have been demonstrated to substantially impact clozapine blood levels. These factors include changes in (tobacco) smoking habits [4], ancestry [5], age, gender [6],

✉ Aslihan Aksar
Aslihan.Aksar@bkh-augsburg.de

1 Department of Psychiatry, Psychotherapy, and Psychosomatic Medicine, Faculty of Medicine, Bezirkskrankenhaus Augsburg, University of Augsburg, Geschwister-Schoenert-Str. 1, 86156 Augsburg, Germany

2 Department of Psychiatry and Psychotherapy, LMU University Hospital, Munich, Germany

3 Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands

4 Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

5 Outpatient Second Opinion Clinic, GGNet Mental Health, Warnsveld, The Netherlands

6 DZPG (German Center for Mental Health), Partner Site München/Augsburg, Augsburg, Germany

caffeine consumption [7], concomitant medication with clinically relevant Cytochrome P450 (CYP) 1A2 interaction [8] and infections [9].

During the SARS-CoV-2 (COVID-19) pandemic, it was shown that individuals with schizophrenia were at a greater risk for COVID-19 infection [10, 11], as well as hospitalization and mortality due to COVID-19, even after controlling for sociodemographic and clinical risk factors [12]. It was also suggested that an increased risk for infections in general [13] and a specific risk for SARS-CoV-2 might be associated with clozapine use [14]. Thus, vaccinations against not only the SARS-CoV-2 but also influenza and pneumococcal diseases are currently recommended to prevent unfavourable somatic outcomes in clozapine-treated patients [15–17]. The recently published Treatment Response and Resistance in Psychosis Working Group (TRRIP) consensus recommendations confirm this strategy [18]. However, in this context experts have proposed that bidirectional interactions between vaccines and drugs may occur [19]. Vaccines may interfere with drug metabolism, most likely via interferon γ overproduction, which might promote a decrease in specific CYP activity. This may result in substantial alterations in serum concentrations of specific drugs in the aftermath of a vaccination [20–23]. Several immunosuppressive compounds such as those licensed for multiple sclerosis, systemic lupus erythematosus and rheumatoid arthritis are suggested to affect vaccine response [24–27]. Clozapine's potential immunosuppressive and pro-inflammatory effects have been observed during clozapine initiation and in long-term clozapine users, leading to suggestions that clozapine may undermine the capacity of the immune system to fight infection. Clozapine was also associated with disruption to adaptive immunity through the suppression of white blood cells and by an increase in pro-inflammatory cytokine levels [13, 28], especially in interleukin-6 (IL-6) [29]. It was also associated with secondary antibody deficiency and a decrease in B cells [13].

Currently, in the scientific literature and in the Vaccine Adverse Event Reporting System (VAERS) database [30], there is a growing number of reports for adverse events occurring following the administration of vaccines in clozapine-treated patients. Established over three decades ago and co-managed by the Centers for Disease Control and Prevention (CDC) and the United States Food and Drug Administration (FDA), VAERS collects information about adverse events following the administration of vaccines throughout the United States. Hence, it represents one of the largest available data sets for the passive surveillance of vaccine interactions and potential vaccine-related side effects. Since data regarding medication are also collected and presented in the reports, they also serve as a valuable source for the evaluation of adverse events following vaccination in patients receiving clozapine. Case report data from VAERS are freely accessible, which renders it a user-friendly tool for clinicians and other healthcare professionals. Due to these special properties, we intended to add an additional layer of insight to the existing literature by adding a case-by-case analysis of the VAERS database to our systematic review of the available literature, focusing on the possible adverse events that may indicate an association between increased clozapine blood levels following the administration of vaccines.

With access to the VAERS database and in light of several recent publications concerning the interaction of clozapine and COVID-19 vaccines, this article represents a timely effort aimed at exploring the current evidence surrounding altered vaccine effectiveness and safety of vaccines in patients being treated with clozapine. Understanding how clozapine might influence vaccine responses and whether any adverse interactions occur is crucial for ensuring the optimal immune protection of these patients. Also, given clozapine's narrow therapeutic range and the potential for pharmacokinetic interactions with other medications, our approach intended to examine the potential effects of vaccination on clozapine serum levels and whether vaccines cause an increase in clozapine-related adverse events. Timely research into the interactions between clozapine and vaccines is necessary to provide informed guidance to healthcare providers and patients in order to ensure optimal safety for both groups. This investigation can aid in making well-informed decisions about vaccination strategies, potentially improving overall public health outcomes within this specific population.

Methods

Methods overview

First, a systematic literature review was carried out to explore the current evidence concerning altered vaccine effectiveness and safety of vaccines within the context of clozapine-treated patients. Subsequently, our focus extended to investigate whether vaccines may be associated elevated clozapine blood levels; therefore, our review approach was expanded with a case-by-case analysis of VAERS database.

Systematic review

This systematic review was conducted adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [31]. We thus searched electronic databases PubMed/MEDLINE, EMBASE, PsycINFO and Cochrane Library using the search string (vaccin*) AND (clozapin* OR clozaril OR leponex). We conducted the search and extracted our data between 30 July 2022, and 1

December 2022. The abstracts and titles of articles identified through electronic searches were reviewed independently by two authors (AA and JL). Disagreements were solved by consultation of a third author (EW, WS and AH). Publications in all languages were considered for inclusion. References of included studies and recent reviews were searched to identify additional studies. The approach was pre-registered on PROSPERO (CRD42022342070).

Inclusion and exclusion criteria

Observational case reports, case series, observational studies (case–control studies, cohort studies, cross-sectional studies), and interventional studies were considered eligible for inclusion, if they examined the effects of vaccination on clozapine-related adverse events or if they evaluated the impacts of clozapine use on vaccination effectiveness. Only studies with English or German language were included.

Quality assessment

Included articles were reviewed and their methodological quality was assessed independently by two authors (AA and JL) using the SIGN criteria [32]. Studies were rated between 1 + + (high-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias) and 4 (expert opinion) (see Tables 1, 2 for further information).

Data synthesis

There was heterogeneity in the specific research questions, in the study groups, interventions, comparisons, outcome measures and outcomes of included studies. Consequently, a descriptive data synthesis was performed to provide a summary of the characteristics and results from included studies in table form and to address the review questions.

VAERS analysis

A case-by-case analysis was performed from 4 August 2022 to 1 December 2022 using the Vaccine Adverse Event Reporting System (VAERS) [30]. Searches on VAERS database was conducted using the freely accessible CDC Wonder online tool with the search terms "clozapine" and "clozaril" as concomitant medication at the time of vaccination. After identifying reports in which individuals were concomitantly exposed to a vaccine of any kind and clozapine, we performed a case-by-case analysis. We extracted data about age and sex of the vaccine recipient, the vaccine manufacturer and vaccine dose, concomitant medication at the time of vaccination, time from vaccination until symptom onset, year of symptom onset, categorization as serious adverse event and incidences which led to hospitalization or death. Classification of adverse events was performed based on the Ontology of Adverse Events (OAE) [33]. Some reports included tests or unspecific events such as "symptom recurrence" or "echocardiogram normal". These were trimmed out in the classification of symptoms and our analysis focused on the medically relevant adverse events.

To examine whether vaccines can cause elevated clozapine blood levels, we followed a multistep process. Our main methodological approach based on the hypothesis that the VAERS records of patients presenting with clozapine intoxication symptoms following vaccinations might be linked to the usage of concomitant medication known to elevate clozapine blood levels.

To investigate this, in the first step, case descriptions were evaluated for each report separately. We identified cases presenting symptoms suggestive of clozapine toxicity, such as sedation, lethargy, hypersalivation, ataxia, convulsions, tachycardia, hypotension, delirium, respiratory depression or failure, cardiac arrhythmias, or seizures. Here, we assessed the occurrence of symptoms case-by-case considering further data such as time to onset, symptom duration and the presence of reasonable alternative causes for the event. In the next step, reports which were identified to present a symptom occurrence pattern likely to indicate clozapine intoxication were extracted. Cases, where the symptoms cannot be clearly associated with clozapine intoxication were resolved by discussion with a senior co-author (WS) and controversial cases, were labelled as unlikely. For instance, the case of a 78-year-old patient, who presented with lethargy, harsh breath sounds, hypoxia and agitation with a positive COVID test was considered unlikely to be associated with a clozapine intoxication, since the symptom onset was after 305 days following the administration of the COVID-19 vaccination and the symptomatology was likelier to explain with a COVID pneumonia. At the end of this process, we had two labelling categories, one regarding the presence of clozapine intoxication symptoms (0 = none, 1 = clozapine intoxication symptoms present) and after examining the cases labelled with "1" in this category, we performed another labelling considering the consistency of clozapine intoxication symptoms with symptom onset (0 = no, 1 = symptom onset in consistent with clozapine intoxication). These data are represented in Supplementary Information.

It is well known that concomitant medication may affect levels in clozapine patients. In some cases, toxic levels can be reached. According to our hypothesis described above, we investigated the concomitant medication in all cases in our next methodological step. The identification of concomitant medication potentially causing relevant increases in clozapine levels was performed using the drug interaction screening program MediQ [34]. So, we created another labelling category regarding to the presence of concomitant medication with drugs known to cause relevant increase in

Table 1 Overview of eligible studies exploring safety aspects of vaccines in clozapine users

	Study design	Study group	Age (mean)	Sex (m:f)	Comorbidities	Clz dose before vaccination	Co-medication	Study objective and administered vaccine	Findings	Sign rating
Lim et al. (2022) [38]	Prospective cohort	A total of 127 and 124 patients on clozapine	N/A	N/A	N/A	N/A	N/A	To investigate haematological changes and adverse events associated with BioNTech–Pfizer COVID-19 vaccine in patients receiving clozapine	No statistically significant difference in the frequency of adverse events between the first and second vaccine dose Top three adverse events were transient low-grade fever ($n=13$), mild injection site reactions ($n=10$) and behavioural disturbances ($n=5$) that were considered unrelated to the vaccine One patient developed tachycardia 10 h post-second dose but recovered after treatment for pneumonia and Klebsiella pneumoniae bacteraemia No major haematological adverse effects detected One (0.8%) and two cases (1.7%) of asymptomatic mild neutropenia after the first and second dose, respectively, with spontaneous recovery, all of these three cases had a history of granulocytopenia	2−

Table 1 (continued)

	Study design	Study group	Age (mean)	Sex (m:f)	Comorbidities	Clz dose before vaccination	Co-medication	Study objective and administered vaccine	Findings	Sign rating
Veerman et al. (2022) [36]	Prospective, observational cohort	133 subjects in treatment with clozapine	52.12	85:48	Changes in the occurrence of fever or inflammation not caused by the vaccination were monitored. No further information	Dosage remained unaltered in 108 subjects. Mean Clozapine level at baseline 451.91 µg/L. No further information	Changes in caffeine or tobacco consumption, and co-medication that might affect CYP1A2 activity in the period between baseline and second COVID-19 vaccination were monitored. No further information	To investigate the safety of COVID-19 vaccination (Moderna, BioNTech–Pfizer, AstraZeneca, Johnson & Johnson) in patients on clozapine as regards plasma clozapine concentration and haematological parameters	Compared to baseline, clozapine blood levels increased significantly (ES = 0.28, p = 0.003) after the second vaccination Clinically relevant increases in clozapine blood levels occurred in 20/92 patients (22%) and in 16/56 patients (29%) during the first and second phases, respectively Clozapine alert levels developed in one patient (1%) following the first dose and in three patients (5%) after the second dose In both phases, changes in white blood cells (WBC) were limited to mild granulocytopenia (3% and 5%), moderate granulocytopenia (1% and 0%) and leukocytopenia (2% and 3%) without cause for extra monitoring according to the guideline	2 +

Table 1 (continued)

	Study design	Study group	Age (mean)	Sex (m:f)	Comorbidities	Clz dose before vaccination	Co-medication	Study objective and administered vaccine	Findings	Sign rating
Raaska et al. (2001) [39]	Prospective cohort	16 inpatients treated with clozapine	38	9:7	7 current smokers, no further information	Mean 464 mg per day, unchanged drug regimen for a minimum of 2 weeks prior to the beginning of and throughout the study	4 subjects on clozapine monotherapy. Others took 1–6 other concomitant drugs	To investigate the effect of influenza vaccine on serum clozapine levels and CRP in patients with schizophrenia	No statistically significant change in serum concentrations of clozapine and CRP at any point. 2 patients developed abdominal pain and pharyngitis, elevated clozapine and CRP serum concentrations (54 and 81 mg/l, respectively) a few days after the vaccination and were excluded from the analysis	2−

clozapine plasma level (0 = no, 1 = yes). In the next step, descriptive analysis was used to examine distribution of incidences of adverse events possibly related to clozapine toxicity in the group of individuals concomitantly exposed to medications known to cause increased clozapine blood levels. Finally, to investigate the causality assessment for a clozapine–vaccine interaction, we used the Drug Interaction Probability Scale (DIPS), a 10-item tool specifically developed to assess the likelihood of drug–drug interactions [35].

Results

Literature search

Included studies and case reports

In total, 40 records were independently screened on title/abstract level and 26 records on full-text level. 12 records were excluded after full-text screening, resulting in 14 records deemed eligible for inclusion which comprised five original articles and nine case reports. Please see Fig. 1 for the PRISMA flow diagram.

Quality of included studies and case reports

According to SIGN criteria, the only controlled study was rated as "2 + ", all other included studies as "2 –" and all case reports as "3" in their methodological quality [36].

Characteristics of included studies

In total the number of studies was low ($n = 5$) and studies differed with respect to research questions, two studies exploring the association between clozapine use and antibody responses to vaccination, whereas three studies explored safety aspects of vaccines in clozapine users. Thereby, our data composition was heterogeneous.

Two studies providing data on the association between clozapine use and antibody responses to vaccination included one cross-sectional study [15] and one retrospective case review [37] investigating immunodeficiency with measurements of serum total immunoglobulins (immunoglobulin (Ig)G, IgA, IgM) and specific IgG antibodies to haemophilus influenza type b, tetanus and pneumococcal polysaccharide vaccines in clozapine-treated patients. An overview and findings of both studies are presented in Table 2. The association between clozapine use in schizophrenia and hypogammaglobulinaemia, presented by the cross-sectional study [15], was consistent with the findings from the second study [37] and the hypogammaglobulinaemia was suggested to be reversible on drug cessation.

Table 2 Overview of eligible studies exploring the association between clozapine use and antibody responses to vaccination

	Study design	Study group	Age (mean)	Sex (m:f)	Study objective	Findings	Sign rating
Ponsford et al. (2018) [15]	Cross-sectional case–control study	123 subjects taking clozapine, 113 clozapine naïve subjects	Clozapine group: 44.4 Control group: 50.4	Clozapine group: 64:30 Control group: 54:44	To investigate the effect of clozapine on antibody levels for haemophilus influenza type b, tetanus and pneumococcal polysaccharide	Immunoglobulins were all significantly reduced in the clozapine-treated group ($n=123$) compared with the clozapine-naive group ($n=111$) Duration on clozapine was associated with decline in IgG A higher proportion of the clozapine-treated group reported taking more than five courses of antibiotics in the preceding year (5.3% ($n=5$) versus 1% ($n=1$)	2−
Ponsford et al. (2020) [37]	Retrospective case review	1791 patients retrospectively assessed, focus on 17 patients treated with clozapine	50	11:6	To investigate the association between clozapine use and hypogammaglobulinaemia	Individuals with schizophrenia receiving clozapine displayed clinically significant panhypogammaglobulinaemia, impaired vaccine responses and disturbed B-cell maturation Duration on clozapine is associated with class-switched memory B-cells decline One patient showed gradual recovery of IgG serum level with clozapine discontinuation	2−

Two prospective cohort studies examined the association between clozapine use and safety aspects of COVID-19 vaccines [36, 38]. Veerman et al. [36] investigated these aspects in cases of different COVID-19 vaccines (Moderna, BioNTech–Pfizer, AstraZeneca, Johnson & Johnson). They reported that there was a significant increase in clozapine blood levels compared to baseline after the second COVID-19 vaccination. Clinically relevant increases in clozapine blood levels were observed in around 22% and 29% of patients during the first and second phases, respectively. Clozapine alert levels were triggered in a small percentage of patients after each dose. Mild changes in white blood cell counts, including granulocytopenia and leukocytopenia, were noted without requiring additional monitoring per

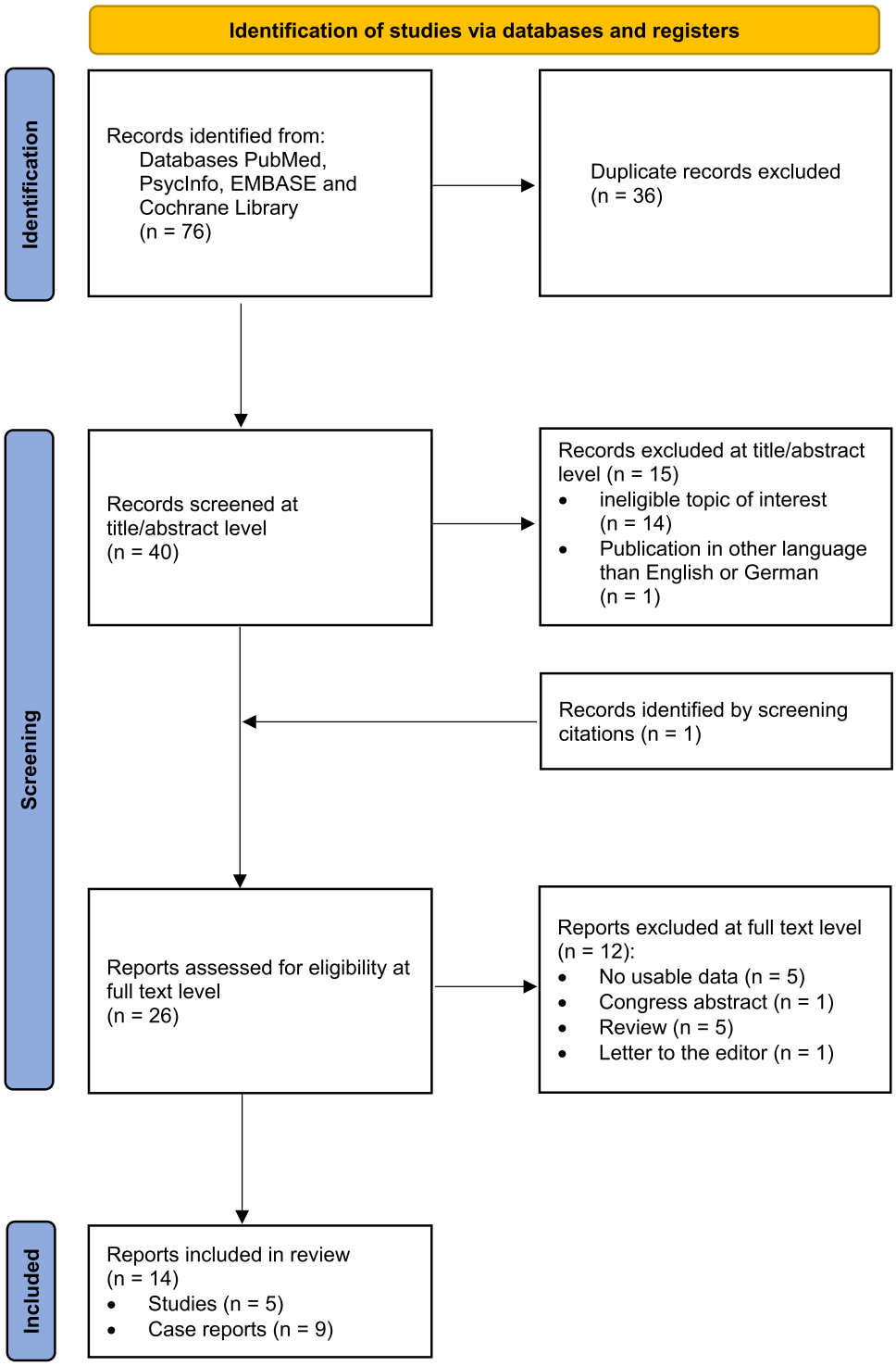

Fig. 1 PRISMA diagram

guidelines. Alterations in caffeine and tobacco consumption was monitored, as well as the concurrent use of medications that could impact CYP1A2 activity during the interval between the baseline and the second COVID-19 vaccination. However, this study did not provide additional details on the specific medications involved. The study by Lim et al. [38] examined adverse events and haematological changes following BioNTech–Pfizer COVID-19 vaccine. They presented no statistically significant difference in the frequency of adverse events between the first and second vaccine dose. Here, data concerning co-medication were not provided. The study by Raaska et al. [39] focused on the effects of influenza vaccination on CRP and clozapine serum concentrations, finding no statistically significant changes. Authors reported that four of the subjects were exclusively on clozapine monotherapy, while the remaining subjects were concurrently taking one to six other concomitant drugs. An overview of the studies exploring the safety aspects of vaccines in clozapine users are presented in Table 1. In summary, the studies collectively suggest that adverse events following vaccinations generally included mild symptoms. In some patients taking clozapine, the second COVID-19 vaccination led to a significant increase in clozapine blood levels. Changes in white blood cell counts were generally mild and did not require extra monitoring. Most patients did not show significant changes in serum clozapine and CRP levels after vaccination.

Characteristics of case reports

Nine case reports comprising eleven cases with administration of COVID-19 vaccines were retrieved [40–48]. Eight patients received the BioNTech–Pfizer COVID-19 vaccine, one patient the Moderna COVID-19 vaccine and two patients the Johnson & Johnson COVID-19 vaccine. Eight case reports provided clinical and haematological data on various adverse events occurring after the vaccine exposure in subjects treated with clozapine. One case report provided data on Anti-SARS-CoV-2 IgG levels after the exposure to COVID-19 vaccine. In two cases, symptoms occurred only after the administration of first dose of the BioNTech–Pfizer COVID-19 vaccine. In another case, symptoms occurred after receiving the first dose of the BioNTech–Pfizer COVID-19 vaccine and were worsened after the second dose. In another case, symptoms were observed both following the first and second dose of the BioNTech–Pfizer COVID-19 vaccine, both with spontaneous resolution in between. In another two cases, symptom onset was reported only in context of the administration of the second dose of the BioNTech–Pfizer COVID-19 vaccine. Further, in case of the Moderna vaccine, symptoms started following the second dose. Finally, in one case following Johnson & Johnson vaccination, symptoms started after the administration of the first dose of the COVID-19 vaccine. Only one case report regarding influenza vaccination was retrieved concerning a presentation with a clinical serious adverse event with late onset of sudden agranulocytosis following an influenza vaccine [40]. Three cases (3.64%) presented with serious adverse events: two patients with delirium (1.82%) [42, 47], one with myocarditis (1.1%) [42] and one with a tonic–clonic seizure (1.1) [43]. Six cases showed blood count abnormalities (5.45%). Four of the 11 cases provided data regarding post-vaccinal plasma clozapine concentrations. 50% showed relevant increases of clozapine concentrations: both presenting with delirium [42, 47] showed a relevant increase in clozapine levels, both after receiving COVID-19 vaccines. Two cases (50%) showed no elevation of clozapine levels. In sum, the clinical presentation of symptoms and the collected data was heterogeneous between cases as detailed in Table 3.

VAERS analysis

In total, 156 reports were obtained from the VAERS database, of which 7 were duplicates, 11 reported no adverse events, but rather interchange of vaccine products, administered extra doses or inappropriate administration schedules, or did in 1 case not specify the type of the vaccine. These respective 19 reports were removed. In the remaining 137 reports, 112 patients were exposed to COVID-19 vaccines (81.8%), 12 patients to influenza vaccines (8.8%) and 13 patients to other vaccines (9.5%). The median age of the patients was 54 years and median days to symptom onset was 4. There were 81 female (59.1%) and 55 male (40.1%) patients. Serious adverse events were reported in 38% of the cases (2 in 12 patients who received an influenza vaccine, 48 of 112 patients who received a COVID-19 vaccine and 2 of 13 other vaccines). Further characteristics regarding other variables are presented in the Supplementary Information. By the case-by-case examination, we identified 16 cases with concomitant use of medication potentially causing relevant increases in clozapine levels using the drug interaction screening program MediQ [34]. Additionally, we evaluated all 137 reports for descriptions of possible clozapine toxicity symptoms, which obtained a total of 13 reports. 5 of these reports were excluded due to the interval until symptom onset consistent with time-dependent nature of CYP inhibition. 2 of the remaining 8 reports required hospitalization. Adverse events showed marked heterogeneity. Most frequently reported adverse events were behavioural adverse events ($n = 91$, 66.4%). See Supplementary Information for further information. None of the 8 reports of patients displaying symptoms compatible with clozapine intoxication received concomitant medication known to potentially cause relevant increases in clozapine blood levels.

Table 3 Overview of eligible case reports

	Sample size	Age	Sex	Comorbidities	Smoking status	Clz dose at time of vaccination	Clz/nclz (norclozapine) levels (ng/ml)	Co-medication at time of vaccination	Administered vaccine	Time to onset	Findings
Jean et al. (2019) [40]	1	56y	M	Hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD)	N/A	N/A	N/A	Simvastatin, metoprolol, lisinopril, aspirin, metformin, haloperidol, and benztropine	Influenza vaccine	4 months	Agranulocytosis with an ANC with 200 cells/uL after more than 156 months of stable neutrophil counts on clozapine
Thompson et al. (2021) [42]	1	51y	M	Diabetes mellitus type 2, gastroesophageal reflux disease, hyperlipidaemia, class II obesity and obstructive sleep apnoea	Non-smoker	300mg/d	1078/288 (4 days after vaccination) 533/192 (3 days prior to vaccination)	Divalproex, fenofibrate, linagliptin, metformin, pantoprazole	BioNTech–Pfizer COVID-19 vaccine (1st dose)	4 days	Delirium, repeated falls, increasing incontinence, elevated clozapine levels with toxic effects and mild, transient decrease of lymphocytes
Makhlouf et al. (2021) [43]	1	62y	M	Hypertension and peripheral neuropathy	Former smoker, abstinence since 2 years	400mg/d	274/247 (5 days after vaccination, after missing 1 dose the day before) CLZ/NCLZ the year preceding hospitalization: ranged from 389 to 505/380 to 384, respectively	Risperidone, gabapentin, glycopyrrolate, trazodone, lorazepam	BioNTech–Pfizer COVID-19 vaccine (1st dose)	3 days	Generalized tonic–clonic seizure lasting 20 min and a fever of 40.3°C

Table 3 (continued)

	Sample size	Age	Sex	Comorbidities	Smoking status	Clz dose at time of vaccination	Clz/nclz (norclozapine) levels (ng/ml)	Co-medication at time of vaccination	Administered vaccine	Time to onset	Findings
Imai et al. (2021) [44]	1	44y	F	N/A	N/A	50mg/d	N/A	Clonazepam, Lemborexant, Lithium carbonate, Adenine, Mecobalamin	BioNTech–Pfizer COVID-19 vaccine (1st and 2nd dose)	Not clearly specified	Gradual decrease of the WBC count after the 1st dose of the vaccination. Next day after the 2nd dose, fatigue, pain in the left parotid gland, a temperature of 37.5 °C and slight elevation of CRP-level. Further decrease of WBC and neutrophil counts 2 days post-second dose. Normalization of WBC count and neutrophil ratio soon after the discontinuation of clozapine

Table 3 (continued)

	Sample size	Age	Sex	Comorbidities	Smoking status	Clz dose at time of vaccination	Clz/nclz (norclozapine) levels (ng/ml)	Co-medication at time of vaccination	Administered vaccine	Time to onset	Findings
Takaki et al. (2022) [45]	1	45y	F	N/A	N/A	112.5mg/day	N/A	Lithium carbonate	BioNTech–Pfizer COVID-19 vaccine (1st and 2nd dose)	3 days after each dose	At 3 days after the 1st dose, decrease of absolute WBC (3.16×10^9/L) and ANC (1.90×10^9/L) observed. At 7 days after the 1st dose, these values had returned to the normal range At 3 days after the 2nd vaccination, drop of WBC to 3.03×10^9/L and neutrophils to 1.92×10^9/L. Return to normal range 7 days post-second dose

Table 3 (continued)

	Sample size	Age	Sex	Comorbidities	Smoking status	Clz dose at time of vaccination	Clz/nclz (norclozapine) levels (ng/ml)	Co-medication at time of vaccination	Administered vaccine	Time to onset	Findings
Tomita et al. (2022) [46]	2	22y/20 years	F/F	N/A	N/A	Case I: 250mg/day Case II: 75mg/day	N/A	Case I: Paroxetine, trihexyphenidyl, levocetirizine, lithium carbonate, bromazepam, midodrine, domperidone, shakuyakukanzoto, sennoside Case II: Domperidone, lemborexant, flunitrazepam, ramelteon, biperiden, lithium carbonate, sodium valproate, rupatadine	BioNTech–Pfizer COVID-19 vaccine (1st and 2nd dose)	Case I: Onset clinical symptoms Not clearly specified. Neutropenia 6 days after the 2nd dose Case II: 3 days after the 2nd dose	Case I: Neutropenia (1850/mm3 (37.9% of white blood cell 4880/mm3) 6 days post-second dose. Nausea, finger tremor and dystonia of the extraocular muscles a few days post-second dose. Laboratory findings and symptoms improved naturally in two days and one week, respectively Case II: Decrease of WBC and neutrophil counts below the lower limits (3730/mm3 and 1440/mm3 (38.6%), respectively) 3 days post-second dose. After discontinuing clozapine, the neutropenia self-resolved naturally

Table 3 (continued)

	Sample size	Age	Sex	Comorbidities	Smoking status	Clz dose at time of vaccination	Clz/nclz (norclozapine) levels (ng/ml)	Co-medication at time of vaccination	Administered vaccine	Time to onset	Findings
Knöchel et al. (2022) [47]	1	42y	M	No further comorbidities	Stable consumption with 5 cigarettes per day	100mg/d by administration of 2nd dose 175mg/day by 5 days after the 2nd dose	270/unknown at the day of administration of the 2nd dose; 868/unknown after 5 days following 2nd dose	During the administration of the 1st dose: Prothipendyl, Haloperidol, Lorazepam During the administration of the 2nd dose: Haloperidol, Lorazepam	Moderna COVID-19 vaccine (1st and 2nd dose)	1 day after the 2nd dose	Agitation and psychomotor restlessness. Worsening of the agitation 5 days after the 2nd dose, also dizziness, gait disturbances, drowsiness, disorientation to place and time, consistent with delirium, hypotension and tachycardia. Elevated clozapine plasma concentrations
Hansbauer et al. (2022) [41]	1	35y	M	N/A	N/A	CLZ initiated 6 days after 1st dose, titration up to 175mg/d (day prior to administration of 2nd dose). 87.5mg/d on the day he received 2nd dose, continued with 175mg/d	250/unknown (3 days after 2nd dose)	Olanzapine, Propranolol	BioNTech–Pfizer COVID-19 vaccine (1st and 2nd dose)	Increase in tachycardia 9 days after 1st dose, worsening by 3 days after 2nd dose	Increase in pre-existing tachycardia, chest pain, increased troponin and CRP levels. Diagnosed with myocarditis

Table 3 (continued)

	Sample size	Age	Sex	Comorbidities	Smoking status	Clz dose at time of vaccination	Clz/nclz (norclozapine) levels (ng/ml)	Co-medication at time of vaccination	Administered vaccine	Time to onset	Findings
Fournier et al. (2022) [48]	2	Case I: in their 20s/Case II: in their 40s	M/F	Case I: Substance use disorder, tobacco use, posttraumatic stress disorder (PTSD) and attention-deficit/hyperactivity disorder (ADHD) Case II: PTSD, ADHD, remote subdural haematoma leading to a seizure disorder and mild cognitive impairment, substance use disorders in sustained remission	Case I: Tobacco use (not further specified) Case II: N/A	Case I: 400mg/d Case II: Not explicitly specified, in a dose range from 200mg/day to 600mg/day	N/A	Case I: lithium carbonate, gabapentin, melatonin, vitamin D3, glycopyrrolate as needed and pantoprazole Case II: venlafaxine extended release, buspirone, prazosin, vitamin D3, vitamin B12, oxcarbazepine, levetiracetam, metoprolol, metformin, rosuvastatin and aspirin	Johnson & Johnson COVID-19 vaccine (1st dose)	3 months after vaccination in both cases	Lower Anti-SARS-CoV-2 IgG levels than expected for being both vaccinated and infected with the virus

Table 4 General assessment of VAERS reports using DIPS

DIPS questions	Answer/score	Comments
(1) Are there previous credible reports of this interaction in humans?	NA/0	There are no previous credible reports of any clozapine–vaccine interaction in humans
(2) Is the observed interaction consistent with the known interactive properties of precipitant drug?	NA / 0	Insufficient data regarding a consistent interaction between clozapine and vaccines
(3) Is the observed interaction consistent with the known interactive properties of object drug?	NA/0	Insufficient data regarding a consistent interaction between clozapine and vaccines
(4) Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	May vary depending on the case	
(5) Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug?	NA/0	Dechallenge unfeasible for vaccines
(6) Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	NA/0	No reports regarding readministration
(7) Are there reasonable alternative causes for the event?	May vary depending on the case	
(8) Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	NA/0	Only 1 record with data regarding clozapine plasma level was detected which showed levels within the normal therapeutic range
(9) Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	NA/0	Confirmation of drug interaction by any objective evidence except elevated clozapine levels is not applicable
(10) Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	NA/0	No reports regarding dose adjustments of vaccines

Higher total scores correspond to higher likelihood of drug–vaccine interaction (i.e. > 8 = Highly Probable; 5–8 = Probable; 2–4 = Possible; < 2 = Doubtful) [35]

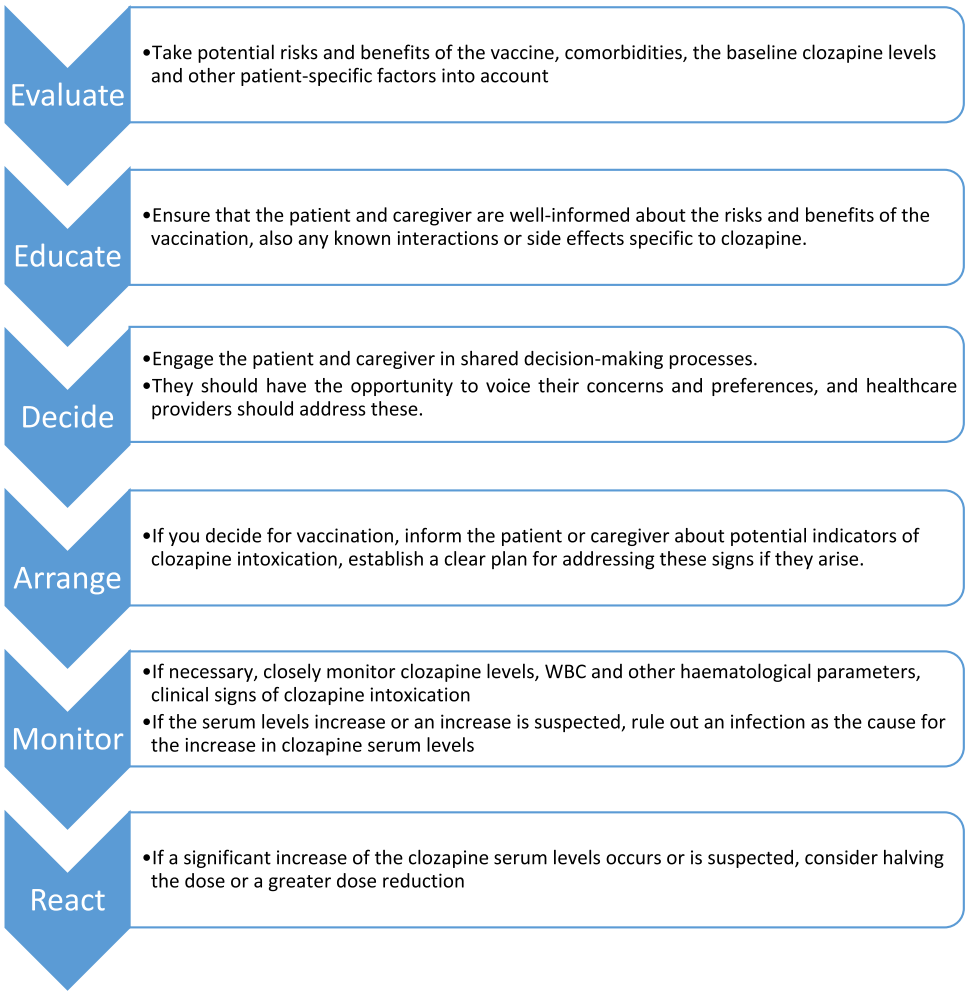

Fig. 2 Recommendations for clinical practice if vaccination considered in a patient treated with clozapine

Next, we performed a general assessment of the VAERS reports regarding the likelihood of vaccine–drug interaction using the DIPS scale [35]. Here, vaccines were considered as the potential "precipitant drug", whereas clozapine was regarded as the "object drug" on the DIPS. Upon the initial evaluation of VAERS records using the DIPS scale, it became evident that due to insufficient pre-existing data regarding vaccine–clozapine interactions, the ultimate summary score for all VAERS reports could attain a maximum of 2 points on the DIPS grading system. A maximum score of 2 indicates a "possible" interaction. Since this would not be sufficient to provide recommendations for the clinical practice, we opted against a detailed case-by-case analysis of the reports using DIPS score. Table 4 illustrates the evaluation of VAERS records using the DIPS.

Discussion

To our knowledge this is the first study to systematically review the literature concerning the connections between vaccinations and clozapine use. We intended to evaluate both the available scientific literature and the VAERS database regarding vaccine effectiveness and safety aspects of vaccination, such as haematological changes or the impact of vaccines on clozapine blood levels in clozapine-treated patients.

A recent systematic review included a literature overview of current evidence regarding haematological effects of COVID-19 vaccines on clozapine [49]. In our study, we intended to pursue a broader approach and explore the current evidence regarding effectiveness and safety of all vaccines in patients using clozapine. It seemed crucial to explore the clozapine–vaccine interaction further, considering the importance of infection prevention and the current TRRIP consensus recommendations for a vaccination against, e.g. SARS-CoV-2 and influenza in clozapine-treated patients [18]. Compared to the review of Bonkat et al. [50], we focused on all aspects of the clozapine–vaccination interaction and we extended our approach to an evaluation of the VAERS database. Since representative studies are lacking, we aimed to consolidate currently published literature by including nine case reports, since, in the absence of higher

quality evidence, a synthesis of lower forms of evidence can be clinically helpful and has historically served to advance medical knowledge [51]. We complemented the review with an assessment and analysis of the VAERS database, focusing on the possible adverse events that may indicate an association between increased clozapine blood levels following the administration of vaccines. The review identified, as expected, a highly heterogeneous literature. No original study fulfilled the criteria for a SIGN rating of 1 + + /1 + or 1 −, showing a significant risk of bias. It was not possible to perform a quantitative analysis due to the low number ($n = 5$) and heterogeneity of the included studies (2/5 exploring the association between clozapine use and antibody responses to vaccination and 3/5 the safety aspects of the vaccination in clozapine users).

We did not find robust evidence showing altered vaccine effectiveness in patients treated with clozapine. Our literature search resulted in two studies investigating associations between clozapine use and antibody responses to vaccination [15, 37]. The first study retrospectively assessed 1791 patients referred with antibody deficiency and found that clozapine was the single most prescribed antipsychotic (17/23) in the study group. It was shown that patients on clozapine displayed clinically significant panhypogammaglobulinaemia, impaired vaccine responses and disturbed B-cell maturation. One patient showed gradual recovery of IgG serum level with clozapine discontinuation [37]. The second study, designed as a cross-sectional case–control and comprising a sample size of 123 patients on clozapine compared with clozapine naïve group with $n = 111$, presented data on the effects of clozapine on adaptive immunity. This was demonstrated by a decrease levels of serum immunoglobulins IgG, IgA and IgM below the reference range in 8.5%, 13.8% and 34% of patients, respectively. The study also presented a decrease of specific IgG antibodies to haemophilus influenza type b, tetanus and pneumococcal polysaccharide vaccines in clozapine-treated patients compared with those on other antipsychotics [15]. These findings may indicate that a possible cause for susceptibility to infection seen in clozapine-treated patients may be due to a secondary antibody deficiency, especially in patients with long-term clozapine use, which might have diagnostic, monitoring and treatment implications. One of the identified case reports presented low COVID-19 immunoglobulin G titres following Johnson & Johnson vaccination and breakthrough infections in patients taking clozapine. They suggested that clozapine may blunt the immune response to (non-mRNA) vaccination against SARS-CoV-2, as well as post-illness antibody protection [48]. The VAERS database search provided no specific data regarding an altered vaccine effectiveness in clozapine-treated patients. In sum, substantial information on post-vaccine immune response in patients receiving clozapine is not available at present; rather, the current evidence is limited on only two studies and requires further exploration. Immune responses to vaccination are complex and can be influenced by multiple factors. Comorbidities, such as diabetes mellitus, chronic kidney and liver disease, as well as poor lifestyle choices such as smoking and sleep deficit, can negatively affect antibody formation after vaccination [41]. The fact that all of these elements are found at a higher rate in individuals with severe mental illness [52–54] could also in part explain the lower antibody levels in these individuals.

Investigating safety aspects of vaccination and the impact of vaccines on clozapine blood levels, we found that there is currently limited evidence regarding the influence of vaccines on clozapine levels or pharmacodynamic aspects of clozapine metabolism. There was only one original research study with a prospective cohort design on a small group of patients ($n = 16$) which demonstrated that influenza vaccination using conventional trivalent influenza vaccine did not have any statistically significant increases in serum concentrations of clozapine and CRP following influenza vaccination [39]. With respect to COVID vaccines, we identified two original studies [36, 38] examining their effect on haematological parameters. One of the studies also assessed the effects on clozapine plasma concentrations [36] in clozapine-treated patients. This prospective, observational study by Veerman et al. [36], was performed on a sample size of 133 patients on clozapine vaccinated with four different mRNA vaccines ($n = 133$ pre-vaccination and one dose, $n = 56$ after 2 doses). Clinically relevant increases in clozapine blood levels occurred in 20/92 patients (22%) and in 16/56 patients (29%) during the first and second phases, respectively. Clozapine alert levels developed in one patient (1%) following the first dose and in three patients (5%) after the second dose. These effects were, however, not clinically significantly relevant after the exclusion of people vaccinated with the Johnson & Johnson vaccine. Alert level increases in patients with pre-existing upper limit higher plasma concentrations could, however, not be ruled out. In general, the authors of this study came to the conclusion that based on their data COVID-19 vaccination seems to be safe with changes in white blood cells (WBC) limited to mild granulocytopenia (3% and 5%), moderate granulocytopenia (1% and 0%) and leukocytopenia (2% and 3%) without cause for extra monitoring. The study by Lim et al. [38] presented no statistically significant difference in the frequency of adverse events or major haematological changes between the first and second vaccine dose in their prospective cohort study on patients receiving two doses of BioNTech–Pfizer vaccines. In this study, top three adverse events were transient low-grade fever ($n = 13$), mild injection site reactions ($n = 10$) and behavioural disturbances ($n = 5$) that were considered unrelated to the vaccine. One (0.8%) and two cases

(1.7%) of asymptomatic mild neutropenia after the first and second dose, respectively, with spontaneous recovery, and all three cases had a history of granulocytopenia. To summarize, the results of vaccination studies showed no major adverse events following vaccination in patients on clozapine, whereas case reports display another picture. The case reports related to safety aspects of vaccines in clozapine-treated patients showed great heterogeneity regarding the observed adverse events following vaccination ranging from haematological changes such as agranulocytosis or drops in WBC counts to generalized tonic clonic seizures or myocarditis. Four of nine case reports provided data on clozapine levels, which showed an increase in only 2 cases. In these cases, although the provided data regarding smoking status, comorbidities and concomitant medication helps us rule out some possible effects of other factors other than the vaccines, data regarding infection are lacking. Hence, an associative link between vaccination and potential increases in clozapine concentration cannot be confirmed or ruled out. The complementary VAERS analysis showed no consistent evidence of an increased risk for clozapine blood level increases or adverse events. According to our search, only 1 VAERS record provided data regarding clozapine levels which was within the normal range. Taken together, there are some findings from case reports suggesting that COVID-19 vaccines may lead to an increase in clozapine blood concentrations, but the evidence is extremely limited and requires larger cohorts or trials [36].

In clinical practice, combining clozapine with other antipsychotic drugs is used as a strategy in case of unmanageable side effects due to clozapine treatment as well as in case of insufficient response to clozapine monotherapy to manage treatment-resistant schizophrenia. As this combination approach is considered associated with an increased risk of adverse events, one could speculate that risks of vaccination could also be more pronounced in this subgroup of patients. Upon detailed examination of the three original studies we obtained, which focused on vaccine safety in patients treated with clozapine, we were able to obtain—albeit limited—information regarding prescribed co-medication (see Table 1). Similarly, both the extracted case reports and VAERS database entries indicated a significant number of patients using clozapine alongside various other neuroactive medications (see Table 3 and supplements). Nonetheless, we were not able to provide subgroup analyses due to the large heterogeneity of combined neuroactive drugs, but from a clinical perspective it may be concluded that combination treatments involving clozapine have a high risk for vaccination-related complications. Hence, the findings of this review must be considered with caution and in light of this limitation. An additional limitation of this review poses the few numbers and lower quality of studies available for the outlined research questions. Further, the obtained studies lacked control groups and stemmed from a few numbers of countries, thus limiting the generalisability of their findings. However, by combining a systematic review approach with a VAERS database search, we were able to compile the currently available medical data on the relevant topics of this review and gain further insight regarding the review questions. At the same time, it is also important to note that there are limitations of a VAERS assessment. VAERS is passive reporting system which cannot completely capture all potential adverse events since data are restricted to individuals and clinicians who voluntarily enter information and since reports may include incomplete, inaccurate, coincidental and unverified information [30]. In addition, reliable causal link between the observed adverse events and vaccination let alone the triangular association between concomitant medication, vaccination and adverse events are often lacking, making it difficult to discern if other factors may have caused the adverse event. Moreover, case reports are at risk for a publication bias as it is unlikely that cases with no complications after vaccination are published.

In sum, based on our findings, no serious safety concerns seem to apply when patients on clozapine are receiving vaccines. However, it is important to note that due to the limited evidence, it could be premature to draw conclusions about altered vaccine effectiveness, an increased risk regarding clozapine intoxication or for adverse events following vaccine administration in clozapine-treated patients. For the clinical practice it may be important to mention that according to the TRRIP consensus published in 2023 a vaccination against, e.g. SARS-CoV-2 and influenza, in patients receiving clozapine and to aim for a low threshold for vaccinations in general is recommended [18], which takes increased rates of pneumonia among patients treated with clozapine compared to other antipsychotics into account [28]. Moreover, patients with schizophrenia are at a high risk of severe somatic comorbidities [55], and thus, the risk–benefit evaluation is in favour of a vaccination despite a potential increased risk of side effects when receiving clozapine. After vaccinations, clozapine levels, WBC and other signs of an intoxication with clozapine should be evaluated. In addition, if indicated, a dose reduction as much as by half when a clinically relevant increase is suspected or in patients with risk factors including patients with clozapine blood levels approaching the upper limit of the therapeutic range seems to be plausible [36]. Educating patients or caregivers about possible symptoms of clozapine intoxication, being aware of potential interactions of clozapine can help ensure the safety.

In this regard, the studies we reviewed provided no evidence regarding safety aspects of vaccination in clozapine-treated patients in case of comorbidities such as substance use disorders or other somatic disorders. Notably, recent research has indicated a higher incidence of myocarditis or pericarditis following COVID-19 vaccination [56]. As a

result, individuals receiving clozapine treatment, especially those with a higher risk of myocarditis or cardiomyopathy, such as those concurrently using valproate sodium, on higher cumulative clozapine doses, undergoing rapid titration, or exposed to illicit substances [57], may require more rigorous cardiac monitoring. In general, when dealing with patients who have comorbid conditions, it is recommended to perform a comprehensive evaluation of the condition's severity, taking potential risks into consideration. Moreover, it is crucial to establish closer monitoring of specific risks if necessary. Involving a multidisciplinary healthcare team to effectively manage these comorbid conditions may be necessary. Additionally, educating both patients and their caregivers about the potential risks is recommended to ensure their well-being.

Figure 2 illustrates the clinical recommendations for the patients treated with clozapine receiving a vaccination.

Future studies could usefully evaluate the potential association between clozapine and vaccines in more detail to ensure a better understanding of the nature of this interaction, using broader and prospective data sets and focus on intrinsic factors such as age, gender, genetic polymorphisms, comorbidities, antipsychotic combination therapies or concomitant neuroactive medication, type of vaccine, dosage and the duration of clozapine use, since the impact of the interaction may vary depending on various factors. Since a co-existing infection during the time of vaccination may also effect drug metabolism, ruling out an infection may also be important before drawing conclusions on vaccine–drug interactions [46].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00406-023-01729-0.

Author contributions AA, WS and AH conceptualized the article, AA and JL performed the literature search, AA and WS performed the data analysis, AA wrote the article, and WS, EW, AH and JL critically revised the work. All the authors read and approved the final manuscript.

Funding None.

Data availability The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

Conflict of interest W. Strube has received a speaker's honorarium from Mag & More GmbH and neurocare and was a member of the advisory board of Recordati. E. Wagner has been invited to advisory boards from Recordati. A. Hasan has received speakership fees from Lundbeck, Otsuka, Janssen and Recordati and was the member of advisory boards for these companies as well as for ROVI. All other authors report no conflict of interest.

References

1. Meltzer HY (1997) Treatment-resistant schizophrenia—the role of clozapine. Curr Med Res Opin 14:1–20. https://doi.org/10.1185/03007999709113338
2. Northwood K, Pearson E, Arnautovska U et al (2023) Optimising plasma clozapine levels to improve treatment response: an individual patient data meta-analysis and receiver operating characteristic curve analysis. Br J Psychiatry. https://doi.org/10.1192/bjp.2023.27
3. Mauri MC, Volonteri LS, Colasanti A et al (2007) Clinical pharmacokinetics of atypical antipsychotics: a critical review of the relationship between plasma concentrations and clinical response. Clin Pharmacokinet 46:359–388. https://doi.org/10.2165/00003088-200746050-00001
4. Wagner E, McMahon L, Falkai P et al (2020) Impact of smoking behavior on clozapine blood levels—a systematic review and meta-analysis. Acta Psychiatr Scand 142:456–466. https://doi.org/10.1111/acps.13228
5. de Leon J, Rajkumar AP, Kaithi AR et al (2020) Do Asian patients require only half of the clozapine dose prescribed for caucasians? A critical overview. Indian J Psychol Med 42:4–10. https://doi.org/10.4103/IJPSYM.IJPSYM_379_19
6. Castberg I, Westin AA, Skogvoll E, Spigset O (2017) Effects of age and gender on the serum levels of clozapine, olanzapine, risperidone, and quetiapine. Acta Psychiatr Scand 136:455–464. https://doi.org/10.1111/acps.12794
7. Carrillo JA, Benitez J (2000) Clinically significant pharmacokinetic interactions between dietary caffeine and medications. Clin Pharmacokinet 39:127–153. https://doi.org/10.2165/00003088-200039020-00004
8. Urichuk L, Prior T, Dursun S, Baker G (2008) Metabolism of atypical antipsychotics: involvement of cytochrome P450 enzymes and relevance for drug-drug interactions. CDM 9:410–418. https://doi.org/10.2174/138920008784746373
9. Clark SR, Warren NS, Kim G et al (2018) Elevated clozapine levels associated with infection: a systematic review. Schizophr Res 192:50–56. https://doi.org/10.1016/j.schres.2017.03.045
10. Wang Q, Xu R, Volkow ND (2021) Increased risk of COVID -19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. World Psychiatry 20:124–130. https://doi.org/10.1002/wps.20806
11. Jeon H-L, Kwon JS, Park S-H, Shin J-Y (2021) Association of mental disorders with SARS-CoV-2 infection and severe health outcomes: nationwide cohort study. Br J Psychiatry 218:344–351. https://doi.org/10.1192/bjp.2020.251
12. Tzur Bitan D, Krieger I, Kridin K et al (2021) COVID-19 prevalence and mortality among schizophrenia patients: a large-scale retrospective cohort study. Schizophr Bull 47:1211–1217. https://doi.org/10.1093/schbul/sbab012
13. Ponsford MJ, Pecoraro A, Jolles S (2019) Clozapine-associated secondary antibody deficiency. Curr Opin Allergy Clin Immunol 19:553–562. https://doi.org/10.1097/ACI.0000000000000592
14. Govind R, Fonseca de Freitas D, Pritchard M et al (2021) Clozapine treatment and risk of COVID-19 infection: retrospective cohort study. Br J Psychiatry 219:368–374. https://doi.org/10.1192/bjp.2020.151
15. Ponsford M, Castle D, Tahir T et al (2019) Clozapine is associated with secondary antibody deficiency. Br J Psychiatry 214:83–89. https://doi.org/10.1192/bjp.2018.152
16. Gee S, Gaughran F, MacCabe J et al (2020) Management of clozapine treatment during the COVID-19 pandemic. Therap Adv Psychopharmacol 10:204512532092816. https://doi.org/10.1177/2045125320928167

17. Bayraktar İ, Yalçın N, Demirkan K (2021) The potential interaction between COVID-19 vaccines and clozapine: a novel approach for clinical trials. Int J Clin Pract. https://doi.org/10.1111/ijcp.14441
18. Wagner E, Siskind D, Falkai P et al (2023) Clozapine optimization: a delphi consensus guideline from the treatment response and resistance in psychosis working group. Schizophrenia Bull. https://doi.org/10.1093/schbul/sbad030
19. Pellegrino P, Perrotta C, Clementi E, Radice S (2015) Vaccine-drug interactions: cytokines, cytochromes, and molecular mechanisms. Drug Saf 38:781–787. https://doi.org/10.1007/s40264-015-0330-8
20. D'Arcy PF (1984) Vaccine-drug interactions. Drug Intell Clin Pharm 18:697–700. https://doi.org/10.1177/106002808401800904
21. Kramer P, McClain CJ (1981) Depression of aminopyrine metabolism by influenza vaccination. N Engl J Med 305:1262–1264. https://doi.org/10.1056/NEJM198111193052106
22. Goldstein RS, Cheung OT, Seguin R et al (1982) Decreased elimination of theophylline after influenza vaccination. Can Med Assoc J 126:470
23. Renton KW, Gray JD, Hall RI (1980) Decreased elimination of theophylline after influenza vaccination. Can Med Assoc J 123:288–290
24. Pellegrino P, Carnovale C, Perrone V et al (2014) Efficacy of vaccination against influenza in patients with multiple sclerosis: the role of concomitant therapies. Vaccine 32:4730–4735. https://doi.org/10.1016/j.vaccine.2014.06.068
25. Elkayam O (2004) The Effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum 33:283–288. https://doi.org/10.1053/j.semarthrit.2003.10.003
26. Fomin I (2006) Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF blockers. Ann Rheum Dis 65:191–194. https://doi.org/10.1136/ard.2005.036434
27. Kapetanovic MC, Saxne T, Sjöholm A et al (2006) Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. Rheumatology 45:106–111. https://doi.org/10.1093/rheumatology/kei193
28. de Leon J, Ruan C-J, Verdoux H, Wang C (2020) Clozapine is strongly associated with the risk of pneumonia and inflammation. Gen Psych 33:e100183. https://doi.org/10.1136/gpsych-2019-100183
29. Chen M-L, Tsai T-C, Wang L-K et al (2012) Clozapine inhibits Th1 cell differentiation and causes the suppression of IFN-γ production in peripheral blood mononuclear cells. Immunopharmacol Immunotoxicol 34:686–694. https://doi.org/10.3109/08923973.2011.651535
30. Vaccine Adverse Event Reporting System (VAERS) Available online: https://vaers.hhs.gov/index.html (Accessed on 8 January 2023).
31. Page MJ, McKenzie JE, Bossuyt PM et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. https://doi.org/10.1136/bmj.n71
32. Harbour RT, Forsyth L (2008) SIGN 50: a guideline developer's Handbook; Rev. ed.; Scottish Intercollegiate Guidelines Network: Ediburgh (ISBN 978-1-905813-25-4)
33. Ontobee: OAE Available online: https://ontobee.org/ontology/OAE (Accessed on 8 January 2023)
34. MediQ-Startseite Available online: https://www.mediq.ch/ (Accessed on 8 January 2023)
35. Horn JR, Hansten PD, Chan L-N (2007) Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother 41:674–680. https://doi.org/10.1345/aph.1H423
36. Veerman SRT, Moscou T, Bogers JPAM et al (2022) Clozapine and COVID-19 Vaccination: effects on blood levels and leukocytes. An observational cohort study. Acta Psychiatr Scand 146:168–178. https://doi.org/10.1111/acps.13428
37. Ponsford MJ, Steven R, Bramhall K et al (2020) Clinical and laboratory characteristics of clozapine-treated patients with schizophrenia referred to a national immunodeficiency clinic reveals a B-cell signature resembling common variable immunodeficiency (CVID). J Clin Pathol 73:587–592. https://doi.org/10.1136/jclinpath-2019-206235
38. Lim S, Liew E, Leo A et al (2022) Haematological changes and adverse events associated with BNT162b2 mRNA COVID-19 vaccine in patients receiving clozapine—findings from an audit. Acta Psychiatr Scand 146:179–181. https://doi.org/10.1111/acps.13443
39. Raaska K, Raitasuo V, Neuvonen P (2001) Effect of influenza vaccination on serum clozapine and its main metabolite concentrations in patients with schizophrenia. Eur J Clin Pharmacol 57:705–708. https://doi.org/10.1007/s002280100375
40. Jean S, Romain L, Florvil S et al (2019) A case of sudden very late onset of severe clozapine-induced agranulocytosis following an influenza vaccine. Cureus. https://doi.org/10.7759/cureus.4682
41. Hansbauer M, Fastantz E, Lutz J, Hasan A (2022) Myocarditis after clozapine initiation and mRNA SARS-CoV-2 vaccination. J Clin Psychopharmacol 42:502–503. https://doi.org/10.1097/JCP.0000000000001577
42. Thompson D, Delorme CM, White RF, Honer WG (2021) Elevated clozapine levels and toxic effects after SARS-CoV-2 vaccination. J Psychiatry Neurosci. https://doi.org/10.1503/jpn.210027
43. Makhlouf AT, Van Alphen MU, Manzano GS, Freudenreich O (2021) A seizure After COVID-19 vaccination in a patient on clozapine. J Clin Psychopharmacol 41:689–690. https://doi.org/10.1097/JCP.0000000000001488
44. Imai T, Ochiai S, Ishimaru T et al (2022) A case report: clozapine-induced leukopenia and neutropenia after mRNA COVID-19 vaccination. Neuropsychopharm Rep 42:238–240. https://doi.org/10.1002/npr2.12238
45. Takaki M, Yada Y, Sakamoto S et al (2022) A decrease of neutrophils after COVID-19 vaccination in a treatment-resistant patient with schizophrenia taking clozapine. J Clin Psychopharmacol 42:324–325. https://doi.org/10.1097/JCP.0000000000001527
46. Tomita T, Sakamoto Y, Saito M et al (2022) Two patients with schizophrenia treated with clozapine developed neutropenia after receiving a COVID-19 vaccine. IMCRJ 15:29–33. https://doi.org/10.2147/IMCRJ.S350879
47. Knöchel C, Hefner G, Stiehl T, Schmidbauer W (2022) Elevated clozapine blood concentrations after second COVID-19 vaccination with spikevax (COVID-19 vaccine moderna). J Clin Psychopharmacol 42:317–320. https://doi.org/10.1097/JCP.0000000000001522
48. Fournier O, Sanders E, Fetter JC (2022) Low COVID-19 immunoglobulin G titers following vaccination and breakthrough infection in patients taking clozapine. Prim Care Compan CNS Disord. https://doi.org/10.4088/PCC.22cr03388
49. Giles G, Varghese S, Shymko G et al (2023) Clozapine therapy and COVID-19: a systematic review of the prevalence rates, health outcomes, hematological markers, and patient perspectives. Schizophr Bull 49:53–67. https://doi.org/10.1093/schbul/sbac148
50. Bonkat N, Fellendorf FT, Dalkner N, Reininghaus EZ (2022) Severe mental disorders and vaccinations—a systematic review. World J Biol Psychiatry 23:501–516. https://doi.org/10.1080/15622975.2021.2013095

51. Murad MH, Sultan S, Haffar S, Bazerbachi F (2018) Methodological quality and synthesis of case series and case reports. BMJ EBM 23:60–63. https://doi.org/10.1136/bmjebm-2017-110853
52. De Hert M, Correll CU, Bobes J et al (2011) Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 10:52–77. https://doi.org/10.1002/j.2051-5545.2011.tb00014.x
53. Lasser K, Boyd JW, Woolhandler S et al (2000) Smoking and mental illness: a population-based prevalence study. JAMA 284:2606. https://doi.org/10.1001/jama.284.20.2606
54. Murphy MJ, Peterson MJ (2015) Sleep disturbances in depression. Sleep Med Clin 10:17–23. https://doi.org/10.1016/j.jsmc.2014.11.009
55. Plana-Ripoll O, Pedersen CB, Agerbo E et al (2019) A comprehensive analysis of mortality-related health metrics associated with mental disorders: a nationwide, register-based cohort study. The Lancet 394:1827–1835. https://doi.org/10.1016/S0140-6736(19)32316-5
56. Gao J, Feng L, Li Y et al (2023) A systematic review and meta-analysis of the association between SARS-CoV-2 vaccination and myocarditis or pericarditis. Am J Prev Med 64:275–284. https://doi.org/10.1016/j.amepre.2022.09.002
57. Vickers M, Ramineni V, Malacova E et al (2022) Risk factors for clozapine-induced myocarditis and cardiomyopathy: a systematic review and meta-analysis. Acta Psychiatr Scand 145:442–455. https://doi.org/10.1111/acps.13398