COVID-19: Risks, Complications, and Monitoring in Patients on Clozapine

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COVID-19: Risks, Complications, and Monitoring in Patients on Clozapine

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ABSTRACT

The Dutch Clozapine Collaboration Group is frequently asked for advice about the management of clozapine-treated patients when infected with or vaccinated against SARS-CoV-2. We provide state of the art information about the risks of SARS-CoV-2 infection for patients on clozapine and we give advice on measures to be taken, especially in regard to the monitoring of clozapine plasma levels, WBC count and differentiation during COVID-19 and after vaccination. We present an overview of relevant editorials, observational studies, and case studies, in which COVID-19 was reported in patients on clozapine. Patients using clozapine may have a higher risk of infection than patients with schizophrenia spectrum disorders (SSD) using other antipsychotics. SARS-CoV-2 infection can result in a dangerous increase of clozapine plasma levels, and granulocytopenia and lymphocytopenia (generally mild and short-term) may also occur, usually not as a result of clozapine treatment. Clozapine intoxication, pneumonia and delirium are the main complications of COVID-19 in patients on clozapine. In order to prevent clozapine intoxication, reduction of the original dose by half is generally recommended in clozapine users who contract COVID-19. When a cytokine storm is suspected in an advanced stage of COVID-19, reduction by three quarters seems more appropriate. If COVID-19 patients on clozapine develop granulocytopenia, SARS-CoV-2, rather than clozapine, should be considered as the cause. Schizophrenia patients in general and clozapine users in particular belong to a high-risk group that warrants early vaccination on a medical indication.

Introduction

In recent months, patients, relatives, nurses, and especially psychiatrists have asked a strikingly large number of questions regarding the combination of clozapine, the coronavirus disease 2019 (COVID-19), and its vaccination through the question-and-answer service of the website of the Dutch Clozapine Collaboration Group (www.clozapinepluswerkgroep.nl). In this article, we summarize the currently available literature on COVID-19 and clozapine, which we use for evidence-based recommendations for monitoring practice in patients on clozapine who contract a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or who are being vaccinated against COVID-19.

Method

We systematically searched PubMed, PsycINFO, and Embase databases, using the combination of MeSH search terms “COVID-19” AND “clozapine” (date 4 June 2021). We included articles in English and Dutch that reported on clozapine treatment with COVID-19. Two authors independently screened all potentially relevant abstracts and after studying full texts extracted relevant data.

The reference lists of the selected articles were checked for relevant publications. We also included personal communications to the collaboration group and added general information on clozapine or schizophrenia where appropriate.

Results

The initial search yielded 141 articles from the 3 databases. After selection based on title and abstract, 16 relevant publications about COVID-19 in patients on clozapine remained. Most of the excluded articles did not report on risks, complications, or monitoring of SARS-CoV-2 infection in patients on clozapine. We aimed to include original reports as much as possible. After a review of full texts, 3 reports were excluded (▶ **Table 1**). No other relevant articles were found in the reference lists. One case report in press and 3 unpublished case reports, which had been brought to the attention of the collaboration group by clozapine specialist R. Laitman from New York, were added. Therefore 15 reports were included in this review. Details of the selection process are shown in a flowchart (▶ **Fig. 1**).

Risk of COVID-19

In a UK study, patients taking clozapine were found to have a higher risk of a SARS-CoV-2 infection compared with patients with schizophrenia spectrum disorders who were on other antipsychotics (hazard ratio 2.62) [1]. After adjustment for gender, age, ethnicity, body mass index, smoking, and use of the mental health services, the risk for patients on clozapine was still significantly higher (hazard ratio 1.76). Clozapine in itself is associated with increased general infection risk [2]. In general, studies in patients with schizophrenia have found an increased risk for infection with SARS-COV-2 [3, 4], for hospitalization with COVID-19 [3, 5, 6], and for mortality with a factor 1.3 up to 3.3 [4, 5, 7] but not for mood disorders [7].

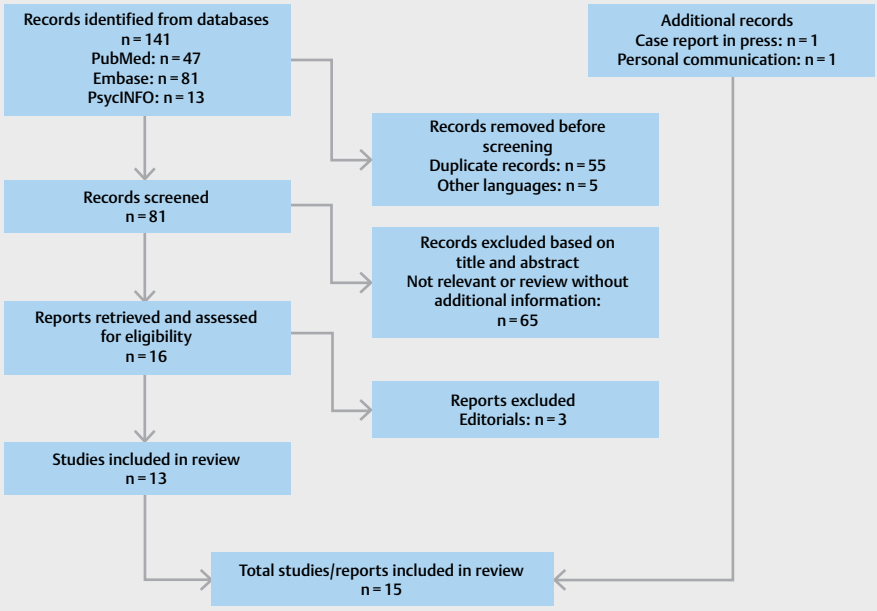
Risk of clozapine intoxication

A few cases have been published about clozapine users with COVID-19 and clozapine toxicity [8–10], Laitman, 2021, personal communication] (see ▶ **Table 2**). The authors point out that cytokines such as interleukin-6 (IL-6) and Il-1, which are increased in inflammation, inhibit the clozapine-metabolizing CYP1A2 enzyme of the cytochrome P450 system and thus may lead to elevated clozapine blood levels or intoxication with symptoms such as sedation, hypersalivation, ataxia, and orthostasis. This is a well-known mechanism that may be aggravated by reduction and/or cessation of smoking during respiratory infections and/or during hospital admission [11, 12]. Dotson et al. (2020) observed seizures, ileus, and delirium as possible complications of elevated clozapine levels [9]. Therefore, an international consensus statement on the use of clozapine during the COVID-19 pandemic recommends that in the event of fever, flu-like symptoms, and the emergence of signs and symptoms of clozapine toxicity, the dose of clozapine should be reduced by as much as half until the patient has been fever-free for 3 days [13]. Thereafter, the dose can be increased in a stepwise manner to the pre-fever dose. Two case descriptions do confirm that halving the dose of clozapine when COVID-19-induced clozapine toxicity occurred was enough to lower the clozapine level sufficiently [14], Laitman, 2021, personal communication]. However, in another case of COVID-19 and clozapine intoxication, the clozapine level turned out to be 3 times as high as usual, and clozapine therapy had to be stopped altogether [10]. Interestingly, the clozapine level was even much higher than during earlier respiratory infections in the same patient, which can be explained by a stronger in-

▶ **Table 1** Literature review on COVID-19 in clozapine users.

Author(s), publication year (PMID)	Observational cohort study	Case report(s)	Editorial	Inclusion
Boland & Dratcu, 2020 (32702224)[24]	x			yes
Bonaccorso et al., 2021 (33527097)[18]	x			yes
Butler et al., 2020 (32974002)[20]	x			yes
Cranshaw & Harikumar, 2020 (32435811)[8]		x		yes
Dotson et al., 2020 (32593477)9		x		yes
Gee et al., 2020 (32542111) *			x	no
Gee et al., 2021 (33703870)[16]	x			yes
Gee & Taylor, 2020 (32728419)[17]	x			yes
Govind et al., 2020 (32713374)[1]	x			yes
Laitman, 2021 (personal communication)		x		yes
Llesuy & Sidelnik, 2020 (32706942)[21]		x		yes
Remington & Powell, 2020 (32584527) *			x	no
Silva et al., 2020 (32718376)[25]			x	yes
Siskind et al., 2020 (32242646)[13]			x	yes
Siskind et al., 2020 (32584530) *			x	no
Smits et al., 2021 (Accepted in Dutch Journal of Psychiatry)[14]		x		yes
Thompson et al., 2021 (33667055)[22]		x		yes
Tio et al., 2021 (33517757)[10]		x		yes

* Editorials that did not add relevant information to the data of original reports were excluded. Only 2 relevant editorials were included that reported on advice on clozapine treatment with COVID-19 and vaccination in clozapine users.



▶ **Fig. 1** Systematic review flowchart.

▶ **Table 2** Case reports of clozapine intoxication in COVID-19.

Study	N	M/F	Clinical symptoms	Lymphocytes ($\times 10^9$/L)	Granulocytes ($\times 10^9$/L)	Clozapine plasma levels (µg/L)		
						Baseline	CO-VID-19	Post-infection
Cranshaw 2020[8]	1	1/0	hypersalivation drowsiness, myoclonus	0.76 *	1.26 *	NM	730	NM
Dotson 2020[9]	3	1/2	confusion, delirium, ileus	NM	1.10 *	106	1360	NM
				NM	14.97	NM	1060	NM
					2.20	458	2154	NM
Laitman 2021	2	1/1	unconsciousness	NM	0.99	600	950	620 * *
			no symptoms	NM	0.60	<50	NM	<50 * * *
Smits 2021[14]	1	0/1	fever, chills, headache coughing, sore throat	0.8 *	2.0	449	830	527 * *
Tio 2021[10]	1	1/0	ataxia, tremor, lethargy, echolalia	NM	NM	553	1813	583

Abbreviations: N: total number; M/F: male/female ratio; NM: not mentioned. * Lymphocytopenia (<1.5 × 10^9/L) and granulocytopenia (<2.0 × 10^9/L) were transient. * * After halving the dose of clozapine. * * * After restarting with half a dose of clozapine.

flammatory response (cytokine storm) in COVID-19. Cron (2021) suggests that cytokine-targeted treatments of COVID-19 are crucial to save lives because a cytokine storm syndrome in patients admitted with COVID-19 pneumonia causes high mortality rates [15]. Patients on clozapine may particularly benefit from IL-6 and IL-1 inhibitors to prevent a severe course of COVID-19 complicated by clozapine intoxication.

Lymphocytopenia and granulocytopenia in COVID-19

At the beginning of the SARS-CoV-2 pandemic, region-specific limits on outings and clinical resource constraints created challenges for patients to access routine clozapine-associated care, including the white blood cell testing required for dispensing. The above-mentioned international consensus statement suggested reducing the test frequency (if necessary) to every 3 months in patients with a low risk for agranulocytosis, for example, in patients who have had continuous clozapine treatment for more than 1 year [13].

A few small cohort studies and case reports of clozapine users who had tested positive for COVID-19 have investigated white blood cell, granulocyte, and lymphocyte counts before, during, and after the SARS-CoV-2 infection (see ▶ **Table 3**) [14, 16–18]. When COVID-19-induced granulocytopenia (<2.0 × 10^9/L) and lympho-

cytopenia ($< 1.5 \times 10^9$/L) occurred, they were mild and transient, with the counts returning to normal values within a few days, as generally occurs in COVID-19. In the Gee and Taylor studies, in 2 patients, clozapine treatment was continued with mild granulocytopenia ($1.5–2.0 \times 10^9$/L) [16, 17]. However, in 4 patients, clozapine treatment was withdrawn because of the moderate granulocytopenia ($1.0–1.5 \times 10^9$/L) that had developed. A striking finding was that 3 of these 4 patients had been on clozapine for more than 6 months without previously developing granulocytopenia. In these 3 patients, neutrophil counts were restored within 3 weeks of testing positive for COVID-19, and clozapine could be given again without reoccurring granulocytopenia. One patient who had only been taking clozapine for 67 days developed severe granulocytopenia (0.5×10^9/L), which was identified as being a side effect of clozapine. After recovery, clozapine was not prescribed again. Another clozapine user with COVID-19 developed severe granulocytopenia (0.99×10^9/L), but clozapine treatment was continued under close monitoring of blood counts and with the addition of lithium 300 mg daily [Laitman, 2021, personal communication]. After 3 days, the granulocyte count was completely back to normal, and lithium was stopped. In a second case with an even lower granulocyte count (0.6×10^9/L), clozapine treatment was discontinued, and 450 mg lithium was started. After 10 days, the granulocyte count had returned to 3.0×10^9/L, and clozapine was cautiously restarted with half of the original dosage, while 450 mg lithium was continued.

The results of these observational studies indicate that (mostly mild) granulocytopenia may occur in the acute phase of a SARS-CoV-2 infection as is the case with other viral infections and that clozapine may be continued without the development of agranulocytosis [19].

Pneumonia

At present, little is known about the morbidity and mortality associated with COVID-19 in clozapine users. It is thought that with clozapine there may be a higher risk of aspiration pneumonia due to an impaired swallowing reflex, sedation, and hypersalivation, particularly if the SARS-CoV-2 infection causes a toxic clozapine level [12]. An unreplicated comparative cohort study showed that clozapine is associated with a substantial reduction in serum immunoglobulins [2]. This secondary antibody deficiency (SAD) may explain the increased vulnerability to infection with COVID-19 [1] and the increased risk of pneumonia in patients on clozapine [12]. Pneumonia seriously exacerbates the patient's condition in COVID-19. In a retrospective case series of 8 clozapine users, 4 patients developed pneumonia, and in 2 of 3 deaths, the cause of death was COVID-19 pneumonia (see ▶ **Table 4**) [20]. Another case report of a clozapine user seeking medical attention only after 2 weeks of flu-like symptoms involves a 50-year-old woman with pneumonia and hypoxia who was admitted to the intensive care unit. Clozapine was continued without monitoring blood levels, and she died after 6 days of a pulmonary embolism [21].

Delirium

Delirium is a common complication after a SARS-CoV-2 infection in a clozapine user; it occurred in no fewer than 6 of the 8 clozapine users with COVID-19 described by Butler et al. (2020) (see ▶ **Table 4**) [21].

Risk of COVID-19 vaccination

There is currently only 1 case report describing complications after COVID-19 vaccination in a clozapine user [22]. Four days after administration of the BioNTech/Pfizer vaccine, a delirious clozapine intoxication and a mild, transient decrease in lymphocytes occurred. This seems reassuring in the light of the hundreds of clozapine users who have been vaccinated in the meantime.

Recommendations for monitoring during the COVID-19 pandemic

Recommendations in the event of fever, flu-like symptoms, or suspicion of COVID-19 are provided in ▶ **Fig. 2**. During the COVID-19 pandemic, the granulocyte count can be monitored in the same way as before the pandemic. Moreover, it is considered safe to reduce the test frequency to every 3 months in patients with a low risk for agranulocytosis [13]. The symptoms of infection due to clozapine-induced agranulocytosis, such as fever, coughing, muscle pain, fatigue, and shortness of breath, are difficult to distinguish from those associated with a SARS-CoV-2 infection. Because leukocytopenia and granulocytopenia may be a reason to stop clozapine treatment immediately, it is important for the treating psychiatrist to consider the cause of the leukocytopenia/granulocytopenia carefully, since stopping clozapine may result in a psychotic relapse or withdrawal delirium, both dangerous complications when adequate physical treatment has to be provided in a general hospital. To avoid unnecessary cessation of clozapine, it is imperative to consider that clozapine-induced agranulocytosis is rare, especially in long-term clozapine treatment [23]. Dependent upon the country and cohort studied, the risk of agranulocytosis after the first 6 months of clozapine treatment is between 0.37 and 0.70/1000 patient-years and, after the first year, 0.11 and 0.59/1000 patient-years. ▶ **Figures. 3** and **4** show step-by-step plans in the event of a decreased neutrophil count in patients on clozapine with a SARS-CoV-2 infection and a rise in clozapine levels due to infection and fever, respectively. Our recommendations are largely consistent with the international consensus statement on the reduction of clozapine dosage in patients who contract SARS-CoV-2 [13]. In general, we recommend reducing the original clozapine dose by half. Because a COVID-19-induced cytokine storm causes clozapine to increase to higher levels compared to other infections, we recommend reducing the original dose by 3 quarters instead of half when an advanced stage of COVID-19 is suspected with the presence of highly elevated proinflammatory cytokines [15].

In the absence of intoxication symptoms, it is possible to continue clozapine treatment safely with the monitoring of blood levels and the clinical picture in case of a SARS-CoV-2 infection [13, 14, 24].

Recommendations regarding COVID-19 vaccination

Due to the aforementioned additional risks of COVID-19 for clozapine users, as well as the risk of possible clozapine-related hypogammaglobinaemia causing an impaired immune response following a SARS-CoV-2 infection [2], we believe that clozapine users have a particularly strong and urgent indication for vaccination

▶ **Table 3** Changes in total leukocyte, neutrophil, and lymphocyte counts over time in clozapine users infected with COVID-19.

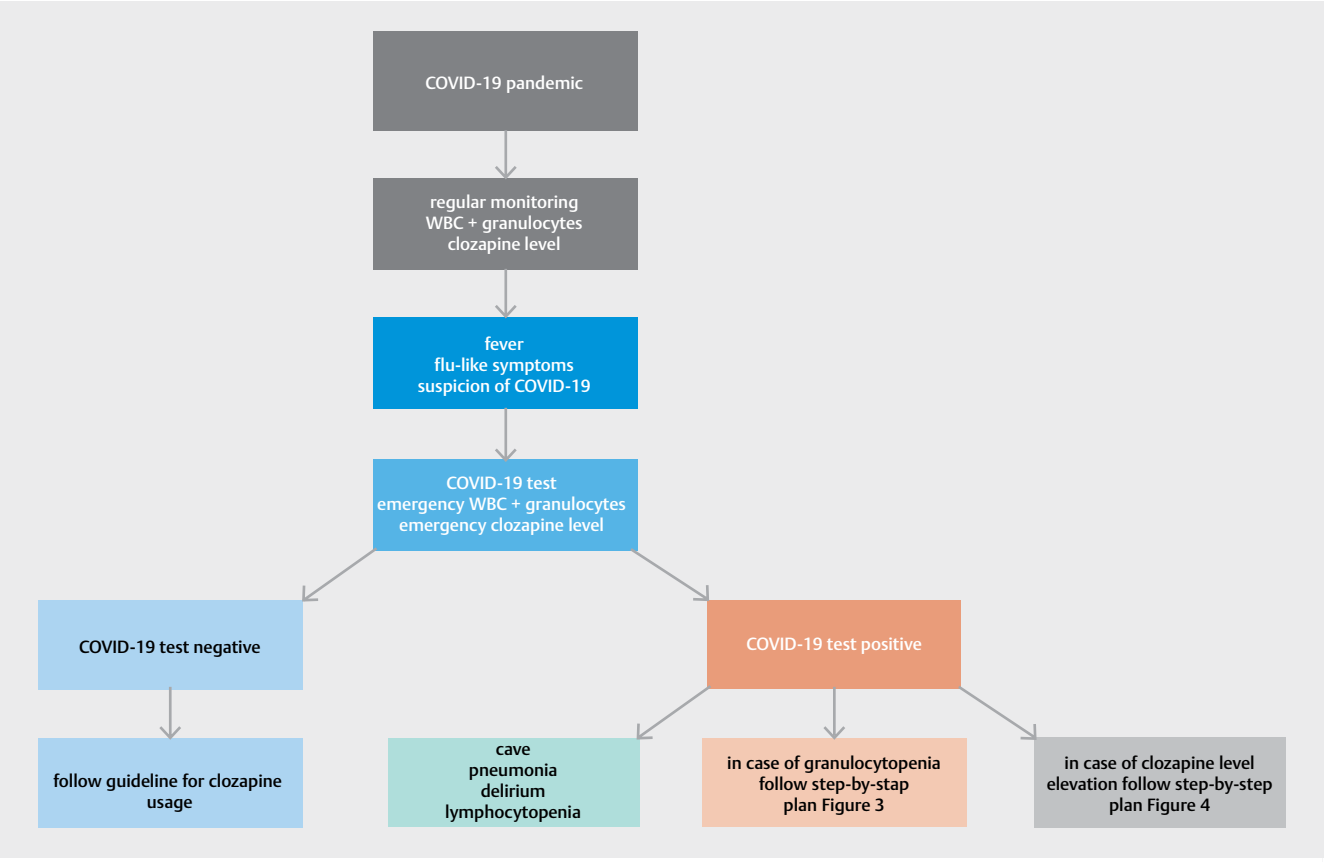
Study	N	M/F	Ethnicity				BEN	Leukocytes (×10⁹/L)				Granulocytes (×10⁹/L)				Lymphocytes (×10⁹/L)			
			Cauc.	Afr. Carib.	Asian	Other		BL	1st wk	2nd wk	3rd wk	BL	1st wk	2nd wk	3rd wk	BL	1st wk	2nd wk	3rd wk
Gee & Taylor, 2020[16]	13	4/9	4	8	1	–	2	7.8	6.4	8.5	NM	4.8	4.2	5.7	NM	NM	NM	NM	NM
Bonaccorso et al., 2021[18]	10	7/3	3	5	2	–	1	5.6	6.0	7.5	NM	5.2	4.1	5.3	NM	NM	NM	NM	NM
Gee & Taylor, 2021[17]	56	36/20	20	24	8	4	5	7.4	5.8	7.4	NM	4.7	3.8	4.7	NM	2.0	1.4	1.9	NM
Smits et al., 2021[14]	1	0/1	1	–	–	–	–	8.6	3.5	3.0	5.7	6.7	2.4	2.0	3.3	1.4	1.0	0.9	1.8

N: total number; M/F: male/female ratio; BEN: benign ethnic neutropenia; Cauc.: Caucasian; Afr. Carib.: African Caribbean; BL: baseline; wk: week; NM: not mentioned.

▶ **Table 4** Complications and changes over time in hospitalized clozapine users with COVID-19.

Study	N	M/F	Ethnicity			BEN	Risk factor				Complication			Outcome		
			Cauc.	Afr. Carib.	Asian		DM	HT	COPD	Smoker	Delirium	Pneumonia	Pulm. embolism	Discharged	Ext. admission	Death
Butler et al., 2020[20]	8	3/5	5	3	0	NM	7	3	4	6	6	4	0	2	3	3
Llesuy & Sidelnik, 2020[21]	1	0/1	NM	NM	NM	NM	1	0	0	1	0	1	1	0	0	1

N: total number; M/F: male/female ratio; BEN: benign ethnic neutropenia; Cauc.: Caucasian; Afr. Carib.: African Caribbean; DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; Pulm. embolism: pulmonary embolism; Ext. admission: extended admission; NM: not mentioned.



▶ **Fig. 2** Step-by-step plan in the event of a fever, flu-like symptoms, or suspicion of COVID-19 during the COVID-19 pandemic.

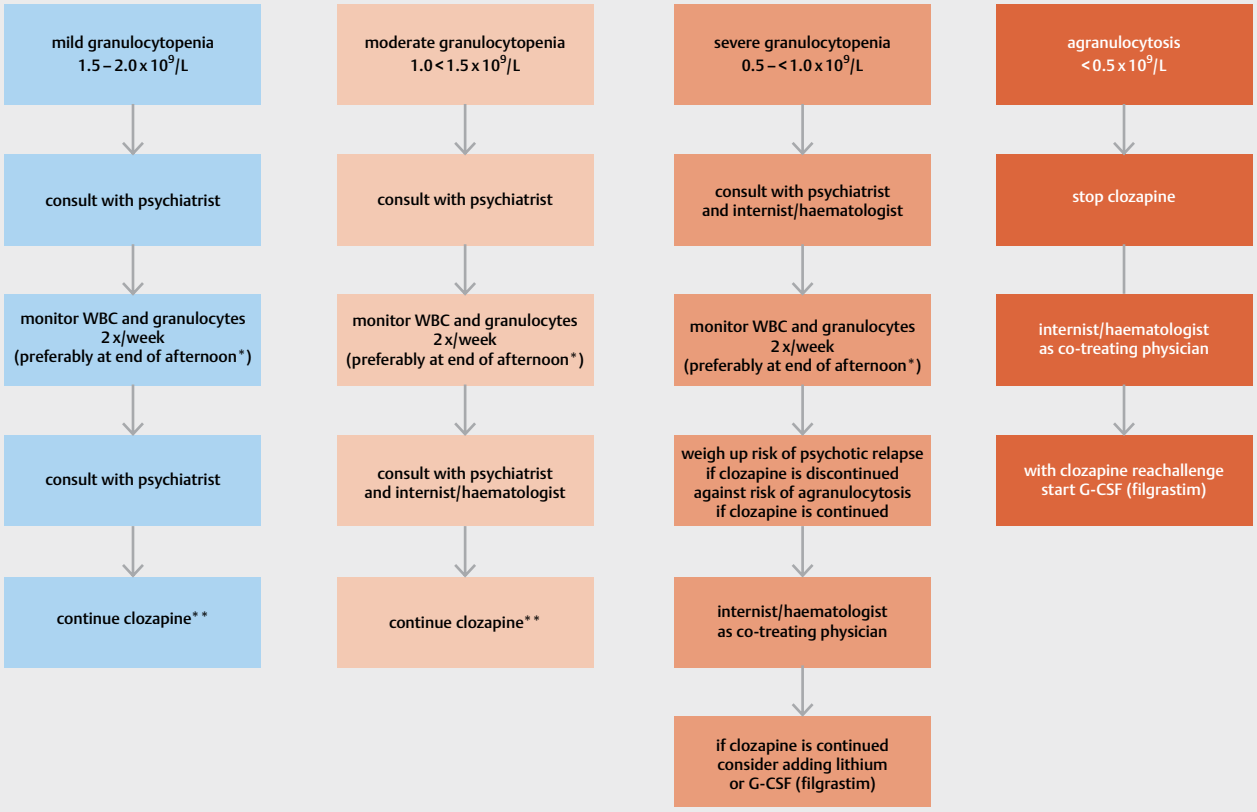
against SARS-CoV-2 [25]. Vaccination against COVID-19 seems no more dangerous for patients with schizophrenia spectrum disorders in general or clozapine users in particular than for the general population. Extensive experience with the influenza vaccine shows no effect on blood levels or the metabolites of clozapine [26]. There is also no evidence that vaccination changes the clozapine blood level by inflammation processes or increases the risk of granulocytopenia [27]. Although SAD has not been affirmed by follow-up research, clozapine-induced immunoglobulin deficiency could be an additional reason to protect this vulnerable patient group from infection [2]. In any case, there are no indications that SAD results in a failed immune response following COVID-19 vaccination. Additional monitoring of the white blood cell count (WBC) and differential and of clozapine levels after administration of the vaccine is therefore not indicated. ▶ **Figure 5** shows how only in particularly vulnerable patients, additional monitoring of blood count, clozapine levels, and C-reactive protein can be considered after vaccination against COVID-19. While viral agents such as SARS-CoV-2 may produce autoantibodies and features of subclinical systemic lupus erythematosus (SLE) [28], clozapine can also potentiate or accelerate autoimmunity, for instance, in clozapine-induced SLE [29]. Because a chronic proinflammatory state, reduced ability to mount an effective immune defense, and a possible higher risk of autoimmune disorders increase with age [30], elderly patients on clozapine might benefit from extra monitoring following COVID-19 vaccination. Moreover, as immune competence decreases with age, the response to COVID-19 vaccination is possibly lessened in elderly patients, while clozapine may compromise the immune response to infections due to antibody deficiency [2].

Conclusion

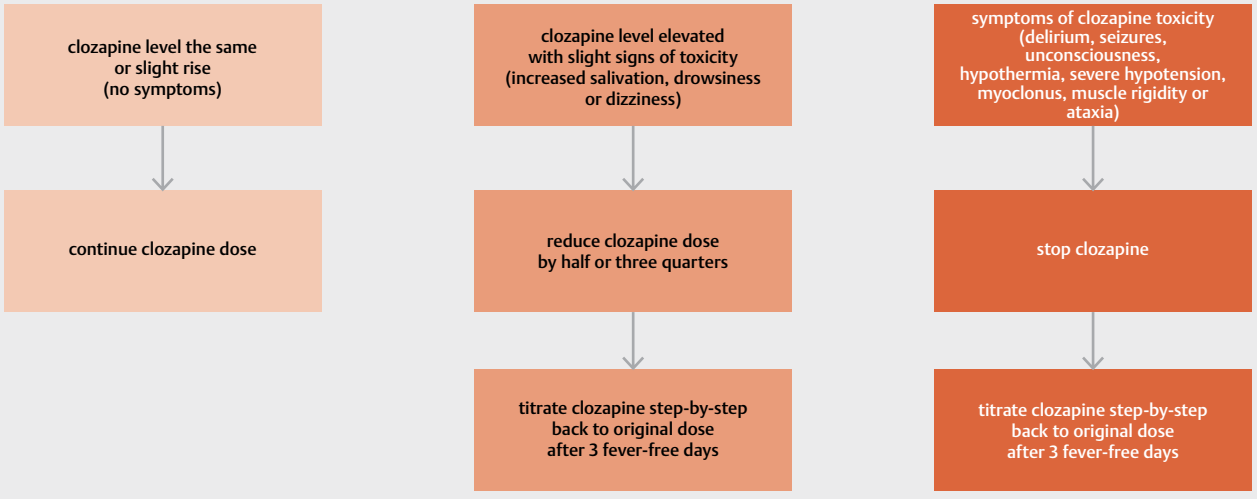
Based on a limited number of observational studies and case reports, our literature review allows for several conclusions and recommendations. Firstly, clozapine users with a SARS-CoV-2 infection have an increased risk of a (mostly transient) lymphocytopenia and granulocytopenia of viral origin. Secondly, COVID-19 infection results, probably due to the accompanying cytokine storm, in a more severe increase of clozapine plasma levels and clozapine intoxication. Pneumonia is another common complication of COVID-19 in patients on clozapine. Vaccination against COVID-19 does not seem to influence WBC, granulocyte count, or clozapine level. Vaccination can be of vital importance to clozapine users given the additional health risks with COVID-19 for this very vulnerable group. We, therefore, urge that patients on clozapine be prioritized for vaccination against COVID-19.

Conflict of Interest

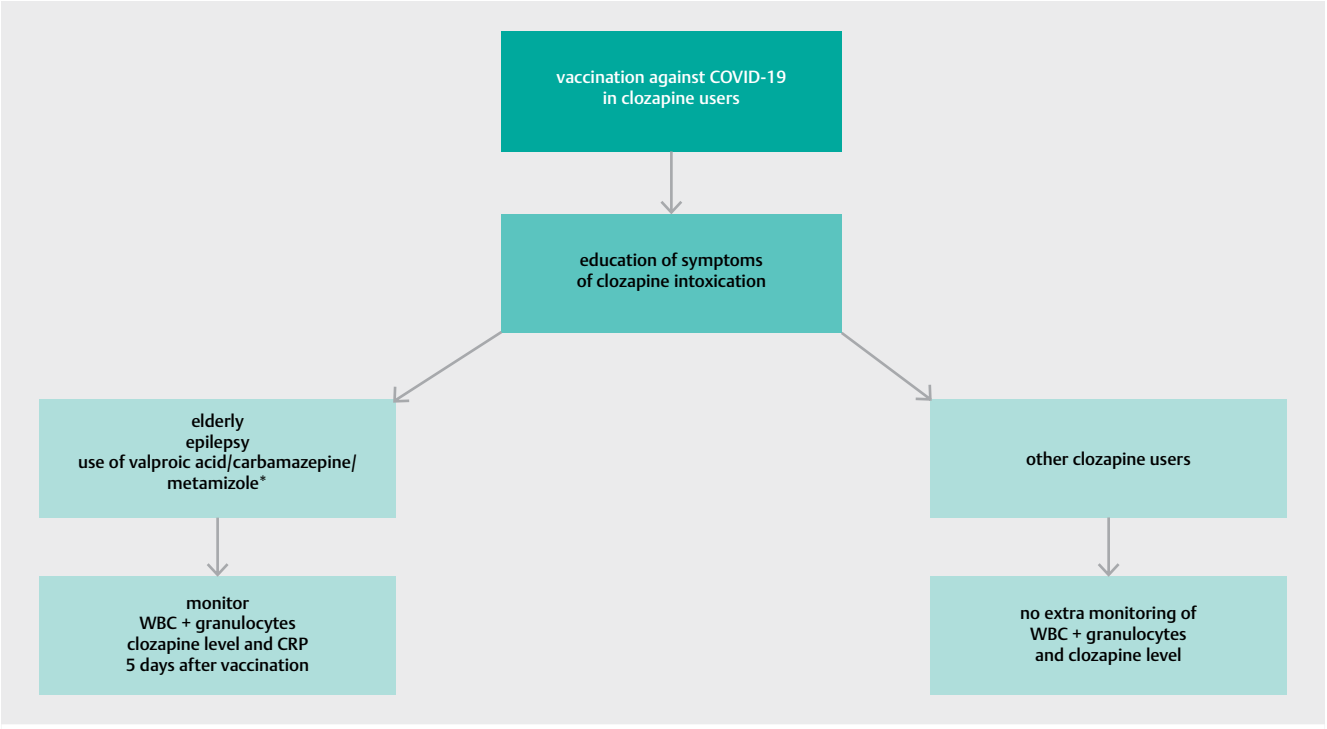
The authors declare that they have no conflict of interest.



▶ **Fig. 3** Step-by-step plan in the event of a decreased granulocyte count in patients on clozapine with a SARS-CoV-2 infection. *Due to daytime fluctuations white blood cell counts are the lowest in the morning and highest at the end of the afternoon. ** Granulocytopenia is not dose-dependent and is therefore not positively affected by dose reduction. Please note: 1. Although the neutrophil count is sufficient to estimate the risk of agranulocytosis, the European Medicines Evaluation Agency (EMEA) text also requires a complete WBC. 2. There is another problem associated with COVID-19: the lymphocytopenia often accompanies the viral infection, and causes a reduction in the number of leukocytes, and sometimes a decrease in the neutrophil count occurs, which is usually slight. 3. Benign ethnic neutropenia should be excluded. 4. The step-by-step plan focuses exclusively on the number of granulocytes, the only type of white blood cell that is relevant to clozapine. 5. The step-by-step plan according to the EMEA text indicates the threshold value of the granulocyte count at which clozapine must be stopped at <1.5 × 10^9/L, whereas according to this step-by-step plan clozapine can still be continued. Because this plan deviates from the registration text, this is an off-label use of clozapine.



▶ **Fig. 4** A step-by-step plan for increased clozapine plasma levels caused by infection and/or fever.



▶ **Fig. 5** Advice on post-vaccination monitoring against COVID-19 in clozapine use. *Valproic acid, carbamazepine, and metamizole can induce leukocytopenia or granulocytopenia.

References

[1] Govind R, Fonseca de Freitas D, Pritchard M et al. Clozapine treatment and risk of COVID-19 infection: Retrospective cohort study. Br J Psychiatry 2020; doi:10.1192/bjp.2020.151, online ahead of print

[2] Ponsford MJ, Pecoraro A, Jolles S. Clozapine-associated secondary antibody deficiency. Curr Opin Allergy Clin Immunol 2019; 19: 553–562

[3] Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: Analysis from electronic health records in the United States. World Psychiatry 2021; 20: 124–130

[4] Jeon HL, Kwon JS, Park SH, et al. Association of mental disorders with SARS-CoV-2 infection and severe health outcomes: Nationwide cohort study. Br J Psychiatry 2021; doi:10.1192/bjp.2020.251, online ahead of print

[5] Fond G, Pauly V, Leone M, et al. Disparities in intensive care unit admission and mortality among patients with schizophrenia and COVID-19: A national cohort study. Schizophr Bull 2020; 47: 624–634

[6] Tzur Bitan D, Krieger I, Kristin K, et al. COVID-19 prevalence and mortality among schizophrenia patients: A large-scale retrospective cohort study. Schizophr Bull 2021; sbab012 doi:10.1093/schbul/sbab012, online ahead of print

[7] Nemani K, Li C, Olfson M, et al. Association of psychiatric disorders with mortality among patients with COVID-19. JAMA Psychiatry 2021; 78: 380-386. doi: 10.1001/jamapsychiatry.2020.4442

[8] Cranshaw T, Harikumar T. COVID-19 Infection may cause clozapine intoxication: case report and discussion. Schizophr Bull 2020; 46: 751

[9] Dotson S, Hartvigsen N, Wesner T, et al. Clozapine toxicity in the setting of COVID-19. Psychosomatics 2020; 61: 577–578

[10] Tio N, Schulte PFJ, Martens HJM. Clozapine intoxication in COVID-19. Am J Psychiatry 2021; 178: 123–127

[11] Clark SR, Warren NS, Kim G, et al. Elevated clozapine levels associated with infection: a systematic review. Schizophr Res 2018; 192: 50–56

[12] De Leon J, Ruan C-J, Verdoux H, et al. Clozapine is strongly associated with the risk of pneumonia and inflammation. Gen Psychiatry 2020; 33: e100183

[13] Siskind D, Honer WG, Clark S, et al. Consensus statement on the use of clozapine during the COVID-19 pandemic. J Psychiatry Neurosci 2020; 45: 200061

[14] Smits F, Bogers JPAM, De Leeuw M. Leukocytopenie: clozapine of COVID-19. Tijdschr Psychiatr 2021; Accepted for publication

[15] Cron RQ. COVID-19 cytokine storm: targeting the appropriate cytokine. Lancet Rheumatol 2021; 3: e236–e237

[16] Gee S, Taylor D. The effect of COVID-19 on absolute neutrophil counts in patients taking clozapine. Ther Adv Psychopharmacol 2020; 10: 2045125320940935

[17] Gee S, Taylor D. COVID-10 infection causes a reduction in neutrophil counts in patients taking clozapine. J Psychiatry Neurosci 2021; 46: E232–E237

[18] Bonaccorso S, Ricciardi A, Ouabbou S, et al. Clozapine, neutropenia and Covid-19: should clinicians be concerned? 3 months report. Brain Behav Immun Health 2021; 13: 100212

[19] Baranski B, Young N. Hematologic consequences of viral infections. Hematol Oncol Clin North Am 1987; 1: 167–183

[20] Butler M, Bano F, Calcia M, et al. Clozapine prescribing in COVID-19 positive medical inpatients: A case series. Ther Adv Psychopharmacol 2020; 10: 2045125320959560

[21] Llesuy JR, Sidelnik SA. Death from COVID-19 in a patient receiving clozapine: factors involved and prevention strategies to consider. Prim Care Companion CNS Disord 2020; 22: 20l02699

[22] Thompson D, Delorme CM, White RF, et al. Elevated clozapine levels and toxic effects after SARS-CoV-2 vaccination. J Psychiatry Neurosci 2021; 46: E210–E211

[23] Schulte PFJ. The risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. Ann Pharmacother 2006; 40: 683–688

[24] Boland X, Dratcu L. Clozapine in the time of COVID-19. Clin Psychopharmacol Neurosci 2020; 18: 450–453

[25] Silva E, Gee S, Smith S, et al. Clozapine and COVID-19. B J Psych Bull 2020; 44: 179–180

[26] Raaska K, Raitasuo V, Neuvonen PJ. Effect of influenza vaccination on serum clozapine and its main metabolite concentrations in patients with schizophrenia. Eur J Clin Pharmacol 2001; 57: 705–708

[27] Morgan ET. Regulation of cytochrome p450 by inflammatory mediators: why and how? Drug Metab Dispos 2001; 29: 207–212

[28] Zamani B, Moeini Taba SM, et al. Systemic lupus erythematosus manifestation following COVID-19: A case report. J Med Case Rep 2021; 15: 29

[29] Pathak S, Cherry S, Samad S, et al. Successful clozapine rechallenge in a patient with suspected drug induced lupus. BMJ Case Rep 2019; 12: e228574

[30] Bektas A, Schurman SH, Sen R, et al. Human T cell immunosenescence and inflammation in aging. J Leukoc Biol 2017; 102: 977–988