

Croatian Society for Schizophrenia and Schizophrenia Spectrum Disorders Croatian Medical Association Guidelines for the Treatment of Patients with Schizophrenia Spectrum Disorders during the COVID-19 Pandemic

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The COVID-19 pandemic has raised the question of whether psychiatric patients, especially those with schizophrenia and other psychotic disorders, are more susceptible to SARS-CoV-2 infection. At this point in time we have to emphasize that there is not enough information, especially scientific and evidence-based, to answer this question. The same is true when considering the course of the disease, and also when considering psychopharmacotherapy itself (primarily antipsychotics, but also all other psychopharmaceuticals, that is, mood stabilizers, antidepressants, anxiolytics, hypnotics and pro-cognitive drugs). In case of an infection with a marked clinical presentation that has to be treated with most commonly used drugs (lopinavir / ritonavir, chloroquine / hydroxychloroquine and antibiotics), we provide available information on their potential interactions with psychopharmaceuticals (Table 1). It should be noted that it is advisable to use haloperidol in patients who are agitated and/or aggressive (whether suffering

from schizophrenia or some other psychotic disorder or in the case of delirium in otherwise non-psychotic patients), also available in the parenteral formulation. Benzodiazepines, on the other hand, are not recommended to the same extent because of their effects on the respiratory centre, especially when the effect of COVID-19 on the respiratory system is considered.

Below, we provide some general information and recommendations for this population of psychiatric patients.

General information

To date, the most common symptoms of COVID-19 are: elevated body temperature, fever, shortness of breath, dry cough, chest pain or pressure, fatigue, muscle pain, and difficulty breathing. However, it is important to point out that, with respect to the potential impact of COVID-19 infection on the course and treatment of psychotic disorders, there is at present no clear evidence

Table 1. Available information on the interaction of different psychopharmaceuticals (available in Croatia, EU) with most commonly used medications in the treatment of COVID-19 infection.

Psychopharmaceutical	Sedation	Lopinavir / Ritonavir	Chloroquine / Hydroxychloroquine	Antibiotics	Additional remarks
ANTI-DEPRESSANTS					
Agomelatine	+				
Amitriptyline	+++	↑ AMI through CYP2D6		↑ QTc with SULF, TRIM, AZI, and CLR	
Bupropion		↓ BUP through CYP2B6	↑ CHLOR through CYP2D6		
Citalopram		↑ CIT through CYP3A4	↑ QTc	↑ QTc with AZI and CLR	
Clomipramine	++	↑ CLOM through CYP2D6; ↑ QTc	↑ QTc	↑ QTc with AZI, CLR, SULF and TRIM	
Duloxetine		↑ DUL through CYP2D6	↑ DUL through CYP2D6		
Escitalopram		↑ ESC through CYP3A4	↑ QTc	↑ QTc with AZI and CLR	
Fluoxetine		↑ FLUO through CYP2D6	↑ CHLOR through CYP2D6	↑ QTc with CLR ↑ FLUO through CYP3A4 with CLR	
Fluvoxamine	+	↑ FLUV through CYP2D6			
Maprotiline	+	↑ MAP through CYP2D6			
Mirtazapine	+++	↑ MIR through CYP3A4		↑ MIR through CYP3A4 with CLR	
Paroxetine	+	↑ PAR through CYP2D6	↑ PAR through CYP2D6 (mild) ↑ CHLOR through CYP2D6	↑ QTc with SULF and AZI (mild) ↑ PAR through CYP3A4 with CLR	
Reboxetine		↑ REB through CYP3A4		↑ REB with CLR through CYP3A4	
Sertraline		↑ SER through CYP3A4		↑ SER through CYP3A4 with CLR	
Tianeptine					Renal metab.

Table 1. (continued)

Psychopharmaceutical	Sedation	Lopinavir / Ritonavir	Chloroquine / Hydroxychloroquine	Antibiotics	Additional remarks
Trazodone	+++	↓ RITONAVIR through MDR1; ↑ TRA through CYP3A4		↑ QTc with SULF, TRIM and AZI; ↓ TRA with SULF (mild); ↑ TRA through CYP3A4 with CLR	
Venlafaxine		↑ VEN through CYP3A4	↑ QTc	↑ QTc with SULF, TRIM, AZI (mild) and CLR; ↑ VEN through CYP3A4	
Vortioxetine		↑ VOR through CYP2D6			
ANTI-PSYCHOTICS					
Amisulpride	++	↑ QTc	↑ QTc	↑ QTc with AZI and CLR	Renal metab.
Aripiprazole		↑ ARI through CYP3A4	↑ ARI through CYP2D6 (mild)	↑ QTc with AZI ** ↑ ARI through CYP3A4	
Clozapine	+++	↑ QTc	↑ agranulocytosis risk; ↑ QTc; ↑ CLOZ (mild)	↑ QTc with AZI; ↑ agranulocytosis risk with SULF; ↑ CLOZ with CLR (mild)	
Fluphenazine	+	↑ FLUP through CYP2D6; FLUP + RITONAVIR ↑ QTc	↑ FLUP through CYP2D6; ↑ QTc	↑ QTc with SULF, TRIM, AZI, CLR	
Haloperidol	+	↑ HAL through CYP2D6; HAL + RITONAVIR ↑ QTc	↑ HAL through CYP2D6; ↑ QTc	↑ QTc with SULF, TRIM, AZI, CLR	
Levomepromazine	+++		↑ LEV through CYP2D6 and CYP3A4	↑ QTc with AZI and CLR	
Olanzapine	++	↓ OLA	↑ QTc **	↑ QTc with CLR (mild) **	Renal metab.
Paliperidone	+				
Promazine	+++	↑ PRO through CYP2D6	↑ PRO through CYP2D6; ↑ QTc	↑ toxicity of SULF; ↑ QTc with SULF, TRIM, AZI, CLR	
Quetiapine	++	↑ QUE through CYP3A4; ↑ QTc	↑ QTc	↑ QTc with AZI and CLR; ↑ QUE with CLR	

Table 1. (continued)

Psychopharmaceutical	Seclation	Lopinavir / Ritonavir	Chloroquine / Hydroxychloroquine	Antibiotics	Additional remarks
Risperidone	+	↑ RIS through MDR1	↑ RIS through CYP2D6 (mild)	↑ QTc with SULF, TRIM, AZI	
Sulpiride	++	↑ QTc	↑ QTc **	↑ QTc with AZI and CLR **	Renal metab.
Ziprasidone	+	↑ QTc	↑ QTc	↑ QTc with AZI and CLR (with CLR contraindicated)	
MOOD STABILIZERS / ANTI CONVULSANTS					
Carbamazepine		↓ LOPINAVIR and ↑ CARB through CYP3A4		↑ toxicity of CARB; ↓ SULF and TRIM	
Gabapentin	+				
Lamotrigine		↓ LAM			
Lithium		↑ QTc	↑ QTc	↑ QTc with CLR and SULF (mild)	
Pregabalin	++				
Valproate	+++	↓ VALP (mild)		↑ SULF (mild)	
ANXIOLYTICS / HYPNOTICS					
Alprazolam	+	↑ ALP through CYP3A4			T _{1/2} 6-20h
Bromazepam	+	↑ BRO (mild)			T _{1/2} 10-20h
Clonazepam	+++	↑ CLON through CYP3A4			T _{1/2} > 20h
Diazepam	++	↑ DIA through CYP3A4			T _{1/2} > 20h
Flurazepam	+++	↑ FLUR through CYP3A4			T _{1/2} > 20h
Lorazepam	++				T _{1/2} 6-20h
Midazolam	+++	↑ MID through CYP3A4 (contraindicated)		↑ MID with CLR through CYP3A4	T _{1/2} < 6h

Table 1. (continued)

Psycho pharmaceutical	Sedation	Lopinavir / Ritonavir	Chloroquine / Hydroxychloroquine	Antibiotics	Additional remarks
Nitrazepam	++				T _{1/2} 10-20h
Oxazepam	++				T _{1/2} 6-12h
Zolpidem	++	↑ ZOL through CYP3A4		↑ ZOL with CLR through CYP3A4	T _{1/2} < 6h

☐ Potentially significant clinical implications. This association should be carefully monitored and evaluated.

☐ Very significant clinical implications. Recommended to avoid.

* Abbreviations: sulfamethoxazole (SULF); trimethoprim (TRIM); azithromycin (AZI); clarithromycin (CLR)

** The risk of QTc prolongation is low for ARI, RIS, PALL, OLA and SUL

that schizophrenia spectrum disorders may be exacerbated or psychopharmacotherapy influenced by the infection alone. Be that as it may, caution should be exercised in patients with schizophrenia or other psychotic disorders with pulmonary comorbidity (e.g. COPD), as it has been reported earlier that administration of antipsychotics (especially higher dosages) increases the risk of acute respiratory failure. Similarly, the elderly and patients with comorbidities (chronic respiratory diseases, but also cardiovascular diseases, diabetes and malignancies) have the highest risk of developing a more severe COVID-19 clinical picture, often warranting respiratory support. Taking into account that there is a considerable number of patients with these comorbidities in the population of those suffering from schizophrenia and other psychotic disorders, it is urgent to follow the recommendations of the Croatian Institute of Public Health. Particular attention should be paid to smokers who are more prone to develop severe COVID-19 clinical presentations. It should be noted that the percentage of smokers among patients with psychotic disorders is higher than 75%.

Should patients in remission be advised to stay home and not report to the hospital?

Patients in remission should not be required to attend regular check-ups, but to wait for the improvement of general conditions and renewal of outpatient psychiatric services. In other words, it is necessary to continue to adhere to earlier recommendations, especially regarding the regular use of prescribed psychopharmacotherapy. Alternatively, it is possible to arrange a telephone consultation with a psychiatrist. Given the circumstances of the current pandemic, it is desirable to allow patients to work in their home environment, but this depends on the nature of their employment and should be agreed upon after

consultation with the family doctor and employer. In any case, patients are advised to ensure that they have a satisfactory home supply of medicines that they regularly take in therapy, in order to ensure the recommended measures of physical distancing.

How to reduce the risk of COVID-19 infection in patients with schizophrenia and other psychotic disorders?

Given that the vaccine for COVID-19 has not yet been developed, the main way to prevent infection is to reduce exposure to the virus and therefore general preventative measures are recommended, as stated on the web pages of the Croatian Institute of Public Health: <https://www.hzjz.hr/wp-content/uploads/2020/03/Dodatne-upute-za-pojedince-kolektive-i-poslodavce.pdf> and <https://www.hzjz.hr/wp-content/uploads/2020/03/Stariji-i-ostali-osjetljivi-na-koronavirus-2.pdf>

Summarized recommendations

- 1) Potential risk factors for COVID-19 infection in patients with schizophrenia spectrum disorders:
 - Over 60 years old
 - Patients who visit health facilities more often
 - Travels or mass gatherings
 - Smoking
 - Patients with comorbidity of lung disease, diabetes, chronic renal or hepatic disease, endocrinological and metabolic disorders, malignancies and other diseases that further immunocompromise the patient
 - Malnutrition
 - Patients on immunosuppressive / immunomodulatory therapy

- 2) Procedures related to diagnostics and therapy:
 - According to currently available information, the risk of COVID-19 infection is not increased with the regular use of psychopharmaceuticals (all groups)
 - It is recommended to continue current psychopharmacotherapy if the disease is in remission
 - In case of worsening of symptoms or suspected relapse, it is necessary to contact the family doctor or psychiatrist in charge or to use emergency psychiatric services
 - It is recommended to delay elective surgery and elective invasive treatment
- 3) Procedures in case of symptoms of respiratory illness (cough, sneezing, sore throat, fever, shortness of breath):
 - Stay at home (don't go to work, school, other collectives, larger family gatherings and public places)
 - If there is a suspected infection with COVID-19, or if it cannot be safely ruled out, epidemiological services should be consulted and their instructions followed
 - Call your chosen physician (telephone / e-mail) regarding the possibility of organizing an emergency check-up. Avoid going to a healthcare facility unless your doctor advised you differently
 - In an emergency, call 112 or 113 (new call centre for any coronavirus questions)

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