



## REVIEW ARTICLE

## Risks Associated with the Use of Psychotropics in Patients Diagnosed with Covid-19: An Integrative Review

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### Abstract

**Background:** In the context of the pandemic, negative implications for mental health increased significantly, increasing the existing associations of psychotropic drugs in this period of combating the new coronavirus.

**Objective:** In this context, this study aimed to verify the health impact of Covid-19 infection in patients with mental disorders who make chronic and non-chronic use of psychotropic drugs.

**Design and setting:** Integrative literature review conducted in Universidade Federal de Campina Grande.

**Method:** The study is descriptive, retrospective, considered a systematic literature review, carried out through a search for original articles, in English, Spanish and Portuguese, available in full, published from December 2019 to July 2020 in the database of Science Direct. Searches will be carried out in August, September and October 2020, using the descriptors: 'Covid-19', 'Sertraline', 'Carbamazepine', 'Quetiapine', 'Pharmacological treatment', 'Psychiatry', 'Psychotic', and using the Boolean operators.

**Results:** In this integrative review, a total of 146 articles were found, with the use of exclusion criteria, 21 articles were selected. The physician's choice of pharmacological treatment should be based on a careful and individualized assessment of each patient, considering the risks that associations between drugs frequently used to treat Covid-19 and those administered to control mental disorders.

**Conclusion:** In this sense, with the evidence presented in this review, the article aims to demonstrate the important correlation between Covid-19 and psychiatric disorders, indicating paths for treatments and optimizing the time for recovery and support of those individuals who develop or make more explicit diseases of mental origin.

### Keywords

COVID-19, Mental disorders, Psychiatry, Public health, Medicines

### Keywords (MeSH terms)

COVID-19, Sertraline, Carbamazepine, Quetiapine, Pharmacological treatment, Psychiatry, Psychotic

### Introduction

The COVID-19 pandemic disrupted essential mental health services in 93% of countries worldwide, while demand for mental health is increasing, according to WHO. Also referring to this situation, there was a 45% reduction in maintenance treatments with opioid agonists for cases of dependence, and more than a third (35%) reported interruptions in emergency interventions, including those for people who had prolonged seizures, severe substance use withdrawal

syndromes and delirium, usually a sign of a serious pre-existing medical condition. Furthermore, 30% reported interruptions in access to medication for mental, neurological and substance use disorders [1].

Furthermore, in 80% of patients, psychotic symptoms appeared more than two weeks after the first somatic manifestation attributed to COVID-19 and disappeared in less than two weeks. Delusions of prejudice, persecutory beliefs and references were the most frequent outcomes. Seizure symptoms were not present in the patient whose onset of psychosis was not preceded by disease treatment. Furthermore, the individual whose psychosis was not preceded by virus manifestation could be an example of a primary psychotic episode triggered by stress [2], with a worse prognosis because of the premorbid schizoid personality [3].

In this context, patients with COVID-19 with known psychiatric disorders should be closely monitored for neurological manifestations, including headache, dizziness and symptoms, changes in mental status, meningeal signs, dyskinesias. Patients with severe infection may have a higher risk of developing neurological sequelae and increased mortality [4]. Aiming to contribute and join efforts to improve mental health and psychiatric events, the present investigation was proposed with the aim of evaluating the evidence available in the literature and understanding the main interactions between medications often used in the treatment of Covid-19 and psychotropic drugs, as well as their systemic effects on patients' bodies.

## Method

### Study

This is a cross-sectional cohort study, with a dissertation-descriptive, retrospective approach, which reviewed the literature to identify scientific production in order to verify the impact on health of Covid-19 infection in patients with mental disorders who undergo chronic and non-chronic use of psychotropic drugs. We chose to carry out a systematic review, defined as an instrument for obtaining, identifying, analyzing and synthesizing the literature directed at a specific topic. It also allows building a broad analysis of the literature, including discussions on the results of publications covering the subject studied.

For the preparation of this study, the following steps were taken: Establishment of the hypothesis and objectives of the integrative review; establishment of inclusion and exclusion criteria for articles (sample selection); definition of the information to be extracted from the selected articles; analysis of results and discussion of results found in research.

### Inclusion and exclusion criteria

The following inclusion criteria were adopted: Fully

available articles, published in Portuguese, English or Spanish, with abstracts available in the selected database, in national and international journals and indexing in the database referred to in the period from December 2019 to July 2020 (first Covid-19 case confirmed in Wuhan, China); published articles whose adopted methodology allowed to obtain strong evidence in the following types: Research articles, case reports, correspondence, discussion, editorials, mini reviews, practical guidelines and short communications; patients who make chronic use of psychotropic medications; inpatients or outpatients and patients with Covid-19. Care was taken to exclude duplicate articles and those that carried out research with animals.

### Data extraction and management

To analyze the results found in the literature, the researchers performed the searches on the platform (Science Direct), individually and comparing the results found through the descriptors: Covid-19, sertraline, carbamazepine, quetiapine, pharmacological treatment, psychiatry and psychotic; by using the Boolean operators "AND" and "OR", in the following order: Covid-19 AND (Sertraline OR Carbamazepine OR Quetiapine) and Pharmacological treatment AND Covid-19 AND (Psychiatry OR Psychotic).

The presentation of the results and the discussion of the data obtained took place in a dissertation-descriptive form, taking into account the following point: Co-administration of psychotropic drugs and first-line drugs in the fight against Covid-19, enabling the reader to assess the applicability of the integrative review elaborated, in order to achieve the objective of this method, that is, positively impact the quality of decision-making for the practice of the relationship of patients with Covid-19 and their relationship with psychotropic drugs.

### Ethical aspects

The present study was not subject to the Ethics and Research Committee, because according to CNS Resolution 510/2016 researches carried out exclusively with scientific texts for literature review do not need to be submitted to evaluation.

## Results and Discussion

In this integrative review, a total of 146 articles were found, without using the exclusion criteria, which were separated as follows:

In the first search, the descriptors Covid-19 AND (Sertraline OR Carbamazepine OR Quetiapine) were used, being initially found 97 articles in total.

From this clipping, systematic review articles (22) and book summaries (7) were removed, as they did not fit the proposed work model (integrative review), leaving a total of 68 articles (research articles (33), case

reports (7), correspondence (22), editorials (1), mini reviews (1) and short communications (4). After the inclusion of the search filters, (21) were excluded due to the time frame, (8) duplicate articles, (2) that did not correspond to the linguistic frame, (24) for being outside the objective; leaving a total of (13) articles, of which are: (6) correspondence, (4) research articles, (1) short communications, (1) case reports, (1) discussion articles and (0) editorials.

Secondly, the descriptors Pharmacological treatment AND covid-19 AND (psychiatry OR psychotic) were used, initially with a total of 110 articles. From this clipping, review articles (23), news (1), practical guidelines (1) and book summary (6) were removed, as they do not fit the proposed work model (integrative review), leaving one total of 78 articles (research articles (46), case reports (2), correspondence (13), discussion (5), editorials (5) and short communications (7)). After the inclusion of the search filters, (28) were excluded due to the time frame, (0) duplicate articles, (3) that did not correspond to the linguistic cut, (39) for being outside the objective; leaving a total of (8) articles, which are: (2) correspondence, (2) research articles, (0) short communications, (1) case reports, (2) discussion articles and (1) editorials.

After reading the articles in full, (21) were selected. The results were analyzed and the most relevant and compatible aspects were identified for the guiding question. 125 works were excluded for not meeting the inclusion criteria or for not meeting the objective proposed by the review.

Therefore, the following information was found as evidence:

### **Coadministration of psychotropics and first line drugs in the fight against Covid-19: Associated risks**

In this pandemic scenario, the study of interactions between psychotropic drugs and those recommended for the treatment of Covid-19 is extremely relevant to prevent harmful prognoses for psychiatric patients. In the context of this association, the prolongation of the QTc heart rate interval (measurement from the beginning of the QRS complex to the end of the T wave) was demonstrated as a significant result. This interval represents the total duration of ventricular electrical activity [5] and the inhibition of cytochrome CYP3A, which increases liver toxicity in patients [6,7]. In addition, the damage caused by Covid-19 to the cardiovascular system is multifactorial and can result both from an imbalance between high metabolic demand and low cardiac reserve, as well as from systemic inflammation and thrombogenesis, which can also occur due to direct cardiac injury by the virus [8]. Notably, physicians, in order to properly treat a patient with Covid-19 who is taking psychiatric medication, need a thorough understanding of these possible consequences.

Thus, among drug associations and their effects on the human body, it was found that hydroxychloroquine (HCQ) can cause anxiety and, less frequently, psychosis, and may also interact with some antipsychotics, increasing the levels of phenothiazines (active substances in the Central Nervous System with sedative effects) [9,10]. In addition, HCQ is known to cause seizures, neutropenia and myocardial toxicity, and its concomitant association with Clozapine (an antipsychotic drug used to reduce suicidal and aggressive behavior, especially in patients diagnosed with schizophrenia), which also has similar side effects compared to HCQ, it should be avoided, as it can be fatal for the patient [11,12]. It is noteworthy that the effect of these drugs (HCQ and Clozapine) combined with the manifestations of covid-19 can worsen the patient's condition. In turn, it should be kept in mind that Chloroquine (CQ) can reduce the seizure threshold and antagonize antiepileptic actions [13]. Thus, it is important that the situations in which the HCQ and the CQ can refer benefits to patients are also evaluated.

Furthermore, Azithromycin, in addition to its QTc interval-prolonging property, can also cause acute and transient increases in hepatic aminotransferase (aspartate aminotransferase (AST) or alanine aminotransferase (ALT)) in 1-2% of cases, as well as there is an increase in about 8%-37% of cases in patients with Covid-19 [14]. Therefore, it should be used with caution in patients using Valproate (a drug often used as a mood stabilizer and affective controller), with regular monitoring of liver function tests, given that Valproate is also related to increased liver toxicity severe, regardless of the time of use [15-18]. In addition, the concomitant use of Azithromycin and Hydroxychloroquine with some antiepileptic drugs (eg, Lacosamide, phenobarbital, Primidone, Rufinamide, Phenytoin, and Carbamazepine) increases the risk of cardiac conduction abnormalities (eg, AV block) and QT interval prolongation/PR [7]. Thus, it is important to highlight these interactions, since all the drugs mentioned above can be administered to patients with COVID-19, decreasing the survival of these individuals.

Other medications that have been used to treat Covid-19, Ritonavir/Lopinavir are contraindicated if the patient is taking Lurasidone or Pimozide (medications for depressive, mood and psychotic disorders), according to the Food and Drug Administration (FDA), as they can cause potentially fatal cardiac arrhythmias and when administered with Midazolam (a medication that promotes a sedative effect), it can cause prolonged respiratory depression [19,20]. In addition, both Ritonavir and Lopinavir, protease inhibitors (PI), are potent CYP3A4 blockers, so any psychotropic drug that is primarily metabolized through CYP3A4 (Buspirone, Clonazepam, Carbamazepine, Lurasidone, Quetiapine, Mirtazapine, Trazodone) should be adjusted in dose or interrupted [6]. Therefore, it is highlighted that Lopinavir/Ritonavir can substantially increase the



serum levels of Quetiapine, Lurasidone, Ziprasidone and Pimozide, as well as those of certain benzodiazepines, such as Midazolam and Triazolam [21]. In this context, in order to reduce the risk of serum toxicity caused by this inhibition of CYP3A4, the combined use of these drugs should be avoided.

Also, the antiviral Remdesivir, an investigational RNA polymerase inhibitor, was recently authorized for emergency use in severe cases of Covid-19. However, this drug can cause elevated liver enzymes. This means that medications such as Valproate and Benzodiazepines must be used with caution, considering that they may also be related to the risk of liver damage [22]. Furthermore, drug combinations between benzodiazepines (Diazepam, Clobazam, Clonazepam) used to control acute seizures and Atazanavir, Darunavir/Cobicistat or Lopinavir/Ritonavir (medications used to treat patients with Covid-19) can increase serum levels of benzodiazepines and the risk of toxicity [21]. Thus, the use of alternative agents or monitoring of benzodiazepine toxicity is a rational approach for the management of acute seizures in patients with Covid-19 [7].

In addition, there is evidence that benzodiazepine phase-out is feasible, safe, and can be completed in primary care as well as in mental health treatment settings [23]. However, instructing these patients to discontinue certain medications, such as benzodiazepines and antipsychotics, can cause them to experience withdrawal symptoms. In addition, patients who have these severe symptoms are often admitted to hospitals, but this circumstance poses a greater risk of acquiring Covid-19 and negatively impacting their health [24]. It should be noted that the virus usually causes lymphopenia, so the leukopenic effect caused by Carbamazepine (a drug often used to treat affective and bipolar disorders) [19] can further increase this adverse condition that would already be present in diagnosed individuals with Covid-19.

Still referring to the verification of leukocyte count, it appears that in patients treated with Clozapine, infection by Covid-19 can cause leucopenia [25]. In this sense, reducing the dosage of Clozapine or replacing it would be a recommended alternative. In addition, for patients who are chronically using Carbamazepine, it is necessary to monitor serum leukocyte levels. This recommendation should also be extended individually to the sodium channel blockers used in trigeminal neuralgia therapy: Eslicarbazepine acetate, oxcarbazepine (level of evidence IV, degree of recommendation C) and lamotrigine (level of evidence II, recommendation degree B), since these drugs have a therapeutic class and interactions with the body similar to those of carbamazepine [26]. Carbamazepine also reduces the levels of Atazanavir, Remdesivir, Chloroquine and Hydroxychloroquine [27]. Therefore,

if proper precautions and care are not taken, the combinations of these drugs mentioned above can be lethal for psychiatric patients who depend on this psychotropic drug to control their underlying diseases.

Regarding corticosteroids, their use in high doses has been identified as a factor associated with psychotic presentations (delusions, disorganized thoughts, hallucinations and changes in feelings/behavior), which can cause manic symptoms when administered intravenously or intramuscularly with the aim of increasing its concentration in the blood [28-30]. Finally, neuropsychiatric symptoms may have been secondary to treatment with high-dose corticosteroids. This drug class represents a significant risk of neuropsychiatric side effects, including mood changes, psychosis, delirium and changes in executive functioning [31].

In the context of selective serotonin reuptake inhibitors (SSRIs), a drug class used as antidepressants and anxiolytics by modulating serotonin in the brain, they work as inhibitors that increase serotonin by controlling its reuptake in the presynaptic cell and then, increasing the level of serotonin within the synaptic cleft so that coupling to the postsynaptic receptor occurs [32]. Sertraline, a member of the (SSRIs), is suggested as a favorable drug for patients with Covid-19 because it has a broad therapeutic index and minimal anticholinergic activity, making it a safe option for elderly patients or patients with underlying cardiovascular disorders [33].

Antipsychotics can help control delirium symptoms, specifically in this patient population, this drug class should be carefully monitored, as their use together with drugs used for Covid-19 (eg, Hydroxychloroquine, Azithromycin) may prolong the QTc interval, causing a risk of arrhythmias (According to the Brazilian Society of Cardiac Arrhythmias, patients with cardiac arrhythmias have a higher risk of serious infection by the new coronavirus). Therefore, if the usual doses of psychotropic drugs taken by the patient are in the low to median recommended levels, it is worth noting that, during the co-administration of these drugs, clinical monitoring of adverse effects (ie, extrapyramidal effects with antipsychotics, sedation with benzodiazepines, adrenergic or serotonergic reactions with antidepressants) and monitoring of drug levels (if possible and/or necessary), in addition to ECG examination for eventual guarantee of the patient's homeostasis [34].

Among the safer antipsychotic drugs, mainly because they do not prolong the QTc interval (if the QTc is greater than 440 mSec in men or 470 mSec in women, there is a risk of developing cardiac arrhythmia), Olanzapine and Aripiprazole can be considered, if necessary, in cases of infection by Covid-19, not needing to discontinue them in psychiatric patients [18]. In general, there is an association between administration of antipsychotics and an increased risk of pneumonia (not demonstrated

in the specific case of Covid-19 infection), but the benefit-risk balance of using or not using the antipsychotic is generally favorable for psychopharmacological treatment [35].

## Conclusion

Given the above, it can be concluded that the decision-making of physicians who carry out psychiatric follow-up on the use of a pharmacological treatment mechanism should be based on a careful and individualized assessment of each patient, always considering the risks that the associations between the drugs often used to treat Covid-19 and those given to control mental disorders. For this assessment it is necessary that the professional is scientifically grounded, to implement effective interventions that meet the real needs of the patient. In this context, the following complications need to be considered: QT interval prolongations; cardiac arrhythmias; liver and serum toxicity; increase or decrease in drug effects, both in terms of Covid-19 treatment and mental disorders; and intensification or onset of psychoses.

In view of the results indicated in the articles included in this integrative review, it is understood the need to intensify efforts to develop research with designs that produce strong evidence related to the topic investigated, especially in the reality of psychiatric practice.

## Author Contributions

Conceptualization: Oliveira VRB, Mota Júnior FRC, Silva VHF, Melo TR and Ferreira SB; methodology: Oliveira VRB, Mota Júnior FRC and Silva VHF; investigation: Oliveira VRB, Mota Júnior FRC and Silva VHF; writing-original draft preparation: Oliveira VRB, Mota Júnior FRC and Silva VHF; writing-review: Melo TR and Ferreira SB.; supervision: Melo TR and Ferreira SB. All authors have read and agreed to the published version of the manuscript.

## Financial Support

The authors did not receive any kind of financial assistance.

## Declaration of Interest

No potential conflict of interest was reported by the authors.

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