Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review of the literature

Psychotropics and COVID-19: An analysis of safety and prophylaxis

Psychotropes et COVID-19 : une analyse de la sécurité clinique et de la prophylaxie

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ABSTRACT

The use of psychotropics during the COVID-19 pandemic has raised two questions, in order of importance: first, what changes should be made to pharmacological treatments prescribed to mental health patients? Secondly, are there any positive side effects of these substances against SARS-CoV-2? Our aim was to analyze usage safety of psychotropics during COVID-19; therefore, herein, we have studied: (i) the risk of symptomatic complications of COVID-19 associated with the use of these drugs, notably central nervous system activity depression, QTc interval enlargement and infectious and thromboembolic complications; (ii) the risk of mistaking the iatrogenic impact of psychotropics with COVID-19

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symptoms, causing diagnostic error. Moreover, we provided a summary of the different information available today for these risks, categorized by mental health disorder, for the following: schizophrenia, bipolar disorder, anxiety disorder, ADHD, sleep disorders and suicidal risk. The matter of psychoactive substance use during the pandemic is also analyzed in this paper, and guideline websites and publications for psychotropic treatments in the context of COVID-19 are referenced during the text, so that changes on those guidelines and eventual interaction between psychotropics and COVID-19 treatment medication can be reported and studied. Finally, we also provide a literature review of the latest known antiviral properties of psychotropics against SARS-CoV-2 as complementary information.

RÉSUMÉ

Mots clés :
COVID-19
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L'usage des psychotropes en période de pandémie de COVID-19, liée au SARS-CoV-2, a fait émerger deux grandes interrogations d'importance inégale. Prioritairement, quelles doivent être les éventuelles adaptations de traitements pharmacologiques à mener chez les patients souffrant de troubles psychiques ? Secondairement, certains psychotropes sont-ils susceptibles de présenter un effet bénéfique contre le SARS-CoV-2 ? L'objectif de la présente revue est d'investiguer ces deux interrogations sur la base des informations données par la littérature. La recherche bibliographique a appliqué une méthode mixte avec une revue systématique des données liées au COVID-19/SRAS-CoV-2 (jusqu'au 01/12/20) et une revue consensuelle pour d'autres informations (en particulier, les risques iatrogènes associés aux psychotropes). Afin d'envisager la sécurité clinique des psychotropes, nous aborderons successivement : (i) les risques de complications symptomatologiques de la COVID-19 liés aux psychotropes avec les impacts en termes de dépression de l'activité centrale, de risque d'allongement de l'intervalle QT, de complications infectieuses et thromboemboliques ; puis (ii) les risques de confusion diagnostique entre l'impact iatrogène lié aux psychotropes et les symptômes de la COVID-19. Une synthèse est ensuite proposée sur les différentes informations disponibles, à ce jour, par psychopathologies, en lien avec leurs traitements psychopharmacologiques, dans le contexte de la COVID-19, dans la schizophrénie, les troubles de l'humeur, les troubles anxieux, le TDAH, mais également les troubles du sommeil et le risque suicidaire. La gestion des traitements de la schizophrénie résistante et de la dépression résistante au temps de la COVID-19 sera traitée. Tandis que les risques spécifiques liés aux traitements de la COVID-19 en termes d'impact psychogène et dépressogène sont également abordés. Les effets dépressogènes, avec de potentielles idées suicidaires, sont ainsi décrits avec les corticoïdes, l'interféron alpha, mais également la chloroquine et l'hydroxychloroquine. Les effets psychotiques aigus sont, quant à eux, rapportés avec les corticoïdes, la chloroquine et l'hydroxycloroquine. L'anakinra, anti-IL-1 et le tocilizumab, anti-IL-6, pour leur action de régulation des cytokines pro-inflammatoires, impliquées dans l'immunopathologie du COVID-19, pourraient présenter un intérêt pour lutter contre les complications neuropsychiatriques de la COVID-19. La problématique spécifique des substances psychoactives au temps de la COVID est également décrite. En cas de COVID-19 avec une symptomatologie respiratoire importante, l'impact de l'arrêt du tabac sur le métabolisme des psychotropes peut être conséquent et nécessiter des adaptations posologiques pour les traitements pris en charge par le CYP1A2. Les publications et sites web de référence pour s'informer sur les psychotropes dans le contexte de la COVID-19 sont référencés afin de faire le point sur les adaptations de prescriptions proposées, ainsi que les interactions médicamenteuses entre psychotropes et les traitements de la COVID-19. Ces données s'appuient notamment sur les informations proposées : (i) par une revue de la littérature établissant des recommandations pratiques fondées sur des preuves (structurée par le centre de référence de l'OMS en santé mentale de l'Université de Vérone) ; (ii) par les sites web des Universités d'Oxford et de Liverpool, proposant respectivement des recommandations pour la santé mentale en générale et sur plusieurs traitements ou classes de psychotropes en particulier et une plateforme de recherche d'interactions médicamenteuses entre les médicaments expérimentaux utilisés contre la COVID-19 et les médications courantes, dont les psychotropes. Le potentiel antiviral des psychotropes contre le SARS-CoV-2 est ensuite décrit sur la base des données fournies, à ce jour, dans la littérature. Dès la fin du mois d'avril 2020, l'évocation du potentiel anti-SARS-CoV-2 de l'halopéridol et de chlorpromazine sont apparues dans la littérature médicoscientifique. Depuis, de nombreux autres psychotropes candidats ont pu être proposés avec notamment: des neuroleptiques phénothiaziniques et leurs proches dérivés, des antidépresseurs tricycliques et des inhibiteurs sélectifs de la recapture de la sérotonine, mais aussi le lithium, la nicotine ou encore la mélatonine. Compte tenu de la diversité des substances pouvant présenter un profil anti-SARS-CoV-2, il apparaît difficile de déceler un unique profil pharmacologique susceptible d'induire une chimioprotection, mais les effets antihistaminiques, conjugués à des propriétés d'amphiphiles cationiques (ou CAD et/ou d'inhibiteurs fonctionnels de la sphingomyélinase acide ou FIASMA) pourraient être des leviers importants d'une telle activité. Globalement, ces données plaident pour l'évaluation clinique rigoureuse des potentiels prophylactiques et/ou curatifs des psychotropes face à la COVID-19. La construction d'une vision ajustée sur leur rapport bénéfice/risque peut se construire en envisageant à la fois leur dangerosité potentielle, avec leurs risques identifiés, mis en perspective avec la possibilité d'envisager des stratégies psychopharmacothérapeutiques de la COVID-19 qui soient bien tolérées et potentiellement prophylactiques.

1. Introduction

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic raised great uncertainty regarding psychotropic drugs. Their potential dangerousness as a risk factor for the development of infections or complications comparable to those of COVID-19 (coronavirus disease 2019) has been established [1,2]; however, the possibility of some of them being proposed as a prevention strategy for SARS-CoV-2 is emerging [3–6].

A large number of recommendations have been proposed worldwide, particularly in the field of pharmacotherapy. These concern both therapeutic strategies to combat COVID-19 and proposals for adapting patients' current prescriptions in diverse medical specialties (emergency medicine, infectiology, cardiology, oncology, etc.).

In psychiatry, the first recommendations addressing medications were very general, simply proposing to weight the risks associated with psychotropic drugs [7]. Since then, more targeted recommendations have been proposed for certain drugs such as clozapine [8] and long-action antipsychotics [9]. The first more assertive recommendations on psychotropic treatments were formalized: (i) in France by the AFPBN (*Association française de psychiatrie biologique et de neuropsychopharmacologie*) – in their consensus-based guidelines [1]; (ii) in England by the University of Oxford with broad recommendations for mental health and more targeted ones for several classes of psychotropic drugs – evidence-based guidelines [10,11]. These different guidelines address: (i) the potential difficulty to adapt to a very dynamic, ever changing scenario [1,10–13]; (ii) the complexity for having to fully articulate these recommendations with somatic concerns and their treatments [1]. At the very least, the consensus idea that certain common treatments which do not require excessive monitoring, such as Selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics or sodium valproate could continue to be administered normally, while other treatments such as lithium, clozapine and benzodiazepines, because of their specific risks, require the elaboration of adapted recommendations [1,10,11,14]. More recently, a structured literature review (WHO RAGs – World Health Organization and Rapid Advice Guidelines), which notably followed the AGREE and AMSTAR-2 methodologies (Appraisal of Guidelines for REsearch & Evaluation and A Measurement Tool to Assess Systematic Reviews, in order to assess the methodological rigour of guidelines and reviews) has been proposed to assess the safety of psychotropics in people with COVID-19 [2].

In parallel with these recommendations, which essentially address the clinical safety of psychotropics, information on the potential prophylactic or curative nature of some of these molecules has rapidly spread. Thus, in April 2020, the anti-SARS-CoV-2 potential of haloperidol [15] and chlorpromazine [5] was discussed in the literature. These data have since been supplemented by expanded lists of psychotropic drugs potentially relevant for SARS-CoV-2 prophylaxis based on the low initial prevalence of COVID-19 in mental health settings [3,6,16].

Herein, we provide a review of the literature regarding, first, the available prescription guidelines of psychotropics during the COVID-19 pandemic and, secondly, the antiviral potential of those substances against SARS-CoV-2. Addressing those topics may prompt us to intensify our efforts to understand the protective action of certain drugs against SARS-CoV-2, in order to re-evaluate and improve the prescription recommendations for these molecules. We hope this review sheds light on those elements, which are indeed essential for an informed decision based on the benefits and risks of each psychotropic drug amid the COVID-19 pandemic.

The literature search method was: (i) for COVID-19/SARS-CoV-2 related data we searched the following terms in the Pubmed: antidepress* [Title/Abstract] OR antipsych*[Title/Abstract] OR benzodiazepin*[Title/Abstract] OR mood stabiliz* [Title/Abstract] OR pharmacother*[Title/Abstract] OR psychopharm* [Title/Abstract] OR psychiatry*[Title/Abstract] OR psychotropic* [Title/Abstract] AND COVID*[Title/Abstract] OR SARS-CoV-2*[Title/Abstract]; (ii) other data were structured through a consensus-based review (e.g. iatrogenic risks associated with psychotropic drugs).

We excluded articles that were not in English or French with only two exceptions: we included one article in Portuguese and another in German about recommendations for prescription of psychotropics during the COVID pandemic. The literature search (systematic and consensus) was updated for the last time on 1 December 2020. The relevance of the references was then independently assessed by 4 authors (HJ, CS, GM and CH), then discussed in order to obtain a consensus on the most relevant works to be kept in the context of this review.

Table 1
General adaptations of prescriptions of psychotropic drugs in patients with co-occurring COVID-19 (adapted from Javelot et al., 2020 [1]).

General recommendations	Follow the standard posology (doses and rhythms of administration) Follow the recommended prescription duration (especially with benzodiazepines for elderly patients and with antipsychotics for dementia) Adapt the dosage according to country recommended guideline in case of hepatic and renal insufficiency Check for all drug interactions, especially those that may lead to an increase in: prescribed drug plasma concentration; torsadogenic risk (which may be related to the previous risk); respiratory distress risk; anticholinergic load
Targeted recommendations	Overall, therapeutic adaptations must be prudent and weighed in terms of the benefit/risk ratio: risk of psychic and/or somatic destabilization (drug withdrawal syndrome in a highly anxiety inducing pandemic period); always privilege maintaining the necessary and sufficient treatments for psychological wellbeing, without modifications not based on evidence; due to the particular risks regarding clozapine (see [127]) it is recommended to follow the recommendations established by Siskind et al. [8]

2. Prescribing psychotropic drugs during the COVID-19 pandemic

2.1. Potential risks of complications due to COVID-19

Please see Tables 1 and 2 for the general adaptations of prescriptions of psychotropic drugs in patients with co-occurring COVID-19 and a synthetic view on psychotropic treatment adaptation in case of COVID-19 organized by drug class (adapted from Javelot et al. [1]).

2.1.1. Central nervous system depression

2.1.1.1. Sedation and confusion. Fatigue and confusion can be found in 23% and 9%, respectively, of COVID-19 patients [1]. While their frequency and intensity don't represent cause for alarm, when associated with sedative psychotropic drugs, there might be a cause for concern in mental health patients. Because of the risk of potentializing sedation, the impact of the following treatments is relevant, especially when using high doses and/or combinations of these medications: opiates (analgesics, antitussives and substitution treatments), antipsychotics – 1st and 2nd generation –, mood stabilizers and/or antiepileptics (e.g. lithium, valproate, carbamazepine, gabapentinoids), barbiturates, benzodiazepines and z-drugs, non-benzodiazepine anxiolytics

Table 2
Psychotropic treatment adaptation in case of COVID-19 – organized by drug class (adapted from Javelot et al. [1]).

Medications		
Benzodiazepines	Risks: sedation, confusion; respiratory distress: in the situations when BZD are contraindicated; in the event of exceeding the maximum doses and particularly of polydrug addiction with morphine; if combined with other high risk treatments	Adaptations: see Table 1; if first time prescription, prefer BZD with short half-life (especially in the elderly patient); there is no indication to switch, as it can compromise the patient's mental wellbeing
Antidepressants	Risks: sedation, confusion; cardiac (QTc prolongation; see CredibleMeds)	Adaptations: see Table 1; if first time prescription prefer antidepressants that are not (or less) sedating and without risk of QTc prolongation; there is no indication to switch, as it can compromise the patient's mental wellbeing
Mood stabilizers: carbamazepine, valproate and lamotrigine	Risks: sedation, confusion; possible increased risk of pneumonia in combination with carbamazepine or valproate + antipsychotics [45]	Adaptations: see Table 1
Lithium	Reassess all treatments that may increase lithemia If fever: perform a lithemia	Adapt dosage according to lithemia and/or signs of lithium overdose (nausea, tremor, thirst and balance disorders) There is no indication to switch, as it can compromise the patient's mental wellbeing
Antipsychotics	Risks: sedation, confusion; cardiac (QTc prolongation; see CredibleMeds); atropine side effects [68,69]; dyspnea, respiratory distress; account for the increased risk of pneumonia with antipsychotics, particularly in elderly and patients with dementia	Adaptations: see Table 1; follow the standard recommendation of avoiding clozapine as first line-treatment, preferring atypical antipsychotics; there is no indication to switch, as it can compromise the patient's mental wellbeing
Clozapine	Risks: elevated risk of infectious pneumonia; pay special attention to: fever, flu-like symptoms and signs of overdose	Suggested 50% reduction in clozapine dose only if fever, flu-like symptoms and signs of clozapine overdose [8] = this adjustment should ideally take into consideration previous patient experience with dosage reduction
Methylphenidate	Risks: rhinopharyngitis, cough, sore throat, dyspnea; digestive symptoms	Adaptations: see Table 1; if symptoms/discomfort present; re-evaluate dosage, ideally in light of previous patient experience of adjustment
Psychoactives substances		
Tobacco (and cannabis)	Risks: abrupt cessation of tobacco (and cannabis) in the face of respiratory symptoms (cough, dyspnea) (or any other health disturbances inducing this effect)	Adaptations: plan progressive dosage reductions for olanzapine and clozapine (ideally monitoring plasma levels); in case of fever, flu-like symptoms and signs of olanzapine or clozapine overdose, a more rapid dosage reduction is possible = these adjustments should ideally be done taking into account the patient previous experience with dosage reduction (and any plasma dosages performed)

(e.g. meprobamate), sedative antidepressants (agomelatine, tricyclics – especially those with strong antihistamine effects: doxepin and trimipramine –, mianserin and mirtazapine, trazodone, esketamine), sedative H_1 antihistamines, centrally acting antiemetics (e.g. metoclopramide, metopimazine), antimigraine medications, central antihypertensives and other drugs such as baclofene, thalidomide and lenalidomide, sodium oxybate, ropinirole, tetrabenazine [4].

Confusion may be precipitated or accentuated by the sedative treatments mentioned above and the use of benzodiazepines and all treatments known to have anticholinergic effects should be carefully monitored. These effects should mostly be accounted for in elderly patients due to their greater sensitivity to these treatments and their adverse effects, which may be accentuated in cases of SARS-CoV-2 infection. For benzodiazepines, the risks of sedation, confusion and falls (excessive sedation/myorelaxation) must be weighted. For anticholinergic effects, there is an increased risk of confusion, but also peripheral side effects such as dry mouth and eyes, constipation, urinary retention. When addressing these effects, the use of anticholinergic impregnation scales is wise [9,10].

2.1.1.2. Respiratory symptoms. Symptoms such as dyspnea and cough are significant in patients affected by COVID-19 (59–82% and 31–55%, respectively) [4]. These elements, associated with other, less frequent symptoms (sore throat, chest pain), also related to the respiratory sphere, lead to a reassessment of the relevance of psychotropic drugs, as well as other treatments, which may contribute to respiratory distress. The latter is indeed aggravated by drugs with sedative properties in conjunction with the combined effects of respiratory muscle weakness and a decrease in spontaneous respiratory effort. This well-known double impact caused by benzodiazepines (sedation and myorelaxation) can be problematic when combined with other treatments with central nervous system depressant effects (see above). Ostuzzi et al. [2] also warn against highly sedating antipsychotics (typically first generation antipsychotics, e.g. phenothiazines and their derivatives), in addition to benzodiazepines, with associated risk factors such as high doses, polypharmacy and pre-existing respiratory disturbances.

In addition to the respiratory depression risk that has been established, the use of treatments that may contribute to the following should be monitored: (i) dyspnea; this adverse effect is reported in particular with all antipsychotics, but also with other substances used in the mental health setting, such as pramipexole, prazosin, beta-blockers such as propranolol and non-steroidal anti-inflammatory drugs (NSAIDs) [4]; (ii) nasal obstruction/congestion; such as with amitriptyline, phenothiazines and alprazolam, or rhinopharyngite-like infections with methylphenidate [4,11].

The risk of respiratory depression is well known for all opiates; in particular: alfentanil, buprenorphine, codeine, dextromethorphan, dihydrocodeine, ethyl morphine (codethyline), fentanyl, hydromorphone, methadone, morphine, nalbuphine, nalmefen, naloxone, naltrexone, noscapine, oxycodone, pethidine, pholcodine, remifentanil, sufentanil, tapentadol, tramadol. These include treatments that may be prescribed in COVID-19: (i) for pain management in the most severe cases; (ii) as antitussive treatment (codeine, ethylmorphine (codethyline), dextromethorphan, noscapine, pholcodine are used as antitussive agents). Furthermore, these same treatments might be overused prior to COVID-19 by patients with addiction. All of these opium derivatives increase the risk of respiratory depression when associated with certain psychotropic drugs, in particular: benzodiazepines, barbiturates and

sodium oxybate (used for narcolepsy, anesthesia and alcohol addiction).

These precautions appear to be particularly important for patients suffering from multiple drug addiction and likely to associate the substances, which poses more risk; benzodiazepines and morphine in particular and substitution treatments (buprenorphine and methadone). This problem can be of particular importance in North America and other countries affected by the opioid epidemic crisis [17,18]. It is also worth highlighting that benzodiazepines and depot antipsychotics should be prescribed with caution for elderly patients at higher risk of respiratory depression [19].

The impact of sedation may also be mitigated when drugs are used as monotherapy and at standard dosages. For example, mirtazapine appears to be a potentially promising treatment for chronic breathlessness, while the use of benzodiazepines may be a good option to relieve the anxiety associated with dyspnea [12,20,21].

Data recently proposed by Ostuzzi et al. [2] is reassuring about the use of antidepressants in people affected by COVID-19; they performed a study with a high AMSTAR-2 score and described the safety of these treatments in patients with chronic obstructive pulmonary disease (COPD) [22,23]. However, more recent data regarding respiratory tolerance of antidepressants in COPD contradicted the latter results [2].

Finally, it is worth noting the extra caution needed for psychotropic drugs with inhalant dosage forms. Inhaled loxapine is contraindicated: (i) for patients with acute respiratory signs or symptoms, including dyspnea, and thus by extension any suspected or proven situation of COVID-19; (ii) for patients with active airway diseases, such as patients with asthma or chronic obstructive pulmonary disease, thus this precaution may also extend to COVID-19.

About esketamine, in the presence of clinically significant or unstable respiratory disease, such as suspected or confirmed COVID-19, this treatment should be administered in an environment with appropriate equipment and personnel for cardiopulmonary resuscitation; careful weighing of the benefits and risks is therefore also essential in this context. The risk of sedation may be increased by the concomitant use of nasal esketamine and other central nervous system depressants. Such combined prescriptions require close monitoring of sedation and respiratory depression and are highly risky in a suspected or confirmed situation of COVID-19.

2.1.2. Headaches, sweating and hyperthermia

Headaches are particularly common side effects of medications in general and of psychotropic drugs in particular. They occur often to very frequently with most psychotropic drugs classes: antidepressants, antipsychotics, mood stabilizers, benzodiazepines and methylphenidate. These effects can be interpreted as potentially complicating viral symptomatology and as a possible source of confounding factors (see below).

Hyperthermia and hyperhidrosis as psychotropic drugs side effects are intuitively associated with serotonergic syndromes, discontinuation syndromes under antidepressants and antipsychotics, and neuroleptic malignant syndrome; which we will discuss later. Nevertheless, regardless of these syndromes, antipsychotics can induce a wide variety of symptoms ranging from benign hyperthermia under clozapine, to hypothermia, while hyperhidrosis is observed with antidepressants (paroxetine, escitalopram, venlafaxine and duloxetine, in particular) and antipsychotics (clozapine, aripiprazole). Finally, hyperthermia related to anticholinergic effects is also well known and is associated with perspiration blockade [4,10]. The deleterious aspect of these effects to a COVID-19 setting must be anticipated, particularly in the elderly population, in which these effects are more dangerous [4,10].

2.1.3. Treatments with risk of QTc prolongation

Overall, the American reference site CredibleMeds (https://crediblemeds.org; [24] – from the Arizona Center for Education and Research on Therapeutics [AZCERT]) is a great consultation resource to obtain an exhaustive list of substances which may cause QTc prolongation; this ranking should nevertheless be considered within each country-specific recommendations in this field [1]. Crediblemeds offers a classification in 4 categories: drugs with known risk of torsade de pointe (TdP), possible risk of TdP, conditional risk of TdP and drugs to be avoided by patients with congenital long QT.

The problem of QTc prolongation in the context of COVID-19 for mental health patients is multi-level. There is an established interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system which can cause sometimes severe hypokalemia and is an important risk factor for the occurrence of TdP [1,25–27]. This is even more relevant because many psychotropic drugs, as well as drugs proposed for the treatment of COVID-19, have been shown to increase the QT interval [1,28]. Thus, patients suffering from mental health disorders, infected with CoV-2-SARS and treated with, for example, hydroxychloroquine or chloroquine and/or azithromycin – and particularly if these treatments are combined – should be carefully evaluated for the benefit/risk ratio of these medications, particularly regarding the risk of their psychotropic treatments to cause QTc prolongation [1,28–30]. Monitoring the QTc, but also of potassium levels is essential in these high risk situations. Indeed, multiple risk factors are presented in the literature for QTc prolongation: female sex, age over 65 years, personal or family cardiovascular history, liver and/or kidney failure, electrolyte disorders, and a recent study has particularly highlighted the specific risks of hypokalemia, antiarrhythmic drugs and drugs with a known risk of torsade de pointe in the CredibleMeds classification [1,27]. These elements thus imply a constant re-evaluation of the benefit/risk ratio of those treatments. Vomiting and diarrhea potentially induced by COVID-19 are also sources of digestive potassium loss that can induce hypokalemia, which should also be monitored and treated.

In addition to these situations, there are also potentially risky associations with treatments that may alleviate the symptoms of COVID-19, particularly digestive symptoms, and which may be dangerous, particularly for patients suffering from mental health disorders [1]. For example, the use of drugs such as metoclopramide and metopimazine can generate extrapyramidal syndrome and increase the risk of its occurrence when combined with neuroleptics [1]. Metoclopramide may also induce neuroleptic malignant syndrome or serotonin syndrome [1]. Moreover, domperidone and metoclopramide pose risks for QTc prolongation and are classified with "known risk" and "conditional risk" respectively, in the Crediblemeds classification (https://crediblemeds.org). Recent pharmacovigilance data seem to validate the safety of metopimazine for QTc [31]. For the respiratory system, the danger may come from short-acting inhaled β_2-mimetics, such as salbutamol (or albuterol), in the case of dyspnea, which are quickly identified by patients as some soothing treatments and may induce drug overuse [32]. Hypokalemia is also a well-known risk with β_2-agonist treatments, particularly at high doses, in combination with other hypokalemic drugs and/or in hypokalemia-inducing situations [32]. These elements therefore call for caution with the use of these anti-asthmatic treatments which, when combined with risky psychotropic drugs and with the hypokalemia induced by COVID-19, could contribute to the occurrence of torsades de pointes.

The recommendations provided so far in the literature on anti-psychotics are generally consensual regarding the risk on QT

[2,14,33,34]. Regarding antidepressants, a recent update on QTc prolongation risks unsurprisingly identified citalopram and, by extrapolation, escitalopram as the drug which carries the biggest risk of QTc prolongation [35]. For this reason, the initial orientation (acute phase) towards citalopram and escitalopram in a SARS-CoV-2 pandemic situation, for reasons of tolerance and minimal interactions with CYP450, may appear questionable especially in the at-risk populations mentioned above [36]. Overall, it is recommended that patients taking medications which increase risk for QTc prolongation and have COVID-19 should have regular potassium measurements and ECG monitoring. Re-evaluation of combined treatments which increase risk of QTc prolongation (associations between psychotropic drugs at risk or psychotropic drugs at risk + antiarrhythmic drugs) should be done in all cases.

Beyond QTc, antipsychotics usage has been associated with serious cardiovascular events like stroke, sudden cardiac death and myocardial infarction and this risk could be higher in the elderly [2,37], whereas antidepressants appears safe in patients with ischemic heart disease and depression in a meta-analysis mainly concerning SSRIs [2,22].

2.1.4. Risks of infectious complications

The links between infectious complications and the use of psychotropic drugs are complex. There are contradictory theories regarding antipsychotic use and its effect on immunity [38], without calling into question the relevance of the global approach to immunopsychiatry, particularly in psychotic disorders [39]. If, for example, schizophrenic patients appear to be more susceptible to infections, the involvement of antipsychotics in this phenomenon is not clearly defined [40]. Nevertheless, recent data have made it possible to affirm that in patients aged 65 or over, hospitalized for pneumonia, an association was found between the use of second-generation antipsychotics and increased mortality, particularly in those suffering from previous mental or cardiac disorders [41].

Rajamaki et al. [42] recently showed that the use of antipsychotics, benzodiazepines and z-substances is associated with an increased risk of pneumonia in the elderly, while there was insufficient data for antidepressants and antiepileptics. Regarding antipsychotics, Dzahini et al. [43] observed that those with sufficient data in the literature are all associated with an increased risk of pneumonia: haloperidol, olanzapine, clozapine, risperidone, quetiapine and zotepine. The authors urge caution in patients initiating antipsychotic therapy and particularly in those with other risk factors for pneumonia (older age, chronic respiratory disease, smoking, dysphagia and cerebrovascular disease) [43]. Pneumonia is also reported to occur more frequently and with more fatal consequences with clozapine than with other second-generation antipsychotics [44]. In addition, data from Yang et al. [45] had revealed that certain mood stabilizing combinations may be at greater risk of inducing pneumonia – olanzapine + carbamazepine and clozapine + valproic acid – contributing to an overall caution about the dangers of polypharmacy in general and with psychotropic drugs [42].

While the mechanism behind antipsychotic-induced pneumonia remains poorly understood, different neurotransmitters seem to be involved: dopaminergic, serotonergic, cholinergic, histaminergic, but also actions linked to the receptors of the thromboxane A2 (TBXA2R) and the platelet activating factor (PTAFR) [46]. Among all these transmitters, anticholinergic effects are well-known to increase the risk of aspiration pneumonia by contributing to a succession of deleterious effects including dry mouth, swallowing disorders and decreased cough reflex [47]. The contribution of these effects in pneumonia in elderly subjects may be particularly important [48,49].

Although the specific risk of aggravation of COVID-19 pneumonia by antipsychotic drugs has not been established, overall, the above data suggest caution. Elements of specific vigilance include: (i) the introduction and use of clozapine (see recommendations below); (ii) the use of antipsychotic drugs in the elderly, with specific consideration of: their risk of complications and death related to COVID-19, sensitivity to polypharmacy and to anticholinergic effects in particular, the need to re-evaluate these treatments and to adopt, whenever possible, the shortest possible treatment duration.

Finally, it should be noted that the risk of infectious complications is increased during neutropenia/agranulocytosis and that certain psychotropic drugs are at high risk of causing this effect. Among the antipsychotic drugs, clozapine is the most known to cause this adverse effect, but phenothiazines and to a lesser extent olanzapine and quetiapine also can cause, yet very rarely, this adverse effect and the other antipsychotic drugs are not without danger [50]. Regarding mood stabilizers, although less risky than clozapine, carbamazepine, oxcarbazepine and to a lesser extent valproate and its derivatives can also lead to neutropenia/agranulocytosis [2,50,51].

To sum up, the amount of influence of psychotropic drugs in the risk of infection remains uncertain, except for the objective situations of neutropenia/agranulocytosis. The systematic review data in this field appear particularly weak (see [2]: the only review selected by the working group on the side of infectiology is that of [43] with an AMSTAR-2 score classified as "critically low").

2.1.5. Risks of thromboembolic events

The link between infections and thromboembolic events is well known [52,53], while the specific link between COVID-19 and such complications is now widely established [54–56]. Data from China, the Netherlands and Italy early described the significant risks of global thromboembolic events (venous and arterial), venous thromboembolism and pulmonary embolism during COVID-19 [54].

The risk factors of venous thromboembolism are known and include: age, acute infection, cancer, previous venous thromboembolism, prolonged immobility, recent major surgery, obesity, and chronic heart or respiratory failure [57]. The presence of two risk factors can be considered as a clinical situation close to that of hospitalized patients, for whom thromboprophylaxis is recommended.

COVID-19, thus, induces many high-risk situations for patients with acute infection and for whom the risk of immobilization is increased: by the disease itself, particularly in the case of active viral pneumopathy, but also by recommendations for confinement and/or social distancing (reduction in the number of discharges, visits). The first risk linked to psychotropic drugs is the contribution to immobility through excessive sedation. This effect can appear mainly at the initiation of a new treatment and with a drug recognized for having sedative effects (see previous chapter: Risk of depression of central activity – Sedation and confusion).

Many factors must be considered in order to explain the increased risk of venous thromboembolism under antipsychotic drugs. Sedation and weight gain appear to be the most reliable and constant ones by increasing immobility and venous stasis in the lower extremities [58]. Nevertheless, hyperprolactinemia, antiphospholipid antibodies, acute phase of a psychotic illness with physical restraint or situations with catatonic syndromes, high-sensitive C-reactive protein (CRP) and other inflammatory markers or hyperhomocysteinemia represent other factors likely to increase the risk of venous thromboembolism [58]. In a large retrospective study, a statistically significant increase in risk of pulmonary embolism was observed in antipsychotics users compared with non-users, while clozapine users had the highest risk, a smaller risk was also noted for users of chlorpromazine, haloperidol, olanzapine, risperidone and ziprasidone and the risk is dose dependent [59].

Antidepressants, as well as depression itself, have been cited as risk factors for venous thromboembolism, but conflicting data exists in the literature [60,61]. Despite the lack of data available concerning this risk with other psychotropic drugs, the contribution to an overall sedation increase, for example with benzodiazepines and mood stabilizers cannot be excluded [62], especially in the context of polypharmacy by psychotropics in elderly people.

The baseline risk of venous and pulmonary thromboembolism is known in COVID-19 and this risk increases in association with mainly antipsychotic drugs.

These elements encourage caution, in a similar manner to what has been suggested for the risk of infection: (i) to know and anticipate the potentially negative vascular consequences of antipsychotics, particularly clozapine (see recommendations below); (ii) to take into account the overall sedative impact of psychotropic drugs, especially in case of sedative polypharmacy and this particularly in situations when other risk factors are present, including, as a priority, age.

2.2. Psychotropic drugs and the risk of diagnostic confusion with COVID-19

Please see Table 3 for information about psychotropic drugs' effects on symptoms of COVID-19 (adapted from Javelot et al. [1]).

2.2.1. Drug withdrawal and abstinence syndrome

The SARS-CoV-2 pandemic is proving to be particularly anxiety-inducing for the general population and thus potentially a trigger of decompensation for patients suffering from mental health disorders. For one side, in the absence of a clear link between the dangerousness of psychotropic drugs and the evolution of COVID-19, the maintenance of the standard therapies for the mental wellbeing of patients must be a priority [2,4]. On the other hand, changes in current treatments that are not justified by the clinical evolution of the patient may expose patients to the following risks: (i) to decompensations of their mental health balance, potentially with all psychotropic drugs; and/or (ii) to withdrawal syndromes with benzodiazepines [20], antidepressants [63], antipsychotics [64] or methylphenidate [65].

It is important to note that the antidepressant discontinuation/withdrawal syndrome, mainly related to SSRIs and to a lesser extent to serotonin-norepinephrine reuptake inhibitors, may represent a major risk factor for differential diagnosis with COVID-19 and may include: influenza-like illness, headache, fatigue, dyspnea, myalgia, nausea, vomiting, diarrhea and confusion [66,67]. Benzodiazepine withdrawal syndrome may also induce some of these symptoms. This information provides a good basis for assessing the risk-benefit ratio before considering treatment discontinuation or drug switches [4].

2.2.2. Other iatrogenic syndromes causing diagnostic confusion

Among the iatrogenic situations that can cause diagnostic confusion with COVID-19, two should be highlighted: serotonin syndrome and neuroleptic malignant syndrome. The two syndromes have common symptoms, which can be seen in SARS-CoV-2 infection such as: sweat, hyperthermia, tachycardia, tachypnea, myalgia and confusion [1]. In serotonin syndrome, digestive symptoms – nausea and diarrhea – can also resemble COVID-19 symptoms.

A long-term exposure to an excess of drugs with anticholinergic effects, which can also be qualified as a strong anticholinergic load, can contribute to confusion and increased body temperature. This situation should be acknowledged in elderly subjects in particular who are more sensitive to these effects. One of the relevant strategies is to re-evaluate current treatments using anticholinergic rating scales (for reviews see: [68,69]).

Other iatrogenic scenarios which can lead to potential clinical confusion with COVID-19 are: the sympathomimetic toxidrome, often related to substances as cocaine, amphetamine and derivatives, but also albuterol [70], and some hypersensitivity reactions as the drug reaction with eosinophilia and systemic symptoms (DRESS), notably observed with anticonvulsants and previously named "anticonvulsant hypersensitivity syndrome".

Moreover, three situations may induce headaches usually linked to some psychotropic drugs: those occurring with lithium, associated with visual disturbances and that can be linked to a papilledema, those occurring with methylphenidate, which may suggest cerebrovascular disorders with cerebral vasculitis and those occurring with monoamine oxidase inhibitors, since it is known that occipital headaches can be associated with hypertensive crisis.

We will not discuss here the neuropsychiatric effects induced by treatments for COVID-19. We discuss it below with a specific focus on psychopathology. Note that the review of the literature by Bilbul et al. [33] exhaustively describes the issue of psychiatric adverse effects induced by COVID-19 treatments.

2.3. Index by mental health disorders

The stressful environment generated by the COVID-19 pandemic is likely to affect the psychological wellbeing of patients, in particular through a decrease in response to psychotropic treatments [71]. While anti-SARS-CoV-2 antibodies have been identified in the cerebrospinal fluid, the neurotropism of SARS-CoV-2 has also been established, with potentially significant impacts on the dopaminergic and serotonergic systems, leading to the aggravation, or even emergence, of psychotic manifestations or mood disorders [72–74]. Other acute neuropsychiatric symptoms have already been observed in patients infected with CoV-2-SARS notably, post-traumatic stress disorder, catatonia, suicidal ideation, seizures, cerebrovascular complications, encephalopathy, encephalitis, neuromuscular disorders, anosmia, ageusia, headache, sleep disorders and disabling fatigue [75,76] or cognitive difficulties, after discharge, in the context of « long covid » (or chronic covid syndrome or CCS) [73]. In this regard, the contribution of anakinra, anti-IL-1 and tocilizumab, anti-IL-6, to decrease the action of proinflammatory cytokines, involved in the immunopathology of COVID-19 (cytokine storm involves release of IL-1β and IL-6), could be of interest in order to study the therapeutic effect of cytokine-blocking agents on the neuropsychiatric complications in survivors of severe form of COVID-19 [77].

2.3.1. Schizophrenia

2.3.1.1. Psychosis and COVID-19. The SARS-CoV-2 pandemic caused both decompensation of stabilized patients [78,79], as well as the emergence of psychotic episodes in individuals with no psychiatric history but presumably affected by the global fear context raised by the pandemic [80–83] and the context of the quarantine [84].

Beyond these data, the emergence of psychotic symptoms in patients affected by COVID-19 seems to be associated with age, with the appearance of acute delirium in patients already showing cognitive decline [85,86]. In a follow-up of neurological and neuropsychiatric symptoms of 153 patients, with an average age of 71 years, affected by COVID-19, 10 of 23 patients with neuropsychiatric disorders experienced new-onset psychosis. While other data from the literature estimate that 0.9 to 4% of infected individuals by the SARS-CoV-2 could develop psychotic spectrum disorders [87]. More recently, Watson et al. [88] reported 42 cases of psychosis in patients infected with SARS-CoV-2 and discussed the potential

Table 3
Psychotropic drugs' effects on symptoms of COVID-19 (adapted from Javelot et al. [1]).

Symptoms associated with COVID-19	Confounding side effects associated with psychotropic drugs	Differential diagnosis	Most common drugs involved (✝ refer to Table 2) (apart from fatigue/confusion: restricted list of main drugs with central effects)	Proposed patient care plan[a]
Fatigue, sedation Confusion	Sedation (due to central nervous system depression) Anticholinergic impregnation	Iatrogenic central nervous system depression Confusion due to iatrogeny	Antidepressants ✝ (Sedative antidepressants: agomelatine, amitriptyline, amoxapine, clomipramine, dosulepin, doxepin, esketamine, imipramine, maprotiline, mianserin, mirtazapine, trazodone, trimipramine) Antipsychotics ✝ Benzodiazepines ✝ Mood stabilizers Morphine and analogs (analgesics, antitussives, addictive drugs) Medications with anticholinergic effects ✝ Sedative Antihistamines H_1 Barbiturics To be taken into consideration when assessing the general state: Sedative drugs; medications which can cause orthostatic hypotension; blood pressure lowering drugs	– re-evaluate the benefit/risk ratio of the implicated drugs (posology: dose and dose frequency) + frequent assessments in order to reevaluate implicated treatments
Dyspnea Chest pains Pneumonia	Dyspnea Bronchoconstriction Risk of pneumonia Aspiration pneumonia Dysphagia Anticholinergic effects and anticholinergic load Other phenomena caused by iatrogeny	Iatrogenic central nervous system depression Anxiety, panic attacks and/or psychogenic dyspnea Iatrogenic bronchoconstriction	Antidepressants ✝ (sedative antidepressants: agomelatine, amitriptyline, amoxapine, clomipramine, dosulepin, doxepin, esketamine, imipramine, maprotiline, mianserin, mirtazapine, trazodone, trimipramine) Medications with anticholinergic effects ✝ Antipsychotics ✝ Benzodiazepines ✝ Carbamazepine or valproate + antipsychotics (pneumonia) [45] Methylphenidate ✝ Morphine and analogs (analgesics, antitussives, addictive drugs) Sedative Antihistamines H_1 Central Antihypertensives (clonidine, methyldopa, moxonidine, rilmenidine) Others: NSAIDs, baclofene, beta blockers, barbituriques, pramipexole, prazosin, thalidomide	– re-evaluate the benefit/risk ratio of the implicated drugs (posology: dose and dose frequency) + frequent assessments in order to reevaluate implicated treatments – perform supplementary exams to distinguish between infectious and iatrogenic factors – management of anxiety accompanying dyspnea (primarily through behavioral techniques)
Fever/hyperthermia Myalgia	Serotonin syndrome (SS) Malignant Neuroleptic syndrome (NMS) Sympathomimetic syndrome Withdrawal syndrome Hypersensibility reaction (drug reaction with eosinophilia and systemic symptoms; DRESS) Agranulocytosis Anticholinergic effects and anticholinergic load	Transpiration, hyperthermia, tachycardia, tachypnea, myalgia and confusion	Medications with anticholinergic effects ✝ Clozapine (benign hyperthermia initially) ✝ Antipsychotics ✝ (NMS) Antidepressants ✝ (SS) Mood Stabilizers and barbiturics (DRESS)	– re-evaluate the benefit/risk ratio of the implicated drugs (posology: dose and dose frequency) + frequent assessments in order to reevaluate implicated treatments – paracetamol is 1st line treatment – ensure sufficient hydration – corticotherapy: risk of unbalancing psychiatric disorder; potentially counterproductive in infection

Table 3 (*Continued*)

Symptoms associated with COVID-19	Confounding side effects associated with psychotropic drugs	Differential diagnosis	Most common drugs involved († refer to Table 2) (apart from fatigue/confusion: restricted list of main drugs with central effects)	Proposed patient care plan[a]
Cough Sore throat Rhinorrhea (Rh)	Anticholinergic effects and anticholinergic load Oropharyngeal dyskinesia	Cough, dryness of the mucous membranes, iatrogenic dysphagia	Medications with anticholinergic effects † Antipsychotics † Methylphenidate (Rh)	– re-evaluate the benefit/risk ratio of the implicated drugs (posology: dose and dose frequency) + frequent assessments in order to reevaluate implicated treatments – prefer non opiate antitussives – prevent deglutition disorders (especially in the elderly) – rhinorrhea; contraindicates use of: all sympathomimetic drugs including methylphenidate; indirect sympathomimetics such as non-selective MAOIs and MAOI B = due to the risk of hypertensive crisis
Diarrhea Nausea/vomits	Gastro-intestinal symptoms secondary to initiation of antidepressant or methylphenidate Withdrawal syndrome Lithium overdose Pancreatitis due to valproate	In the case of lithium overdose: look for characteristic symptoms (tremors, thirst and balance problems)	Antidepressants † Benzodiazepines † Antipsychotics † Lithium † Methylphenidate	– Re-evaluate the benefit/risk ratio of the implicated drugs (posology: dose and dose frequency) + Frequent assessments in order to reevaluate implicated treatment – Ensure sufficient hydration – NSAIDs should be avoided due to renal toxicity that can aggravate dehydration. – Lithium: Lithemia to be performed as soon as possible (possibility of adjusting the dosage in advance) – Valproate and derivatives: perform pancreatic and liver assessment – Methylphenidate: see if side effects improve through food intake – Management of nausea: metopimazine; domperidone if there are no cardiovascular contraindications (QTc prolongation in particular) – Diarrhea management: racecadotril, loperamide, diosmectite

[a] During symptoms management, it is recommended to: take a complete anamnesis, including all of the recent modifications made to psychotropic treatments (introduction, stop, switch, increase, decrease), in order to evaluate the possible iatrogenic involvement, – consider requesting emergency services if the situation requires it.

neurodevelopmental implications of in utero infection and subsequent psychiatric risks.

Multiple causes can be identified for the onset of an acute psychotic episode, but it is clear that their emergence associated with an SARS-CoV-2 infection prompts both: (i) to conceive the immunological and neuroinflammatory pathway as a likely cause of these disorders, by following central and peripheral markers of inflammation; (ii) to consider that beyond antipsychotics, infection-fighting treatments, and in particular immunomodulators, may be effective in combating the psychotic episodes observed [89]. Such results could be observed with tocilizumab, which leads to IL-6 inhibition and could improve cognition in schizophrenia [90,91].

Aware of the potential vulnerability of schizophrenic patients in the pandemic, the risk of interrupting medication should be anticipated and the role of professionals and families is crucial for adherence to antipsychotic treatment and sometimes to ensure access to prescriptions and to the drugs delivery [92,93].

Regardless of its origin, the emergence of an acute psychotic episode in cases of SARS CoV-2 infection provides an incentive to build on the information available in the literature on managing agitation in individuals affected by COVID-19 [94–98]. As a preamble, it should be recalled that the risk of delirium, regardless of infectious causes, may be occasionally increased by benzodiazepines, antipsychotics and tricyclic antidepressants, with the latter two classes also having potentially anticholinergic effects, particularly in the elderly [1,95,99].

In a more structured approach, quetiapine and dexmedetomidine compared with placebo in intensive care units and aripiprazole, quetiapine and risperidone in patients with acute psychosis or dementia, showed some potential benefits for agitation [95]. Haloperidol and other conventional neuroleptics appear to be less relevant because of their adverse effects, including impact on QT and the risk of extrapyramidal symptoms [95,98], while olanzapine and benzodiazepines may appear to be at greater risk of sedation and/or contribute more to respiratory depression [96,98]. A recent network meta-analysis, however, showed that the best strategies for delirium treatment and prevention were haloperidol plus lorazepam and ramelteon, olanzapine, risperidone, and dexmedetomidine, respectively, in placebo/control comparative data [100]. Interestingly, Baller et al. [94], highlight the use of alpha-2 agonist, dexmedetomidine and clonidine, before resorting to antipsychotics, for delirium with cases with COVID-19. These strategies could prove particularly interesting from the perspective of acute delirium situations associated with the COVID-19 cytokine storm, since catecholamines, including norepinephrine (NE), play

a role in this potentially lethal evolution and the alpha-2 agonists such as clonidine, guanfacine, dexmedetomidine, with other NE modulators (e.g. propranolol, prazosin), could be useful therapeutic choices [101].

Recommendations on the use of psychotropic drugs in acute agitation in patients with COVID-19 may also change. Various elements encourage us to anticipate the deleterious impact that SARS-CoV-2 can have on the dopaminergic system and to reflect on the consequences of a subsequent blockage through the use of an antipsychotic. The SARS-CoV, related to the SARS-CoV-2, induces an angiotensin-converting enzyme (ACE) 2 receptors down-regulation which are significantly co-expressed with dopa decarboxylase (DDC) and could in turn induce a dopamine synthesis alteration [102]. Preliminary data also indicates that patients with Parkinson's are mostly requiring additional levodopa dosage following infection by the SARS-CoV-2 [103], while cases of catatonia syndromes have also been reported in COVID-19 delirium [94,104–106]. This information notably guided the cautious recommendations of neurologists in the face of delirium in a COVID-19 situation by encouraging the use of melatonin in first intention, then alpha-2 agonists, before considering a partial dopaminergic agonist antipsychotic as aripiprazole specifically for hypoactive delirium with perceptual disturbance [94]. The possible impact of the anticholinergic effects of some antipsychotics in the aggravation of the COVID-19 cytokine storm must also be evaluated. These elements may guide the choice of antipsychotic treatments in the elderly, for which COVID-19 occurs in a context of immunosenescence and may lead to the disruption of the cholinergic anti-inflammatory pathway [107].

2.3.1.2. COVID-19 treatments and psychotic episodes. Among the COVID-19 treatments likely to induce an acute psychotic episode, chloroquine and hydroxychloroquine have so far been the most reported treatments and indeed, there is a neuropsychiatric effect both severe and known with these substances [33,108–114]. Moreover, corticosteroids can induce cognitive impairment, psychosis and mood changes and the significant predictive factors are notably prednisone use more than 40 mg/day and a history of psychiatric disorders [1,33,90,115]. Delirium has also been rarely reported with azithromycin and colchicine [33,90]. Furthermore, as we mentioned previously, tocilizumab could appear as a cognitive protection agent in the event of a psychotic episode [90,91].

Psychotic symptoms in ten patients infected by the SARS-CoV-2 with no previous history of psychosis were characterized in all cases by delusions (50% described as highly structured), orientation/attention disturbances (60%), auditory and visual hallucinations (40% and 10%), but nine patients had been also previously treated with hydroxychloroquine and antibiotics (all), lopinavir/ritonavir ($n = 6$), tocilizumab ($n = 6$), corticosteroids ($n = 7$) [82]. Such data also show the complex imputability of COVID-19 related psychosis between the infection and iatrogenic origin. Finally, it should be noted that in May, the Spanish Pharmacology Agency reported the occurrence of neuropsychiatric disorders, including acute symptoms of psychosis, but also suicide attempts or suicides, in COVID-19 patients treated with hydroxychloroquine [116].

2.3.1.3. Management of treatment resistant schizophrenia in COVID-19. Among the new pharmacotherapeutic recommendations in the context of SARS-CoV-2 pandemic, those regarding clozapine were established very quickly [8]. These were guided by the known hematological adverse effects this medication may cause, the potential difficulty in maintaining the necessary monitoring during a pandemic, the recently objectified increased risk of pulmonary infections and finally by the risk of clozapine toxicity related to infection due to inhibition of cytochrome P450 1A2 by cytokines [8,44,117].

These recommendations of Siskind et al. [8] propose:

- that the frequency of CBC (Complete Blood Count during blood test) can be reduced to once every 3 months, with dispensation of treatment for up to 90 days (provided that the treatment can be safely stored) for persons meeting all of the following criteria:
  - receiving continuous clozapine treatment for more than one year,
  - never had a neutrophil count of < 2000/μL (or < 1500/μL if there is a history of benign ethnic neutropenia),
  - not having safe or convenient access to biological/blood tests;
- for patients on clozapine with symptoms of infection, an urgent medical evaluation is required, including the performance of a CBC;
- for patients on clozapine who become symptomatic (fever and flu-like symptoms); the emergence of symptoms of clozapine-related toxicity may prompt clinicians to reduce the dose of clozapine by half. It is then recommended that this reduced dose be maintained for up to 3 days after the fever has subsided, then gradually return to the previous dose.

It should be noted that the fever observed during clozapine therapy, particularly at initiation, although it may be a warning sign of neutropenia, is frequently benign and does not always require discontinuation of therapy [118].

Regarding dose adjustment, recent cases of elevated clozapine plasma levels in patients with COVID-19 and presenting granulocytopenia with catatonia and delirium, have been described [119]. Toxic increases in clozapine concentrations may also occur in smoking patients who reduce their tobacco consumption, especially in respiratory infections, and/or increase their caffeine consumption to combat asthenia [1,120]. Thus, regarding enzymatic impacts, one of the priority adaptations in the case of fever may be to limit the doses (and/or use) of CYP1A2 inhibitors: fluvoxamine, caffeine and ciprofloxacin [1].

In the event of a potentially abrupt decrease in dosage on clozapine, the possibility of withdrawal syndrome should be taken into consideration, the manifestations of which may be multiple: psychotic decompensation (hypersensitivity psychosis), cholinergic rebound (which may aggravate pre-existing viral symptoms, including: confusion, nausea, vomiting, diarrhea, headaches, hyperhidrosis), histaminergic rebound with anxiety and potentially motor symptoms such as dystonia, dyskinesia or catatonia [1,121]. Anticholinergics and olanzapine can be used in clozapine withdrawal syndrome [1,121]. Furthermore, the strategy of clozapine dosage reduction must also be adapted with the possible need to implement combinations of antipsychotic drugs in the face of treatment efficacy reduction. While such combinations may be considered, it should be remembered that the use of clozapine in combination with amisulpride, olanzapine, quetiapine, risperidone and zotepine is also associated with an increased risk of pneumonia [122]. The excess risk of pneumonia with clozapine compared to other antipsychotic drugs is also well identified [8,44] and leads to a cautious anticipation of its use at the time of COVID-19, with constant re-evaluation in the light of the most recent data [123–128]. Gowing et al. [127] identified 6309 individuals using antipsychotics, with schizophrenia-spectrum disorders and 102 tested positive for COVID-19; patients who take clozapine exhibited an increased risk of COVID-19 infection compared with those who take other antipsychotic medication. Besides, the challenge of using ECT in a pandemic may also represent a barrier in access to care for patients with resistant schizophrenia (we discuss

the literature on this subject in the chapter on resistant depression; see below) [1].

2.3.1.4. Long-acting neuroleptics. The prescription of long-acting neuroleptics may be a difficult decision to make in a pandemic. For one side, these treatments contribute to an improvement in patient compliance and can therefore be assets for maintaining psychological stability. On the other hand, they require regular injections, exposing both patients (potentially among themselves, in waiting rooms) and caregivers to a risk of SARS-CoV-2 contamination. This latter aspect, combined with periods of confinement and the closure of some care sites, may have led to a consequent decrease in the use of long-acting neuroleptics in some locations. For example, a Romanian university psychiatric department saw its prescription of long-acting risperidone halved and long-acting olanzapine reduced by 90% between December 2019 and March 2020, with likely consequences on patient's wellbeing [9]. On the other hand, a psychiatric service in the USA was able to maintain physical appointments to administer long-acting injectable neuroleptics during confinement by applying barrier measures [129]. This service also offered the option of switching to the oral form for patients who did not wish to visit the site, despite the lack of clear recommendations for switching in this context [129]. Furthermore, in order to prevent the risk of respiratory depression in the elderly, some hospitals proposed to reduce prescription of depot antipsychotics and to switch to oral form to gain greater flexibility regarding dosage and reversibility [19].

More specifically, olanzapine long-acting injectable (LAI) is associated with risk of post-injection delirium/sedation syndrome (PDSS), but it remains a rare effect. Recommendations have been made to highlight the importance of this long-acting treatment modality [130]. In probabilistic terms, the risk of exposure to SARS CoV-2 outweighs the risk of developing PDSS. In situations where 2 or 3 hours of monitoring (time frame varies from country to country) proves impractical or dangerous, it is proposed to consider a monitoring period of 30 minutes to one hour, or even to temporarily remove it if a responsible person can perform the monitoring [130].

Moreover, the switch from paliperidone palmitate once-monthly injection to paliperidone palmitate 3-monthly injection is also a suitable modification in order to prevent exposure to SARS-CoV-2 associated with the maintenance of monthly consultations, which can be conceived in the form of telemedicine. Guidelines from the University of Oxford state that initiation of treatment with extended-release injectable neuroleptics is possible for patients who would benefit from them [10]. In the event of suspicion or confirmation of COVID-19, it is advisable to perform the injection at home with appropriate protective equipment for caregivers.

2.3.2. Depression

2.3.2.1. Depression and COVID-19. Since the beginning of the COVID-19 pandemic, most studies of mental health in the general population have described an increase in symptoms such as depression and anxiety [131]. The rising rates of depression during the pandemic can be an environmental consequence, but also a consequence of COVID itself. In a large study on health-care workers in China, 50% of people reported symptoms of depression, ranked ahead of symptoms of anxiety or insomnia [132]. Moreover, the possibility of an increase in the proportion of depressed patients as a result of CoV-2-SARS infection has been raised in the literature (see e.g.: [131,133,134]), while meta-analytic data from 10 studies recently reported a pooled prevalence of 22.8% of depression among healthcare workers [135].

Other viruses have been linked to psychological impacts such as depression, for example Epstein–Barr virus, varicella-zoster virus, human immunodeficiency virus or influenza A (H1N1). Survivors of the Spanish flu seem to have exhibited symptoms including depression, sleep disturbances, difficulty coping at work and increased suicide rates in the United States [133]. Such a tsunami of post viral depression appears all the more important to anticipate if people might suffer from clinical recurrences of COVID-19 symptoms after recovery by re-infection or reactivation (CCS) [133,136]. As previously explained, DDC is a major enzyme involved in dopamine but also serotonin synthesis and is co-expressed with ACE2 receptor and the SARS-CoV-2, as SARS-CoV, could induce ACE2 down-regulation and thus a dopamine and serotonin disturbance and consequently an impact on mood [102]. These elements could prove to be essential in understanding the best way to treat patients with possible post-COVID-19 depression.

2.3.2.2. Treatments for COVID-19 and depression. Among the treatments for COVID, those associated with the highest risk of mood depressant effects, with potential suicidal ideation are corticosteroids and mostly interferon alpha [33,137,138]. The possible consequences on mood must be acknowledged, especially since the adoption of SSRIs is described as effective in combating this iatrogenic depression [139,140]. For chloroquine and hydroxychloroquine, although identified as being less at risk than corticosteroids, there are case reports (essentially for chloroquine) and data from few studies or from pharmacovigilance (for hydroxychloroquine); these elements lead to caution about the possibility of mood depression or even suicidal effects [112,116]. Tocilizumab is associated with conflicting data regarding its mood depressor risk [33] and remains more known by its status as a cytokine regulatory agent [141].

2.3.2.3. Management of resistant depression with COVID-19. Among the strategies for resistant depression, two available options are facing barriers to access, for different reasons, elucidated below.

First, electroconvulsive therapy (ECT) has been the subject of extensive literature since the beginning of the pandemic; herein, we highlight in particular the difficulty of sustaining this care due to several challenges; among them the problem of general anesthesia and the need to adapt procedures, while recalling the importance of maintaining access to this strategy in terms of the benefit/risk ratio for patients who require it [142–151]. The non-invasive brain stimulation, transcranial magnetic stimulation and low intensity transcranial electrical stimulation (transcranial direct current stimulation and transcranial alternating current stimulation), could also be an adaptive choice for extending the benefit of ECT in related-COVID-19 settings with compromised access to anesthesia [152].

Regarding esketamine, its use may be limited during COVID-19 because of the risk associated with the inhalant form and a contraindication in the event of significant pulmonary insufficiency (see previously). Its use has been described, with intranasal esketamine self-administered under clinical supervision via telemedicine [153]. The use of ketamine/intravenous/intranasal esketamine in depressive episodes related to neuropsychiatric complications of COVID-19 should not be overlooked [154]. Ketamine seems to derive its therapeutic action, at least in part, from a decrease in the production of pro-inflammatory cytokines, including IL-6, involved in the immunopathology of COVID-19 [154]. Thus, just as patients with an active inflammatory state seem to require the use of pro-dopaminergic or glutaminergic drugs, such as ketamine, to avoid an alteration of the neurotransmission systems affecting the response to first-line antidepressant drugs, post-COVID-19 depressions could also require this type of drug strategy [154].

2.3.3. Anxiety disorders

The concept of "stress" generated by the COVID-19 pandemic has been one of the most common expressions used to describe

the psychological impact of this unique situation. The pandemic generated moderate to severe levels of stress- or anxiety-related symptoms in 25% of the general population in China [155]. COVID-stress syndrome has been proposed as five components of COVID-19-related distress which notably include fear of the dangerousness of COVID-19 and direct or indirect traumatic exposure to COVID-19 [155].

Available data about SARS-CoV-1 survivors showed a dramatic increase in the prevalence of all psychiatric diagnoses and exhibited high levels of anxiety disorders, predominantly PTSD, panic disorder and obsessive compulsive disorder (54.5%, 32.5% and 15.6%, respectively) [134,156].

The consequences of an explosion of anxiety disorders should encourage the use of structured recommendations by the World Federation of Biological Psychiatry, recalling that the chronic treatment of these disorders is based on SSRIs or venlafaxine, while benzodiazepines are to be used during the first weeks, in the treatment of short-term distress and p.r.n. (*pro re nata* medication or "as needed") [157]. Monitoring the consumption of benzodiazepines in such a context is important in order also to avoid the respiratory side effects these treatments may have. A crisis of tranquilizers, including benzodiazepines, in addition to the opioid crisis, at the time of COVID-19 could have dramatic consequences in this sense.

More specifically, the legitimate concern about the emergence of post-COVID PTSD cases must prompt us to reexamine the validity of the pharmacological tools available to us in this context [158].

In this respect, if hydrocortisone cannot be considered as a routine treatment for PTSD, it will be interesting to follow the possible results of studies, in post-COVID-19 PTSD, since this therapeutic strategy has already demonstrated its efficacy versus placebo in 3 studies [159].

Pandemic and the fear of contamination can generate an intuitive increase in obsession and compulsion severity for patients with OCD, with a potential aggravation during the quarantine [160]. Such consequences can also lead to the inappropriate use of certain treatments, such as chloroquine or hydroxychloroquine, which can lead to cardiac toxicity, or even death, in some people [161]. The recommendations regarding OCD during COVID-19 pandemic recall that most patients can be treated with SSRI for the two first choices and clomipramine could be an alternative (after an ECG) [162]. An important warning from the sanitary authorities concerns the increased risk in young people and other vulnerable patients about "activation", agitation, dysphoric states or newly emergent or increased suicidal ideations, which lead to the recommendation "start low and go slow" for treating children and adolescents with antidepressants [162].

Finally, concerning panic disorder and the COVID-19 pandemic, it would be interesting to follow both the overall evolution of this disorder, but also the specific prevalence rate of the respiratory subtype. While several studies have investigated the psychological consequences of the current pandemic, to date very few studies have focused on panic disorder specifically [32,163]. This might seem surprising given the predominance of respiratory symptoms in both COVID-19 and panic disorder, on the one hand, and the generalized fear of contamination and fear of suffocation heightened by the pandemic, on the other hand [32,163]. Salbutamol, a short-acting β-stimulant can be overused in many situations; in patients with asthma, in comorbid situations with asthma and panic disorder (or the latter disorder alone misdiagnosed as asthma) or in the respiratory subtype of panic disorder [33]. As previously explained this overuse could represent a particular danger for patients with diarrhea and vomiting during COVID-19 due to the digestive potassium leakage, leading to augmenting the risk of severe hypokalemia in patients taking psychotropics and thus possibly causing QTc prolongation (see previously; [33]).

2.3.4. Bipolar disorder

It is well-known that bipolar patients are sensitive to numerous factors which can trigger manic or depressive states such as: stress environment and or disturbances in circadian rhythm and overuse of toxic substances, mainly alcohol consumption [164]. In the literature, two cases of manic episodes are described in the context of the pandemic; one without infection by SARS-CoV-2, but precipitated by the stress due to the virus, after more than 15 years of stability, the other linked to the infection and without a history of mental disorders [165,166].

The link between seropositivity for coronaviruses and the risk of mood disorders and suicide has also been established [164,167]. Among the treatments for bipolar disorder, lithium remains the gold standard. However, the need for regular blood tests may interfere with its safe use during a pandemic. As proposed by NICE (National Institute for Health and Care Excellence), measurement of plasma levels is recommended every 3 months for the first year, then every 6 months [168]. After the first year, plasma lithium levels measurements are maintained every 3 months only for older people and people taking drugs that interact with lithium, who are at risk of impaired renal or thyroid function, raised calcium levels or other complications, who have poor symptom control, with poor adherence, whose last plasma lithium level was 0.8 mmol per litre or higher. In every other case plasma lithium levels can be measured every 6 months. During COVID-19 due to the pandemic and restricted access to biological monitoring, these blood tests can be spaced out, with a decision on a case-by-case basis, but especially for patients who are stable and do not present any risk factors [10].

Factors that alter the salt/water balance, infections with fever, dehydration, initiation of drugs that alter lithium excretion, can all induce lithium intoxication [169]. These elements should therefore be taken into consideration during a SARS-CoV-2 infection, even though up to 60% of patients affected by COVID-19 would be apyretic [1].

Some drugs interact with lithium and may increase its plasma concentration, mainly: non-steroidal anti-inflammatory drugs, converting enzyme inhibitors, angiotensin receptor blockers, loop and thiazide diuretics and corticosteroids [1]. In combination with lithium, antipsychotics may induce neurological signs suggestive of neuroleptic malignant syndrome or lithium intoxication, whereas with SSRIs the risk of serotonin syndrome is increased. These dangerous syndromes may be misdiagnosed by COVID-19 (see above) [1].

Besides drug interactions, dehydration and/or infections with fever may also cause an increase in lithemia [169]. Two recently reported cases of COVID-19 with lithium toxicity remind us of this [170].

Overall, patients should be informed of the signs suggestive of lithium intoxication, including: nausea, tremor, thirst and balance disorders. The appearance of these signs requires rapid control of lithemia, with the necessary safety conditions in relation to patient/caregiver contact, and adaptation of treatment.

2.3.5. Suicide risk

The massive stress induced by the pandemic has quickly raised concerns of an increase in suicides [171–177]. This fear is supported in part by data describing an increase in the number of suicides in the USA during the Spanish Influenza outbreak and in Hong Kong by the elderly in 2003 during the SARS-CoV-1 epidemic [171]. The increase in suicide attempts and suicides can be linked to several factors: acute psychic decompensation in people with or without a psychological history in the face of stress directly linked to the pandemic [173,174], in people undergoing indirect psychological suffering: loneliness and social isolation with quarantine, especially in elderly patients, unemployment, job loss [172,177] and for

COVID-19 survivors due to psychological and/or neurobiological consequences [176].

Overall, psychiatric illnesses are associated with suicidal behavior, and it is estimated in the USA that only 42.6% of adults suffering from psychiatric disorders received adequate care in the past year [175]. Moreover, the data from a large international study revealed that more than half of people with major depression, generalized anxiety disorder, and alcohol use disorder were untreated [175]. These data plead not to undertreat patients who require pharmacological treatment but to pursue intensively the detection of people requiring it, without delaying the start of treatment. From this perspective, telemedicine can play a key role in maintaining the continuity of care.

Antidepressants, for all steps, initiation, dosing changes and discontinuation (stopping before 2 months) have been associated with significant risk for suicide attempt [178]. Benzodiazepines and antipsychotics use may also increase the risk of suicide [179,180]. However, for all these data, indication bias and substantial confounding factors exist [178].

Nevertheless, it is important to recall that most pharmacoepidemiologic studies show a protective effect of antidepressants against suicide [181]. In addition, the precautions previously detailed regarding the use of clozapine and lithium during SARS-CoV-2 pandemic should also be reconsidered in light of the prophylactic effects of these treatments on the risk of suicide [182,183]. For these two treatments, a possible dosage reduction in response to signs of infection should ideally be considered, taking into account the clinical response observed to previous dosage reductions, in order to determine the height of this adjustment and whether a treatment of the same class should be implemented, or the dosage adjusted [1].

2.3.6. Sleep disorders

Global stressful circumstances related to pandemic and mass home confinement can have a dramatic impact on sleep-wake rhythms in general and night-time sleep in particular [184]. In an observational study for assessing subjective neurological symptoms in patients with COVID-19, sleep impairment appeared as the most frequent symptom and was more frequent in patients with more than 7 days of hospitalization [185].

A task force of the European CBT-I (Cognitive Behavioural Therapy for Insomnia) Academy proposed practical recommendations for sleep-disturbances induced by the COVID-19 pandemic [184]. However, as a second-line of treatment if CBT is ineffective or unavailable, some pharmacological treatments can be considered with benzodiazepines, hypnotic benzodiazepine receptor agonists – also known as z-drugs: zaleplon, zolpidem, and zopiclone – for short-term use, or sedative antidepressants like agomelatine, doxepin, mirtazapine, trazodone, and trimipramine [184].

Antidepressants can be useful if benzodiazepines and derivatives are deemed inappropriate or if a psychic comorbidity validates their use [184]. However, as we have explained previously, z-drugs, like benzodiazepines and sedative antidepressants, are at risk of causing or worsening dyspnea, particularly in cases of high doses and/or combinations between them or with other risky treatments. As the elderly are particularly sensitive to the risks of respiratory distress with benzodiazepines and to the respiratory effects associated with SARS-CoV-2, referral to melatonin as a first-line option in these populations may seem relevant. On the other hand, it can be deleterious to modify the treatment of a person suffering from sleep disturbances with a benzodiazepine or a z-drug, especially during an anxiety-provoking period such as a pandemic. Stopping treatment with benzodiazepines or derivatives should not be sudden at the risk of inducing rebound insomnia caused by withdrawal syndrome. In other cases, placing melatonin as the first line option is also supported by the treatment plan proposed by neurologists in the event of delirium (see above; [94]) and, in part, due to these possible preventive effects on COVID-19 progression (see below: [4,6,186,187]).

2.3.7. Attention-deficit hyperactivity disorder

The COVID-19 pandemic and the lockdown that followed it proved themselves to be a big challenge for parents of children with attention deficit hyperactivity disorder, be it the hyperactive/impulsive form or the predominant inattentive/distractible type. This is a notorious issue that has been publicly discussed during the European confinement – and the European ADHD Guidelines Group (EAGG) has proposed directions for management of ADHD during the COVID-19 pandemic [188]. Continuity of treatment, mostly with specific legislation and/or therapeutic follow-up, can become an additional burden for patients and their parents. The EAGG advocates for continuity of treatment with constant dosage, hoping for flexibility in access to these treatments, to avoid exacerbation of the disorders and to promote patient acceptance of barrier measures [188]. It is also necessary to question the usefulness of the weekend therapeutic window, which can be detrimental to family balance in a situation of confinement or withdrawal to a small family nucleus [188]. Sleep phases may also be staggered during this health crisis, leading to disorganization of routine. Sleep hygiene advice can then judiciously complement the effects of melatonin (5 to 6 mg/evening) [188]; this treatment can also sometimes help to combat iatrogenic insomnia, linked to psychostimulants (off-label use).

More recently, this same task force inside the EAGG has proposed new recommendations for starting ADHD medication during the pandemic [189]. We invite the reader to look at the original documents for further details, but in essence, they propose that before the start of the medication: (i) a summary of the clinical history of the patient, including parameters like exercise resistance and cardiological monitoring; (ii) a summary of the family disease history, in particular for identifying cases of sudden death for first-degree relatives aged less than 40; and (iii) baseline monitoring with blood pressure and heart rate on three separate occasions – if needed, this can be done by another person aided by telephone guidance [189].

In addition, Javelot et al. [1] pointed out that methylphenidate can cause symptoms important for differential diagnosis with COVID-19, such as nasopharyngeal (see previously), and digestive symptoms – the last ones particularly during the beginning of the treatment, with possibility of diarrhea, abdominal pain, nausea, and vomiting. Headaches are also quite common with the use of psychostimulants, and the EAGG reminds that paracetamol should be preferred over ibuprofen for pain management [188]. Regardless, the use of analgesics should not delay a diagnosis for COVID-19, and in this sense, the availability of SARS-CoV-2 laboratory tests for case tracing becomes even more important.

2.4. Psychoactive substances and COVID-19

Inhalants such as tobacco and cannabis are likely to induce coughing, increasing the overall risk of infection and its severity, while many psychoactive substances can contribute to decreased alertness (alcohol, cannabis, synthetic drugs). The symptomatology of COVID-19 can therefore be amplified by the consumption of these products, in its peripheral and central consequences. Alcohol may exacerbate the risk of smoking-related chronic obstructive pulmonary disease, increase the risk of community-acquired pneumonia, but may also contribute to a deterioration in pulmonary function regardless of smoking status [190,191].

For smokers, in particular, polycyclic aromatic hydrocarbons in tobacco smoke strongly induce the CYP1A2 enzyme for smoker patients, meaning that medication is metabolized much faster.

When these patients stop smoking, the absence of the hydrocarbons slows the usual rate of metabolization, and thus increases drug concentration in plasma and potential adverse side effects. Increases in plasma concentrations of psychotropic drugs (or psychoactives substances) metabolized mainly by CYP1A2 are expected for: caffeine, clomipramine, clozapine, doxepin, duloxetine, fluvoxamine, mirtazapine, olanzapine, pimozide, propranolol, ramelteon, rasagiline, riluzole, ropinirole, theophylline, thiothixene, trifluoperazine and in a lesser extend for almotriptan, amitriptyline, asenapine, chlorpromazine, desipramine, diazepam, fluphenazine, frovatriptan, haloperidol, imipramine, maprotiline, melatonin, naratriptan, nortriptyline, perphenazine, rivastigmine, selegiline, thioridazine, trazodone, ziprasidone, zolmitriptan and zolpidem [192,193].

One should be aware of these effects in case of sudden smoking cessation impulsed by COVID-19 respiratory symptoms in smokers. Therefore, in such cases for patients under clozapine or olanzapine, a dosage reduction of 30% to 40% with 10% reduction on daily dose every four days might be proposed, or otherwise a dosage reduction by a factor of 1.5 in two to four weeks [194,195]. However, other stronger or faster dosage adjustments can be necessary if there are infectious COVID-19 symptoms [8], and also having in mind that there is genetic influence over the level of inducibility of CYP1A2 by smoking [196], which encourages doctors to follow prioritarily the clinical evolution of the patient over a standardised reduction scheme.

Alcohol can potentiate the effects of sedative drugs (see above) and worsen the risks of dyspnea and respiratory distress in combination with other substances or drugs at risk (especially morphine and benzodiazepines) [1,197].

In general, the pandemic has increased consumption of cannabis products and benzodiazepines, which could be linked to the feeling of stress induced by an anxiogenic environment [198] that appeared alongside COVID-19. Moreover, drug misuse could have shifted toward alternative substances and home-made "New Psychoactive Substances" (official terminology of the European Union) and increase the risk of atypical presentations of intoxications [198].

2.5. Reference websites and publications about psychotropics and COVID-19

The SARS-CoV-2 pandemic has forced the entire medical-scientific community to adapt to an urgent and exceptional health situation. Unlike any time before, the vast production of articles related to this field requires recurrent synthesis efforts to identify relevant and practical information. Several publications and reference websites play an important role in guiding the clinician; articles often make it possible to answer specific questions in targeted literature reviews [2,33,95] and/or to establish local recommendations, adapted to the health system of each country and the treatments available there [1,199,200], but can be quickly overlooked in the current scenario, given the expressive number of new articles being published every day. Websites, on the other hand, allow for regular updates, but often offer more generalist content, requiring either the selection of useful information (see below, e.g. the University of Liverpool website) or reference to local practice recommendations (see below, e.g. the University of Oxford website).

2.5.1. Adaptations of psychotropic drugs prescriptions in the COVID-19 pandemic

The Oxford Precision Psychiatry Lab (OxPPL), an international multi-disciplinary working group, has released the platform "COVID-19 & clinical management of mental health disorders" (link: https://oxfordhealthbrc.nihr.ac.uk/our-work/oxppl/covid-19-and-mental-health-guidance) ([10]; announced in Smith et al. [11]). The OxPPL provides evidence-based medical recommendations addressing several themes/issues raised by mental health clinicians during the pandemic [11]. The recommendations propose several sections, 4 of which are directly related to psychopharmacotherapy with information about benzodiazepines, z-drugs, clozapine, lithium and long-acting injectable antipsychotics. Moreover, the section "inpatient wards" contain information on medication for acute episodes and the section "end of life care" provides internet links to useful pharmacotherapeutic recommendations in this area [10]. The platform allows the free sharing of scientific information validated by OxPPL members. Although there is no independent reading committee for the validation of the information communicated, each user has the possibility to share queries transmitted to the working group. Translations of the OxPPL guidelines are available in Chinese, French, Italian and Turkish [10].

The impact of COVID-19 on psychotropics safety is discussed in numerous reviews (i.e. in English: [33,201]). A more structured approach regarding safety of psychotropic medications in people with COVID-19 was made by WHO (World Health Organization) Collaborating Centre for Research and Training in Mental Health and Service Evaluation (University of Verona; [2]). This review concluded that all classes of psychotropics showed acceptable safety risks for use in patients with COVID-19 and proposed 12 evidence-based recommendations. These recommendations mainly include: (i) the detection of drug interactions between psychotropic drugs and COVID-19 treatments (as proposed by the Liverpool site in a non-selective manner, see below); (ii) monitoring of the risk of respiratory depression with in particular benzodiazepines and antipsychotics with highly sedative profiles; (iii) cardiovascular risk, firstly linked to QTc-prolongation, with psychotropic drugs known to be at risk, as well as treatments for COVID-19, for those identified at risk, and secondly, the thromboembolic risk, with antipsychotics and antidepressants; (iv) the risk of infection which may be increased with psychotropic drugs and particularly with clozapine, carbamazepine and oxcarbazepine; (v) finally, the risk of contributing to delirium with anticholinergic treatments, benzodiazepines and lithium.

Concerning the management of acute psychopathology in patients with COVID-19, some authors have also proposed cases centered recommendations for acute anxiety [202] and delirium in elderly population, severe mental illness in median aged patients with few medical comorbidities and non-severe mental illness with depressive and/or anxiety symptoms [203]. About delirium or acute agitation in patients with COVID-19, the more structured work is also from the WHO team in Verona [95] and complementary data can be found in three other articles [94,96,98]. We have previously proposed a synthesis of all these data.

Bilbul et al. [33] offer a unique and exhaustive vision, to the best of our knowledge, about the psychiatric safety of COVID-19 treatments.

2.5.2. Drug interactions between psychotropic drugs and COVID-19 treatments

Interactions between psychotropic drugs and COVID-19 treatments have been the subject of several reviews ([14,96,203]; this last one for the most commonly used medications in delirium) and sometimes targeted to certain COVID-19 treatments ([204,205]; with ritonavir/lopinavir combination and remdesivir [206]; with ritonavir/lopinavir combination and chloroquine/hydroxychloroquine) or certain classes of psychotropic drugs [207,208].

The publications offering the most comprehensive view of these interactions to date are proposed by Bishara et al. [34] and Ostuzzi et al., 2020 (in article and additional file; [2]). These data provide

a synthetic and targeted overview of the psychotropic medications which interact with COVID-19 treatments, by extracting data from the University of Liverpool website.

The Liverpool Drug Interaction Group is a working group made up of members of the Department of Pharmacology of the University of Liverpool extended to other international specialists according to the themes addressed; this group has worked on several databases on drug interactions with anti-HIV and hepatitis antiretrovirals, as well as anti-cancer drugs. This working group now offers a platform to search for drug interactions between experimental drugs used against COVID-19 and other regularly prescribed medications (https://www.covid19-druginteractions.org/checker). Based on pharmacokinetic, pharmacological, toxicological and literature data, the tool allows to identify potential drug interactions between each drugs. This particularly exhaustive tool can both complicate the work of the clinician who would like to extract information relating only to psychotropic drugs in a timely manner, but also allow to find new therapeutic interactions related to the treatment of COVID-19. New treatments have already been referenced in this way in the website since the syntheses of Bishara et al. [34] and Ostuzzi et al. [2], which argue for direct use of the University of Liverpool website.

3. Possible antiviral effects of psychotropics against SARS-CoV-2

Please see Table 4 for synthetic information about the main neurotransmitters modulators (psychotropics) with potential anti-SARS-CoV-2 activities.

3.1. Epidemiology

Concerning the role of existing psychoactive drugs amidst the pandemic, both the potential dangerousness of certain psychotropics, like clozapine [8], and the possible beneficial side effects of others, like haloperidol and chlorpromazine [5,15,209], were quickly raised. Regarding the possible benefits, it is important to note that the proportion of patients with COVID-19 or with serious development of the disease was not higher within mental health institutions at the start of the pandemic [5,16,210], which was originally not expected. During the first lockdown in Europe, it was observed that inside psychiatric facilities, the units which dedicated to COVID-19 patients remained relatively empty [6], and that the proportion of medical staff affected by the disease was higher than that of the patients [5]. There are many possible explanations for this phenomenon, including the relative isolated location of some institutions or even the natural social distancing of some psychiatric patients [16]. However, these hypothesis did not consider other factors that should have made these populations more vulnerable to COVID-19, such as the difficulty for certain patients to respect measures to prevent infection and the fact that very often psychiatric patients also suffer from comorbidities which put them at high risk for contracting SARS-CoV-2, like cardiovascular and pulmonary diseases, obesity and diabetes [3,6]. Therefore, the lack of a plausible explanation for this initial lower rate of infection among inpatients led the community to investigate the possibility of chemoprotection created by psychotropics [3,5,6,16].

3.2. In vitro evidence and theoretical basis for antiviral actions

Many pathways are available for explaining the hypothesized antiviral activity of psychotropics. Three main areas should be further studied: (i) the psychotropics' antiviral activity against SARS-CoV-2 itself [15,211–213]; (ii) the psychotropics' antiviral activity against other coronaviruses, such as MERS-CoV, or SARS-CoV-1 [214,215]; (iii) the psychotropics' antiviral activity against other types of viruses [3,6,213,215]; (iv) the hypothesis of anti-SARS-CoV-2 activity by drugs with similarities to the ones in items (i) to (iii), in this case defined by structure-activity relationship (SAR) similarities between the drugs [3,6]. Also, there is pharmacoepidemiological data connecting the lowest incidence of COVID-19 in psychiatric patients with the use of certain commercial drugs. This was verified in different settings: for a single unit of an institution [5], for a whole mental health establishment [6], and for countrywide pharmacoepidemiological data [3].

Furthermore, the data from [214,215] showed some psychotropic drugs were present in treatment schemes which showed anti-SARS-CoV-1 and/or anti-MERS-CoV activity [3,214,215]. These sources recognized the potential efficacy of many first generation antipsychotics against coronaviruses, and in particular verified the possible benefits of phenothiazines (about half of the substances examined), and other substances from pharmacochemical classes structurally related to them, notably thioxanthene and diphenylbutylpiperidine [3,214,215].

Based on this, chlorpromazine has been put forward for its anti-SARS-CoV-2 potential [5,209,211,213,216–219]. Chlorpromazine is usually found in high concentrations in the lungs and its antiviral activity could be due to its interference with clathrin-mediated endocytosis and post-entry effects on viral replication [3,5,6]. However, because of the large number of phenothiazines that showed some anti-coronavirus activity [214,215], it's likely that this antiviral effect is not restricted to chlorpromazine, and could be instead a drug class effect. This means that certain phenothiazines which are more used than chlorpromazine in some countries (like cyamemazine or alimemazine in France) could also provide comparable anti-coronavirus effects [3,6,218,220,221]. This hypothesis is supported by the recently published data in [213], which demonstrated the anti-SARS-CoV-2 activity of seven psychotropics studied in [215]. In this study, five out of the seven psychotropics showing anti-SARS-CoV-2 activity were phenothiazines or derived substances.

3.3. Clinical evidence and the locus of potential effects

These results were the starting point for the use of pharmacoepidemiological data associated with antiviral efficacy data as proposed in two recent articles [3,6]. They allowed us to identify a list of 20 drugs with chemoprotective potential for mental health patients in France; they are, in alphabetical order: alimemazine, aripiprazole, cetirizine, chlorpromazine, citalopram, clozapine, cyamemazine, escitalopram, haloperidol, hydroxyzine, lithium, levomepromazine, melatonin, nicotine, paroxetine, quetiapine, sertraline, trihexyphenidyl, tropatepine, valproic acid (for details, see Table 4).

Moreover, Lithium has been analyzed by a number of different publications, like chlorpromazine, and these articles have described its potential anti-SARS-CoV-2 effects [6,222–229]. Interestingly as well, a 2013 study on the risk of pneumonia in bipolar patients has also demonstrated a dose-dependent protective effect with lithium, and this effect was not observed with any other antipsychotic or mood stabilizer in this study [45].

However, some other substances which are less prescribed, and for which there is therefore less pharmacoepidemiological data available, could also be promising in terms of anti-SARS-CoV-2 effects. Among those, many are also phenothiazines, and we highlight: fluphenazine, promethazine, thiethylperazine and trifluprazine, since they have demonstrated anti-SARS-CoV-1 and/or anti-MERS-CoV efficacy and also effects on other viruses [222], and propericiazine (periciazine), pipotiazine, metopimazine and mequitazine [3]. Thioxanthenes, which are related

Table 4
Main neurotransmitters modulators (psychotropics) with potential anti-SARS-CoV-2 activities.

Pharmacochemical class International nonproprietary name (or other standardized name)	Pharmacological class	Antiviral activity			CAD/FIASMA	Comments
		Hypothetical for SARS-CoV-2 (and in vitro demonstration#)	SARS-CoV-1 and/or MERS-CoV	Others viruses		
Phenothiazines[a,b,c]		[3,4]	[214,215]	[214,215]		Probable class effect against SARS-CoV-2 [3,4]
Chlorpromazine[c]	FG antipsychotic	[3,5,211#,213,216–220,231,232,270]	[214,215]	[214,215]	+/+	Clinical trials: NCT04366739 – repurposing of chlorpromazine in COVID-19 treatment (reCoVery), phase 2; NCT04354805 – administration of chlorpromazine as a treatment for COVID-19, phase 2/3
Alimemazine (or trimeprazine)[a,b]	Antihistamine	[3,6,212#]			+/not confirmed	Pharmacochemically-related to chlorpromazine with demonstrated antiviral activity against MERS-CoV, SARS-CoV-1 and other viruses [3,6] and potential anti-SARS-CoV-2 activity [211,213]
Cyamemazine[a,b,c]	FG antipsychotic	[3,6]			+/not confirmed	
Fluphenazine	FG antipsychotic	[3,215#]	[214,215]	[215]	+/+	
Levomepromazine (or methotrimeprazine)[a]	FG antipsychotic	[3,271]#	[271]		+/not confirmed	
Metopimazine	Antiemetic	[3]			+/not confirmed	
Mequitazine	Antihistamine	[3]			+/not confirmed	
Pipotiazine	FG antipsychotic	[3]			+/not confirmed	
Propericiazine (periciazine/pericyazine)	FG antipsychotic	[3]			+/not confirmed	
Promethazine	Antihistamine	[3,213#,232]	[214,215]		+/+	
Thiethylperazine	FG antipsychotic	[3,215#]	[214,215]	[215]	+/not confirmed	
Triflupromazine	FG antipsychotic	[3]	[214,215]		+/+	
Thioxanthenes						
Flupent(h)ixol	FG antipsychotic	[3,212#]			+/+	Pharmacochemically-related to chlorpromazine (and flupentixol) with demonstrated antiviral activity against MERS-CoV, SARS-CoV-1 and other viruses for chlorpromazine [3] and potential anti-SARS-CoV-2 activity (chlropromazine [211,213] and flupentixol [212]
T(h)iot(h)ixene		[3]	[214,215]		+/not confirmed	
Zuclopent(h)ixol		[3]			+/not confirmed	
Diphenylbutylpiperidines						
Fluspirilene	FG antipsychotic	[3,213#]	[214,215]		+/not confirmed	Pharmacochemically-related to fluspirilene with demonstrated antiviral activity against MERS-CoV, SARS-CoV-1 (3) and potential anti-SARS-CoV-2 activity [213]
Penfluridol		[3]			+/+	
Pimozide		[3]			+/+	
Butyrophenones						
Haloperidol[a]	FG antipsychotic	[3,15#,211#]			+/not confirmed	Pharmacochemically-related to astemizole with demonstrated antiviral activity against MERS-CoV and SARS-CoV-1 [3,214,215]
Pipamperone	FG antipsychotic	[3]			+/not confirmed	
Imipramine derivates						
Clomipramine	Tricyclics antidepressants	[3,213#,230#,231]	[214,215]	[215]	+/+	Pharmacochemically-related to phenothiazines Probable class effect against SARS-CoV-2 [230]
Amitryptiline		[230#]		[272]		
Desipramine		[230#]				
Imipramine		[230#,232,234#]		[272]		
Maprotiline		[230#]				
Dibenzodiazepines and derivates						
Clozapine[b]	SG antipsychotic	[6]		[6]	+/not confirmed	Conflicting data from Govind et al. [127]
Quetiapine[b]	SG antipsychotic	[6]			+/not confirmed	
Quinoline derivates						
Aripiprazole[b]	S/TG antipsychotic	[6]		[6]	+/not confirmed	
Atropine derivates						
Benz(a)tropine	Anticholinergic	[3,215#]	[214,215]	[215]	+/+	Pharmacochemically-related to benztropine with demonstrated antiviral activity against MERS-CoV, SARS-CoV-1, other viruses [3,214,215] and potential anti-SARS-CoV-2 activity [213]

Table 4 (*Continued*)

Pharmacochemical class International nonproprietary name (or other standardized name)	Pharmacological class	Antiviral activity			CAD/FIASMA	Comments
		Hypothetical for SARS-CoV-2 (and in vitro demonstration#)	SARS-CoV-1 and/or MERS-CoV	Others viruses		
Trihexyphenidyl[a]	Anticholinergic	[3]			+/not confirmed	
Tropatepine[a]	Anticholinergic	[3]			+/not confirmed	
Diphenylbutanamine						
Cetirizine[b] (psychotropic status can be discussed)	Antihistamine	[3,6]		[6]	+/not confirmed	Pharmacochemically-related to chlorphenoxamine with demonstrated antiviral activity against MERS-CoV and SARS-CoV-1 [3,214,215] and with clemastine and cloperastine with potential antiviral activity against SARS-CoV-2 [15,211,212]
Hydroxyzine[a,b]	Antihistamine	[3,6]		[6]	+/+	
Citalopram[b]/escitalopram[b]	Antidepressant	[6] (es/citalopram) [230#] (escitalopram)		Citalopram [6]	+/not confirmed	Pharmacochemically-related to diphenylbutanamines with potential related activity (see above)
Others						
Lithium[a,b]	Mood stabilizer	[3,6,222–229]		[3,6]	−/−	Previous interesting data about lithium and risk of pneumonia [45]
Valproic acid and derivates[b]	Mood stabilizer	[6,273]		[6]	−/−	No obvious anti-SARS-CoV-2 activity with valproic acid [15]
Fluoxetine	Antidepressant	[230#,234#]		[274,275]	+/+	NCT04377308, fluoxetine to reduce intubation and death after COVID19 infection and NCT04570449, pilot randomized controlled trial: fluoxetine to reduce hospitalization from COVID-19 infection (FloR COVID-19)
Fluvoxamine	Antidepressant	[232]			+/+	First clinical trial demonstrating the possible prophylactic efficacy of a psychotropic drug against SARS-CoV-2 (NCT04342663, a double-blind, placebo-controlled clinical trial of fluvoxamine for symptomatic individuals with COVID-19 infection [STOP COVID])
Paroxetine[a]	Antidepressant	[3,263]		[3,6]	+/+	
Sertraline[b]	Antidepressant	[6,230#,232,233]		[6]	+/+	
Nicotine[b]	Substitution therapy tobacco smokers	[3,6,248]		[6]	Partial/not confirmed	Numerous clinical trials, see for example: NCT04583410 – efficacy of nicotine in preventing COVID-19 infection in caregivers (NICOVID-PREV), phase 3; NCT04429815 – impact of smoking and nicotine on the risk of being infected with COVID-19 (MAGIC), phase 3; NCT04598594 – evaluation of the efficacy of nicotine patches in SARS-CoV2 (COVID-19) infection in intensive care unit patients (NICOVID-REA), phase 3
Melatonin[b]	Hypnotic/antijet lag	[3,6,186,187,263]		[3,6]	−/−	Description of antioxidant and anti-inflammatory effects, and use as chronoregulator and immunomodulatory agent, in addition to a possible antiviral action [186,187] Numerous clinical trials, see for example: NCT04474483 – safety and efficacy of melatonin in outpatients infected with COVID-19 (COVID-19), phase 2; NCT04353128 – efficacy of melatonin in the prophylaxis of coronavirus disease 2019 (COVID-19) among healthcare workers. (MeCOVID), phase 2/3; NCT04568863 – efficacy of intravenous melatonin on mortality in adult patients admitted to the intensive care unit with COVID-19 (MELCOVID), phase 2

FG: first generation; SG: second generation; S/TG: second/third generation.

[a] At least on 4% of prescriptions in French psychiatric hospital [276].

[b] In the 18 most commonly used drugs by patients in the Psychiatric department of Henri Mondor Hospital, Creteil, France (Villoutreix et al., 2020).

[c] About 25% of patients with chlorpromazine or cyamemazine in the GHU PARIS Psychiatrie & Neurosciences, Sainte-Anne, Paris, France (data provided by Emmanuelle Advenier–Iakovlev, pharmacist).

to phenothiazines, have also showed benefits in some cases, as with thiothixene, demonstrating anti-SARS-CoV-1 and anti-MERS-CoV activity [214,215]. It should be noted that other first generation antipsychotics could also be of interest, such as fluspirilene (anti-SARS-CoV-1 and anti-MERS-CoV efficacy demonstrated; [214,215]), of which pimozide and penfluridol are derivatives (diphenylbutylpiperidine derivatives; [3]), as well as pipamperone, structurally linked to haloperidol (butyrophenones derivate; [3]).

Among phenothiazines and their derivatives, 7 of them have recently had their SARS-CoV-2 activity confirmed: alimemazine/trimeprazine, chlorpromazine, flupentixol, fluphenazine, fluspirilene, promethazine and thiethylperazine [211–213], while the effect of haloperidol has also been studied [15,211].

Analyzing antidepressants, imipramines, which also have a structural link to phenothiazines, may be of interest, in particular clomipramine which has demonstrated anti-SARS-CoV1, anti-MERS-CoV activity [215,230,231] and probably anti-SARS-CoV-2 activity according to Weston et al. [213], while the potential of imipramine, amitriptyline, desipramine and maprotiline should be considered [3,230,232]. The anti-SARS-CoV-2 efficacy of these four tricyclics was recently confirmed by Carpinteiro et al. [230]. SSRIs could potentially be of class interest [230,232–234]. The first clinical trial demonstrating the possible prophylactic effects of a psychotropic drug was recently published with fluvoxamine. Compared to placebo ($n = 72$), patients treated with fluvoxamine ($n = 80$; increase to 300 mg/day) had a lower likelihood of clinical deterioration over 15 days [235].

All the above data encourages the study of anti-SARS-CoV-2 properties of psychotropic medications, beyond standard therapeutic usages, so that new drug mechanisms against COVID-19 can be identified.

For instance, the antihistaminic effect H_1 seems to be involved in anti-coronavirus activity in general and anti-SARS-CoV-2 in particular. The H_2 effect, which has also been studied for COVID-19 with famotidine, will not be analyzed here since it is not predominantly associated with psychotropics. Among anti-H_1 antihistamines, chlorphenoxamine has shown anti-SARS-CoV-1 and anti-MERS-CoV activity [214,215] and is pharmacologically related to some often prescribed medications – i.e., alimemazine/trimeprazine, hydroxyzine and cetirizine – and with less common ones – i.e., pheniramine, brompheniramine, chlorphenamine, dexchlorpheniramine, diphenhydramine, doxylamine, triprolidine, clemastine, cloperastine, azelastine, desloratadine, and loratadine [3,6,15].

Among the above mentioned substances, alimemazine/trimeprazine, azelastine, clemastine, and cloperastine have confirmed anti-SARS-CoV-2 activity [211,212]. These effects are especially worth noting since, beyond the SAR linking certain substances, the anti-H_1 effect appears to be the common denominator of all 11 substances identified as "neurotransmitters inhibitors" by Dyall et al. [214,215], with anti-coronavirus efficacy.

This anti-H_1 property is present in treatments qualified as antihistamines, but also in first generation antipsychotics such as phenothiazines and thioxanthene and tricyclic antidepressants. Other substances like astemizole, – a butyrophenone derivative similar to haloperidol – which is classified as an antihistamine, and benztropine – an atropine derivative – which has antihistamine and anticholinergic effects, presented anti-SARS-CoV-2 activity according to Sauvat et al., [211] and Weston et al., [213]. Citalopram, which was mentioned in Villoutreix et al. [6] because of its structural connection to diphenylbutanamines (as was the case with escitalopram and fluoxetine), has shown the strongest anti-H_1 properties among SSRIs. Moreover, the antipsychotics proposed by Villoutreix et al. [6] – i.e., clozapine, olanzapine, and quetiapine – also have strong antihistamine properties.

In addition to the beneficial and potentially prophylactic effects of certain antihistamines, i.e., the aforementioned phenothiazines, blocking the H_1 histamine receptor could also prevent complications related to SARS-CoV-2 infection. IL-6 secretion from human lung macrophages is positively regulated by histamine, and it is one of the key messengers produced in COVID-19's cytokine-storm [236,237]. For this reason, some authors have proposed that the antihistamine effects of molecules like olanzapine or quetiapine could be useful in order to prevent COVID-19-associated adult respiratory distress syndrome (ARDS) [236]. The cytokine regulatory ability has also been hypothesized with antidepressants as anti-inflammatory agents against COVID-19 and thus it would be possible to prevent cytokine-storm by evoking all SSRIs (and other antidepressants; [101]) or in a targeted manner with fluoxetine [238]. However, even though cytokine regulation seems to be acquired with the use of antidepressants, the specificity of such a mechanism over IL-6 has been put in question by recent data [239–242].

Other pharmacological mechanisms which could be useful against SARS-CoV-2 through psychotropics were also identified and herein we highlight: the modulation of sigma receptor activity [15,211,212,243,244], modulation of ACE-2 receptor activity [245,246], and modulation of 5-HT_{2A} receptor activity [247].

Moreover, nicotine was evoked early on as a substance with anti-SARS-CoV-2 properties because of the low incidence of smokers hospitalised during the beginning of the pandemic in China [248]. Smoking, however, cannot be seen as a therapeutic strategy against COVID-19, and there is robust evidence pointing to it as a risk factor leading to more severe forms of the disease [249]. Nevertheless, it seems that the halt in smoking (and consequently, in nicotine intake) caused by hospitalization in severe COVID-19 cases can be an aggravating factor for smokers [250,251]. Through its immunomodulatory effects and its complex interactions with renin-angiotensin system, nicotine can offer a potential prophylactic option for COVID-19 and/or a protective factor against cytokine-storm only in current smokers during hospitalization [251].

Other data on psychoactive substances such as cannabis, cannabis-derived products [252] – with oral cannabis/cannabinoids (for example: cannabidiol, dronabinol and nabilone – approved by the FDA), oromucosal sprays (nabiximols – approved in Canada and in many European countries) –, and oxytocin [253–255], which is available as an injectable treatment in several countries should also be highlighted. However, the possible benefits of cannabis and its derivatives must be carefully evaluated and communicated to avoid that retailers of these products make unsupported medical claims about their products given the risks involved.

A number of favorable chemical properties with anti-SARS-CoV-2 activity have been identified and those are shared by a large number of psychotropic drugs. For instance, cationic amphiphilic drugs (CADs) are a group of compounds that share at least two features: a cationic center, and a lipophilic portion [256]. CADs have lysosomotropic effects and may disturb endosomal processes for viral entry [6,215,257] and thus could have significant anti-SARS-CoV-2 activity. Recently, a new pharmacological group named FIASMA, acronym for Functional Inhibitors of Acid SphingoMyelinase, has been proposed [258]. Their pharmacological action inhibits Acid SphingoMyelinase (ASM), an enzyme that, when abnormally activated due to higher ceramide levels, could be behind several neuropsychiatric diseases, including depression [258]. Usually, FIASMAs have the following properties: they are CADs, they violate Lipinski's Rule-of-5 (Lo5), a rule for determining the bioavailability of compounds, more often than other non-FIASMA drugs, have the ability to cross the blood-brain barrier, and induce phospholipidosis [258]. An interesting fact concerns

the distribution of FIASMAs in the anatomical therapeutic chemical (ATC) drug classification system, since over 40% of the known FIASMAs belong to groups N04, N05 and N06 – which are anti-Parkinson drugs, psycholeptics and psychoanaleptics, respectively –, and this supports the great importance of psychotropics in FIASMA and the fact that their clinical effects may be related, at least in part, to their functional inhibition of ASM [258]. The acid sphingomyelinase/ceramide system seems to play an important role in bacterial and viral infections and Carpinteiro et al. [230] demonstrated that SARS-CoV-2 activates and uses this pathway for infection. In this sense, Carpinteiro et al. [230] and Schloer et al. [234] showed the benefit of amitriptyline, imipramine, desipramine, maprotiline, fluoxetine, fluvoxamine and sertraline, which display properties to inhibit ASM and therefore appear as a potential strategy against SARS-CoV-2.

However, it should be noted that recent data suggest that having a psychiatric disorder could increase the risk of being affected, of developing a severe form or of dying of COVID-19 [210,259,260]. Moreover, psychotropic drugs could increase COVID-19 mortality in the elderly [261]. This reinforces the need for studying the reported drug prophylactic factor in psychiatry settings. Conflicting data exist for nicotine (see previously). Moreover, it is important to assess whether the increased risk of aggravation in mental health patients hospitalized for COVID-19 arise from the reduction or cessation of all or part of their psychotropic medications with potential anti-SARS-CoV-2 activity.

Taken together, these data suggest that the use of certain substances usually prescribed in psychiatric settings, like phenothiazines or some antidepressants, should be studied for their potential efficacy against SARS-CoV-2 [3–6,214,215]; see Table 4 for a summary of data on psychotropic drugs and antiviral activity against coronaviruses. However, one must have in mind the side effects that come with such treatments; their sedative potential – particularly dangerous for patients with respiratory depression [1,2] –, their anticholinergic effects, and most importantly their possible cardiovascular impact and their risk for increasing the QT interval [1], call for caution.

Up until now, the data presented on the prophylactic properties of psychotropic drugs are not enough to change the existing guidelines for them, since these should be primarily guided by safety criteria [2]. Nevertheless, having in mind the unpredictable evolution of the COVID-19 pandemic, the possibility of having an extended sanitary crisis that could last months, or even years, should be taken into account, and in this case new and more conclusive information on the eventual benefits of psychotropics against coronavirus disease could change existing recommendations on these treatments.

For instance, if based only on the safety information currently available, sedative neuroleptic medication like phenothiazines and tricyclic antidepressants should be avoided because of their multiple undesirable anticholinergic and antihistaminic side effects (recommendation No. 4 in Ostuzzi et al. [2] and see Jarvis et al. [262]). However, if for example new data appears that is able to strongly confirm the benefits of chlorpromazine for COVID-19 patients (see clinical trials in Table 4), then certainly these guidelines could be subject to changes.

It should be noted that, if phenothiazines do show chemoprophylaxis for mentally ill patients, then other related treatments should also be investigated. Thiethylperazine has already shown anti-MERS-CoV activity [215] and anti-SARS-Cov-2 activity on the data in Weston et al. [213], and metopimazine could show class effect activity. Since they are both antiemetic medications, they could be doubly indicated against COVID-19 cases showing digestive symptoms. Also, investigating other drug classes, loperamide, which has minimal central nervous system side effects and has shown structural similarity both with fluspirilene – was shown to have anti-SARS-CoV-1, anti-MERS-CoV [214,215] and anti-SARS-CoV-2 [213] activity and with pimozide and penfluridol (diphenylbutylpiperidine) – presents anti-SARS-CoV-1, anti-MERS-CoV and anti-HCoV229E [215] efficacy. Overall, this should lead us to be aware of symptoms such as nausea/vomiting and diarrhea following COVID-19, and to target them first with a combination of thiethylperazine or metopimazine + loperamide.

3.4. Evidence for severe adverse reactions

Data is also ambiguous concerning the potential cardiologic effects of some treatments. On the one hand, caution is rightfully strongly encouraged for psychotropics with torsades de pointes (TdP) risk (see Osttuzi et al. [2] – recommendation No. 6; [1]); however, on the other hand, a few of these drugs which present potential risk of the QTc interval prolongation also show prophylaxis and/or healing potential against SARS-CoV-2 ([3,6] and see Table 4). This shows that clinical investigation on these treatments should still be conducted in order to establish the existing risks and benefits of them in COVID-19 cases.

For drugs such as clozapine and lithium, the monitoring required is even more necessary, given their potential toxicity in patients suffering from COVID-19 (this is particularly the case for clozapine) [8,127,128,170]. However, given the therapeutic gains associated with them, notably for suicide prevention (see [182,183] and see above), these treatments should also be carefully investigated to check for their benefits in patients with COVID-19 [6].

Furthermore, concerning sleep disorders – which, as mentioned previously, now affect both COVID-19 patients and people suffering from anxiety due to the pandemic – melatonin appears as the first choice hypnotic therapy in the SARS-CoV-2 crisis thanks to its good tolerance, to the absence of withdrawal syndrome risk and impact on respiratory capacities, and to its potential benefits of use on COVID-19 [3,6,263]. This is all the more true since melatonin is now considered to be one of the first line treatments for agitation [94].

While there is data which seems to confirm positive effects of some drugs for COVID-19 cases, there is also evidence that suggests otherwise, recommending further investigation for dangerous effects of certain medications. Dextromethorphan, for instance, can be used to treat dry cough, a symptom present in almost 70% of COVID-19 cases according to the World Health Organisation [264], and can also be associated to quinidine in the first and only FDA-approved treatment against pseudobulbar affect. However, as recently proposed by data in Gordon et al. [15], it appears that dextromethorphan evoked pro-viral activity, which is contradictory with other sources of information that considered it safe for patients affected by COVID-19 [265].

3.5. Practical recommendations

As it can be demonstrated by the conflicting information mentioned in the last paragraphs, rigorous clinical evaluation of the prophylactic and/or healing potential of psychotropics for COVID-19 must be conducted. An accurate adjusted framework of their risks and benefits can be constructed by examining the danger of its side effects – central nervous systems risks, respiratory depression, increased infectious and cardiovascular risks – in perspective alongside the possibility of creating different psychopharmacotherapeutic strategies for COVID-19 and mentally ill patients [6,248,266].

Since it is not possible to retrospectively identify the substance(s) involved in the initial prophylaxis in patients with mental health disorders, it is necessary to prospectively investigate whether a possible shared pharmacological effect by a group of substances play a role in this hypothetical chemoprotection. It

appears particularly relevant to check whether the "antihistamine load" (with potentially one or more drugs presenting anti-H1 antihistamine effects and with a profile of CAD and ± FIASMA) in mental health patients reduces the risk of having severe forms of COVID-19. If such is the case, a multifactorial chemoprophylaxis, based on the additive or synergistic efficacy of several psychoactive compounds with the different endocytic pathways that they affect [3,232], might have played a protective role against COVID-19 in patients with mental health disorders at the onset of the pandemic.

4. Conclusion

Considering the unforeseen sanitary situation caused by the COVID-19 pandemic, a number of difficulties arise in structuring relevant recommendations for clinicians.

The speed which information can be become obsolete encourages people to turn to on-line and regularly updated sources, such as the AZCERT website (for QT informations), the Liverpool and Oxford universities sites (for drug-drug interactions and general recommendation for psychiatric care during the pandemic, respectively), even though there are necessary adjustments to be made in order to adapt these general recommendations to the restrictions and available treatments of each country.

Another challenge is knowing whether the most relevant recommendations come from the best constructed pharmacoepidemiological reviews evaluating similar, but not identical, situations [2], or from individual psychopharmacological knowledge of each treatment concerning the evolving information available for this emerging disease [267]. Similarly to what was recently suggested by Ostuzzi et al. [2], although drug safety seems to be feasible in all psychotropic drug classes, this analysis by the AMSTAR-2 criteria can only rely on very few high quality data whose extrapolability to the current sanitary situation is debatable: only two studies with antidepressants in adults with depression and ischemic heart and chronic obstructive pulmonary diseases presented high AMSTAR-2 scores. This information must be analyzed in order to establish cautionary measures for the respiratory and cardiovascular systems (recommendations No. 3 to 5 and No. 6, 7 and 9, respectively), for the infection risk (recommendation No. 8), and central effects risk (recommendation No. 10).

This shows that the data in academic studies must be constantly re-evaluated, so that the risk associated with the drug can be anticipated (preventive pharmacovigilance; e.g. clozapine and risk of pneumonia – [2,3,8]), while recommendations are progressively adjusted according to new knowledge on the disease.

A distinction should also be made between the guidelines on psychopharmacologic treatments given to patients suffering from COVID-19 [2] with little or no history of psychiatric disease and the drug safety recommendations for patients with chronic use of psychotropics, even in the case of similar treatments. For instance, the guidelines in case of acute hallucinations in COVID-19 patients may be different if the person has not had any psychiatric treatment before or if he or she has had previous hallucination episodes that were controlled with regular medication that was potentially interrupted; in the latter case it would be preferable to reintroduce or readjust treatment despite coronavirus disease.

In addition to this, weighing risks and benefits of psychotropic treatments could also be reconsidered in the medium term because of the positive effects of certain treatments [3,6,15,211–213]. In order to consider this information, clarification and confirmation of the low initial prevalence of COVID-19 cases in psychiatry and the possible implication of chemoprophylaxis by psychotropic drugs is required. This confirmation is even more relevant since certain psychotropic treatments with potentially positive effects on COVID-19 cases, such as the phenothiazines, could cause undesirable adverse side effects which are highly counterproductive for COVID-19 recovery, as: sedation, respiratory depression, anticholinergic effects and accentuation of the disease impact on the central nervous system, prolonged QTc interval and prothrombotic effects.

These facts should encourage the community to observe in the months and years to come how much the preventive pharmacovigilance and antiviral efficacy of psychotropics could influence one another, in order to well determine the risks and benefits assessment guiding their use. It seems recommendable to re-discuss and question regularly the tradeoff of such treatments in the months to come, as new data appears with the evolution of the pandemic.

The observation of long COVID-19 cases reminds us that our concerns about the disease will most likely not vanish with the end of the pandemic [73]. The higher rates of psychotic disorders in adulthood for children born during influenza pandemics, the increase of cases of autism, schizophrenia and epilepsy in the case of maternal viral infections during pregnancy and the memory of lethargic encephalitis in the years following the Spanish flu, could build the risk of an "ultimate/third neuropsychiatric wave" after the infectious waves of COVID-19 [73,268,269]. These complications and these potential neuropsychiatric consequences also prompt us to define the best use of psychotropic drugs in the face of these emerging issues.

Disclosure of interest

The authors declare that they have no competing interest.

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