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COVID-19 inpatients with psychiatric disorders: Real-world clinical recommendations from an expert team in consultation-liaison psychiatry

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ABSTRACT

Background: : The management of coronavirus disease 2019 (COVID-19) in patients with comorbid psychiatric disorders poses several challenges, especially regarding drug interactions.

Methods: : We report three representative case-scenarios on patients with psychiatric disorders and COVID-19 to provide a practical approach based on the existing literature and the clinical experience of an expert team in consultation-liaison psychiatry.

Case-centered recommendations: : Psychopharmacological ongoing treatments should be prioritized and most doses should be reduced 25–50% of original dose if the patient receives lopinavir/ritonavir, with some exceptions including quetiapine, asenapine, olanzapine, sertraline, lamotrigine, bupropion, and methadone. If the psychopharmacological usual doses are in the low-to-median range levels, a dose change during COVID-19 drugs co-administration is not recommended, but only ECG and clinical monitoring of adverse effects and drug levels if required. Furthermore, when introducing a psychopharmacological drug, dose titration should be progressive, with ECG monitoring if cardiotoxic interactions are present.

(A) In agitated delirium, olanzapine is recommended as first-line antipsychotic and quetiapine should be avoided.

(B) In severe mental illness (SMI), essential treatments should be maintained.

(C) In non-SMI with depressive/anxiety symptoms, psychological support should be provided and symptoms identified and treated.

Limitations: : Most recommendations on pharmacological interactions provide only a limited qualitative approach and quantitative recommendations are lacking.

Conclusions: : Patients with psychiatric disorders and COVID-19 should be managed on a personalized basis considering several clinical criteria and, should not be excluded from receiving COVID-19 treatments. Risks of pharmacological interaction are not absolute and should be contextualized, and most psychopharmacological treatments should include an ECG with special attention to QTc interval.

Introduction

More than 4,500,000 infections have been confirmed worldwide in the coronavirus disease 2019 (COVID-19) pandemic, with approximate mortality of 6.6% (*WHO. Coronavirus disease (COVID-19) Situation Report-118 Highlights*, 2020), but the numbers may be much higher. Global attention has largely been focused on the psychological impact on the general population and the prevalence of mental health outcomes among exposed healthcare workers (Anmella et al., 2020; Lai et al., 2020; Liu et al., 2020), with people with existing mental health disorders having been overlooked (Vieta et al., 2020).

In times of epidemics, people with mental health disorders are more

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susceptible to infections, including pneumonia. Explanations include higher rates of smoking, the presence of cognitive impairment, negligence of risks, confinement conditions in psychiatric wards and residential centers (especially in elderly populations), restrictions in regular outpatient evaluations, pharmacological treatment, and unequal access to healthcare settings (Seminog and Goldacre, 2013). Additionally, this population could be more influenced by the emotional distress related to the pandemic outbreak and the confinement situation. This increased susceptibility may result in relapses or worsening of preexisting psychiatric conditions leading to hospitalization (Yao et al., 2020). Mental health home hospitalization care has been proposed as an alternative to address this problem, but this is not possible when COVID-19 involves serious respiratory symptoms (Garriga et al., 2020).

Very little has been published on COVID-19 patients with comorbid psychiatric disorders, which may make the treatment more challenging and potentially less effective (Sartorius, 2013). In particular, the management of these patients regarding the psychopharmacological interactions with COVID-19 treatments has not been properly addressed. A recently published work by The University of Liverpool about pharmacological interactions with experimental COVID-19 treatments has been of aid for clinicians (Liverpool Drug Interactions Group, 2020). The interactions are divided up into increased and decreased exposure (measured by blood levels of medications) and known, possible or conditional risk of QT prolongation and/or torsade de pointes (TdP) for each drug interaction (Liverpool Drug Interactions Group, 2020). However, real-world clinical scenarios are challenging and case-centered recommendations for psychiatric patients are lacking.

Both patients with mental disorders (The Lancet Psychiatry, 2019) or COVID-19 showed higher risk of being stigmatized (Kaufman et al., 2020), hence psychiatric patients with COVID-19 might suffer from a *double-stigma*, with consequence on health-assistance availability, social isolation, and worst health outcomes (Henderson et al., 2014). Thus, stigma and the lack of training in psychopharmacology of medical teams involved in COVID-19 treatment might cause unequal access to COVID-19 drugs. This may lead to avoid the use of COVID-19 treatments in psychiatric patients for preventing interactions, or conversely to abrupt suspension of the psychopharmacological treatments when COVID-19 treatments are required.

We report 4 clinical cases in three representative case-scenarios on COVID-19 inpatients with psychiatric disorders in order to provide a practical approach based on the existing literature and the clinical experience of an expert team in consultation-liaison psychiatry.

Clinical case-scenarios

Delirium in the elderly population

A 68-year-old male, with paranoid personality disorder and depressive disorder on treatment with quetiapine 200 mg/24 h without previous non-psychiatric medical record, was referred to our consultation-liaison psychiatry unit for confusion and agitation during weaning from prolonged mechanical ventilation. He was admitted for COVID-19 pneumonia with respiratory insufficiency and had been treated with lopinavir/ritonavir (LPV/r) 400/100 mg/12 h, hydroxychloroquine 400 mg/24 h, azithromycin 250 mg/24 h, intravenous methylprednisolone 40 mg/24 h and interferon-β 8mU/24 h. Quetiapine had been interrupted since the first day of admission due to a high risk of pharmacological interactions. During weaning, with dose reduction of propofol and remifentanil and addition of dexmedetomidine 1000 mcg 6 ml/h intravenous perfusion, the patient presented with agitation, disorientation, and confusion. Intravenous haloperidol 7,5 mg/24 h was started, with close ECG monitoring, with a marked improvement of delirium. When LPV/r was discontinued, quetiapine 200 mg/24 h was gradually reinstated and the dose of haloperidol decreased. No corrected QT (QTc) prolongation or other side effects due to drug interactions were present.

Severe mental illness (SMI) in median-aged patients

A 53-year-old male, with moderate intellectual disability and unspecified psychosis on treatment with risperidone 4,5 mg/24 h, paroxetine 20 mg/24 h and topiramate 150 mg/24 h without previous non-psychiatric medical record, was referred to our consultation-liaison psychiatry unit for medication adjustment. He was on treatment with LPV/r 400/100 mg/12 h, hydroxychloroquine 400 mg/24 h and azithromycin 250 mg/24 h due to COVID-19 pneumonia. The dose of topiramate was maintained while risperidone was decreased to 3 mg/24 h, and paroxetine to 10 mg/24 h due to moderate risk of interaction with COVID-19 treatments (Liverpool Drug Interactions Group, 2020). In the first days the patient presented with behavioral disturbances and was treated with olanzapine 5 mg if needed. When LPV/r was discontinued, the dose of risperidone and paroxetine were increased to usual doses, and olanzapine discontinued. No QTc prolongation or other side effects due to interactions were present.

A 61-year-old male, with delusional disorder and personality disorder on treatment with olanzapine 15 mg/24 h, mirtazapine 15 mg/24 h and valproate 1000 mg/24 h, without previous non-psychiatric medical record, was referred to our consultation-liaison psychiatry unit for medication adjustment. He was receiving treatment with LPV/r 400/100 mg/12 h, hydroxychloroquine 400 mg/24 h, and azithromycin 250 mg/24 h due to COVID-19 pneumonia. The initial valproate level was 45 μg/mL within the therapeutic range (40.0–100.0 μg/mL) without adjustment of LPV/r dose, which can be increased around 40% with valproate (Liverpool Drug Interactions Group, 2020). The psychopharmacological treatment was maintained since the patient showed no acute psychiatric symptoms and the risk for major pharmacological interactions was low. Afterwards, meropenem and metronidazole were added due to bacteremia. After antibiotics were commenced there was a significant reduction in valproate levels to 10 μg/mL (below therapeutic range), likely due to an interaction with meropenem. However, the valproate dose was maintained due to the short treatment duration of meropenem (5 days). When meropenem was discontinued the levels of valproate returned to the therapeutic range. During his admission the patient remained well from a psychiatric perspective with no obvious symptoms, QTc prolongation or side-effects related to his medications.

Non-SMI with depressive and/or anxiety symptoms

A 68-year-old woman, with depressive disorder, generalized anxiety disorder, and history of lymphoma, was referred to our consultation-liaison psychiatry unit for medication adjustment. She had been on venlafaxine 225 mg/24 h for more than 5 years, and vortioxetine 10 mg/24 h and trazodone 50 mg/24 h had been added 5 months ago due to worsening of depressive symptoms. The first day of admission, LPV/r 400/100 mg/12 h, hydroxychloroquine 400 mg/24 h and azithromycin 250 mg/24 h were started due to COVID-19 pneumonia, and only venlafaxine 225 mg/24 h was maintained. On the second day of admission, venlafaxine was interrupted due to mild QTc prolongation (443 ms), and our consultation-liaison psychiatry unit was consulted the following day. Since her admission, the patient presented with insomnia, worsening of anxiety and mood lability. Psychological support was provided and venlafaxine 150 mg/24 h, vortioxetine 10 mg/24 h and trazodone 50 mg/24 h were reintroduced progressively with ECG monitoring. Following these interventions there was a rapid improvement in the patient's mood and sleep without any QTc prolongation or other side-effects during her admission.

Discussion

The combination of the most common first-line COVID-19

Table 1
Clinical risk of interaction of psychopharmacological drugs with COVID-19 treatments.

Pharmacological group	Clinical risk of interaction[a]		
	High	Moderate	Low/absent
Antidepressants	–	Agomelatine, amitriptyline, bupropion, citalopram, clomipramine, escitalopram, imipramine, mianserin, mirtazapine, paroxetine, nortriptyline, reboxetine, trazodone, venlafaxine	Duloxetine, fluvoxamine, fluoxetine, phenelzine, sertraline, vortioxetine
Antipsychotics	Quetiapine, pimozide, ziprasidone,	Aripiprazole, asenapine, cariprazine, chlorpromazine, clozapine, fluphenazine, haloperidol, levomepromazine, lurasidone, perphenazine, risperidone, sulpiride, thioridazine, tiapride, zotepine, zuclopenthixol	Amisulpiride, olanzapine, paliperidone, loxapine[b]
Mood stabilizers	Carbamazepine	Lithium, lamotrigine, oxcarbazepine, valproate	Gabapentine, pregabaline, topiramate, zonisamide
Anxiolytics/hypnotics	Hydroxyzine, midazolam	Alprazolam, bromazepam, clonazepam, clorazepate, chlordiazepoxide, buspirone, clobazam, diazepam, flunitrazepam, flurazepam, triazolam, zolpidem, zoplicone	Lorazepam, lormetazepam, oxazepam, temazepam
Addiction treatments	Disulfiram[c], nalmefene[d]	Methadone	Buprenorphine/naloxone, baclofen, disulfiram[c], naltrexone

Abbreviations: LPV/r: lopinavir/ritonavir.
[a] The most common COVID-19 treatments (azithromycin, hydroxychloroquine, LPV/r and tocilizumab) have been considered to assess the clinical risk of interaction with psychopharmacological drugs.
[b] Inhaled loxapine may be useful, especially in case of pre-agitation, but it may be used only when COVID-19 respiratory symptoms are absent or mild.
[c] LPV/r oral solution contains 42% alcohol. Disulfiram may induce a toxic reaction due to aldehyde dehydrogenase inhibition. No such interaction is expected with LPV/r tablets.
[d] Due to lack of information on nalmefene interaction risk we recommend its suspension during COVID-19 treatment.

experimental treatments (azithromycin, hydroxychloroquine, LPV/r and tocilizumab) include several serious interactions which would normally contraindicate their co-administration. These include cardiotoxicity (all of them increase the QT interval, requiring ECG monitoring) and pharmacokinetic interactions (azithromycin may increase the levels of ritonavir) ("Drug Interactions Checker – Medscape Drug Reference Database," 2020; Liverpool Drug Interactions Group, 2020). However, these three drugs are usually co-administered in inpatients with moderate-to-severe COVID-19 pneumonia because the benefits of recovery, due to a multitarget synergistic effect, clearly outweigh the risks of interactions in most patients (McCreary and Pogue, 2020). Clinical decisions are generally made on a benefit:risk ratio framework, which will guide our recommendations. The clinical risk of interaction of specific psychopharmacological drugs with COVID-19 treatments is exposed in Table 1.

Regarding the drug-related risk for cardiotoxicity, drug-associated QTc interval prolongation by itself is insufficient to predict TdP and sudden deaths. For instance, haloperidol is rarely associated with QTc prolongation but nonetheless there are reports of its association with TdP and, ziprasidone is usually associated with QTc prolongation but there are no cases of TdP (Hasnain and Vieweg, 2014). Therefore, the inherent cardiac risk of each drug (independently of their QTc prolongation) as well as other cardiac risk factors, such as older-age, cardiovascular status, comorbid conditions, electrolyte disturbances and genetics, are usually required in addition to QTc prolongation for TdP to occur. In most cases, however, TdP does not occur until the QTc is over 660 ms. For this reason, psychopharmacological treatments with risk of cardiotoxic interactions should include an ECG evaluation with special attention to QTc interval, but always considering the presence of drug-inherent cardiac risks and co-existing cardiac risk factors (Shah et al., 2014).

Several clinical criteria need to be considered for a precise characterization to make a clinical decision on the pharmacological management of COVID-19 inpatients with psychiatric disorders, which are summarized in Table 2.

Once the previous clinical criteria have been considered in each individual, we propose the following personalized recommendations for each presented real-case scenario (Fig. 1):

As a general recommendation, despite pharmacokinetic interactions, especially with LPV/r (CYP3A4 inhibitors), but also with hydroxychloroquine (CYP2D6 inhibitor), the changes in drug concentration do not seem to have a concerning magnitude (with the exceptions of quetiapine, lamotrigine, bupropion or methadone, with more than 50% of concentration change), if given with LPV/r. Therefore, if the usual doses of psychotropic drugs taken by the patient are in the low-to-median recommended levels, we do not suggest a dose change during COVID-19 drugs co-administration, but would advise ECG, clinical monitoring of adverse effects (i.e. extrapyramidal effects with antipsychotics, sedation with benzodiazepines, adrenergic or serotoninergic reactions with antidepressants) and monitoring of drug levels (if possible and/or required). In cases where prescribed doses are higher or above recommended levels, we recommend a reduction of the usual dose and monitoring. Needless to say, personalized recommendations are warranted in every case and patients with mental health disorders, even with complex psychopharmacological treatments, should not be excluded from receiving COVID-19 treatments.

In case of agitated delirium (A), the symptomatic treatment should be prioritized by using the less-contraindicated and more effective psychopharmacological options and medical comorbidities and treatments should be considered. Olanzapine is recommended as first-line antipsychotic due to its sedative capacity, high effectiveness and low risk of interaction with COVID-19 treatments and quetiapine should be avoided due to severe interaction with LPV/r. However, other antipsychotics can be used and, especially in critical patients in intensive care units, intravenous haloperidol with strict ECG control starting at low doses can be considered as in the first reported case. Furthermore, the neuro-invasive potential of SARS-CoV-2 may be associated with centrally mediated respiratory failure via direct infection of the pontine and medullary respiratory centers (Li et al., 2020). Therefore, respiratory depression effects of antipsychotics and benzodiazepines need to be monitored, especially in patients with delirium (Kotfis et al., 2020).

In case of SMI (B), the level of impairment due to the disorder and if a current episode is present (severity, level of judgment and insight) should be evaluated and the psychopharmacological treatments should be prioritized (essential to complementary) evaluating the risk of relapse if withdrawal. Essential treatments (at lowest therapeutic dose if interaction and with ECG control if cardiotoxicity) should be maintained. In this regard, in the second case, the doses of risperidone and paroxetine were decreased due to low risk of psychotic decompensation and high probability of pharmacological interaction. In the third case, the risk of interaction not only with COVID-19 treatments but with antibiotics should not be disregarded, as some patients may require them due to bacterial coinfection. Meropenem can decrease valproate levels, due to decreased intestinal absorption or increased renal clearance of valproate ("Drug Interactions Checker – Medscape Drug

Table 2
Clinical criteria for a personalized approach on COVID-19 inpatients with psychiatric disorders.

Psychiatric considerations	Type of psychiatric disorder and impairment	Severe mental illness (SMI) (schizophrenia, bipolar disorder, schizoaffective disorder) Non-SMI (anxiety, obsessive-compulsive disorder) Level of impairment due to disorder
	Current episode	Severity of episode Level of judgment (impaired in psychosis or delirium) Level of insight
	Evolutive course	Recent clinical stability Risk of relapse (if medication withdrawal, COVID-19 distress) Number of episodes, severity of relapses, durations of stability Stage of illness (prodromal-mid-chronic): tendency to deteriorating course in SMI.
	Current psychopharmacological treatment and history	Mono or polytherapy Prioritize essential-to-complementary treatments: Essential: Antipsychotic in schizophrenia, mood stabilizer in bipolar disorder, Antidepressant in depression Complementary: hypnotics, anxiolytics Consider latency of effect and pharmacokinetics if withdrawal: Rapid cholinergic rebound with clozapine Rapid withdrawal effect with venlafaxine or paroxetine Gradual loss of antidepressant effects LAI antipsychotics: 2–20 weeks half-life Consider interactions with COVID-19 medications (Fig. 1)
Non-psychiatric considerations	Patient's general characteristics	Age (>65 worse prognosis) Global functioning and dependence (Barthel index: mobility, dressing, grooming, feeding) Pregnancy (stage and teratogenic risk) Social and family situation (support)
	Severity of COVID-19	Mild upper respiratory symptoms Moderate pneumonia Severe: acute respiratory distress syndrome (ARDS), likely or requiring ICU
	Medical comorbidities and treatments	Pluripathological and/or fragile patient End-stage or terminal chronic disease (renal insufficiency, advanced diabetes or cancer, etc.) Cardiopathy (higher risk of QT prolongation) Hepatic insufficiency (higher risk of pharmacokinetic interactions) Arterial hypertension (especially with ACE inhibitors), worse prognosis Non-psychiatric associated treatments (especially if cardiotoxic or with pharmacokinetic interactions)
	COVID-19 treatments	Mild-moderate: hydroxychloroquine + azithromycin Moderate-severe: LPV/rv + hydroxychloroquine + azithromycin (± antibiotics[a]) Severe-critical: (LPV/r + hydroxychloroquine + azithromycin) + other anti-inflammatories[b] (± antibiotics[a])

Abbreviations: ICU: intensive care unit; LAI: Long-acting injectable; LPV/r: lopinavir/ritonavir.
[a] If pneumococcus pneumonia is suspected (i.e. ceftriaxone, teicoplanine, meropenem).
[b] Corticosteroids, IL-6 inhibitors (tocilizumab, sarilumab, siltuximab), IL-1 inhibitors (anakinra), JAK inhibitors (baricitinib), colchicine.

Reference Database," 2020). This should be considered especially in patients with bipolar disorder and high risk of relapse. However, when valproate is not an essential treatment, as in the third case, it may be enough with valproate level monitoring.

In case of Non-SMI with depressive and/or anxiety symptoms (C), psychological support should be provided, relevant symptoms identified (insomnia, anxiety, fear, depression, etc.) and consider the patient's preferences regarding treatment strategies. In the fourth case, the antidepressant venlafaxine was reintroduced in a patient with low risk of interaction but high likelihood of discontinuation syndrome. Considering that vortioxetine had a lower risk of interaction than venlafaxine, the dose of vortioxetine was increased while venlafaxine was decreased.

As limitations, it should be highlighted that the recommendations on pharmacological interactions with COVID-19 experimental treatments provide only a limited qualitative approach by contraindicating coadministration, recommending a dose adjustment or close monitoring or exposing unlikelihood of interaction. However, quantitative recommendations are required by clinicians. For instance, methadone, lamotrigine or bupropion concentrations are reduced at ≈50% by coadministration with LPV/r, quetiapine dose should be reduced to 1/6 if co-administered with LPV/r and valproate increases ≈40% the concentration of LPV/r (Liverpool Drug Interactions Group, 2020). The accuracy of quantitative recommendations may enhance clinical precision in the common scenario in which drug co-administration cannot be avoided.

Furthermore, in case of starting a new medication or planning a treatment switch, some antipsychotics including quetiapine, haloperidol, risperidone, ziprasidone or pimozide, mood stabilizers as carbamazepine and tricyclic antidepressants, should be avoided in front of alternative treatments with a more favorable interaction profile with a potential treatment for COVID-19 (see Fig. 1).

In conclusion, patients with mental health disorders with COVID-19 should be managed on a personalized basis considering several clinical criteria (Table 2) and, should not be excluded from receiving COVID-19 treatments. Most antipsychotics and antidepressants, lithium and methadone should include an ECG evaluation with special attention to QTc interval and consider the presence of drug-inherent cardiac risks and co-existing cardiac risk factors. Risks of pharmacological interaction are not absolute and should be contextualized and, antibiotics should not be disregarded for interactions. Psychopharmacological ongoing treatments should be prioritized (essential versus complementary) and most doses should be reduced (25–50% of original dose) if the patient receives LPV/r due to its inhibitory pharmacokinetic effect with some exceptions: quetiapine should be 85% reduced, asenapine, olanzapine, and sertraline should be slightly increased and, lamotrigine, bupropion

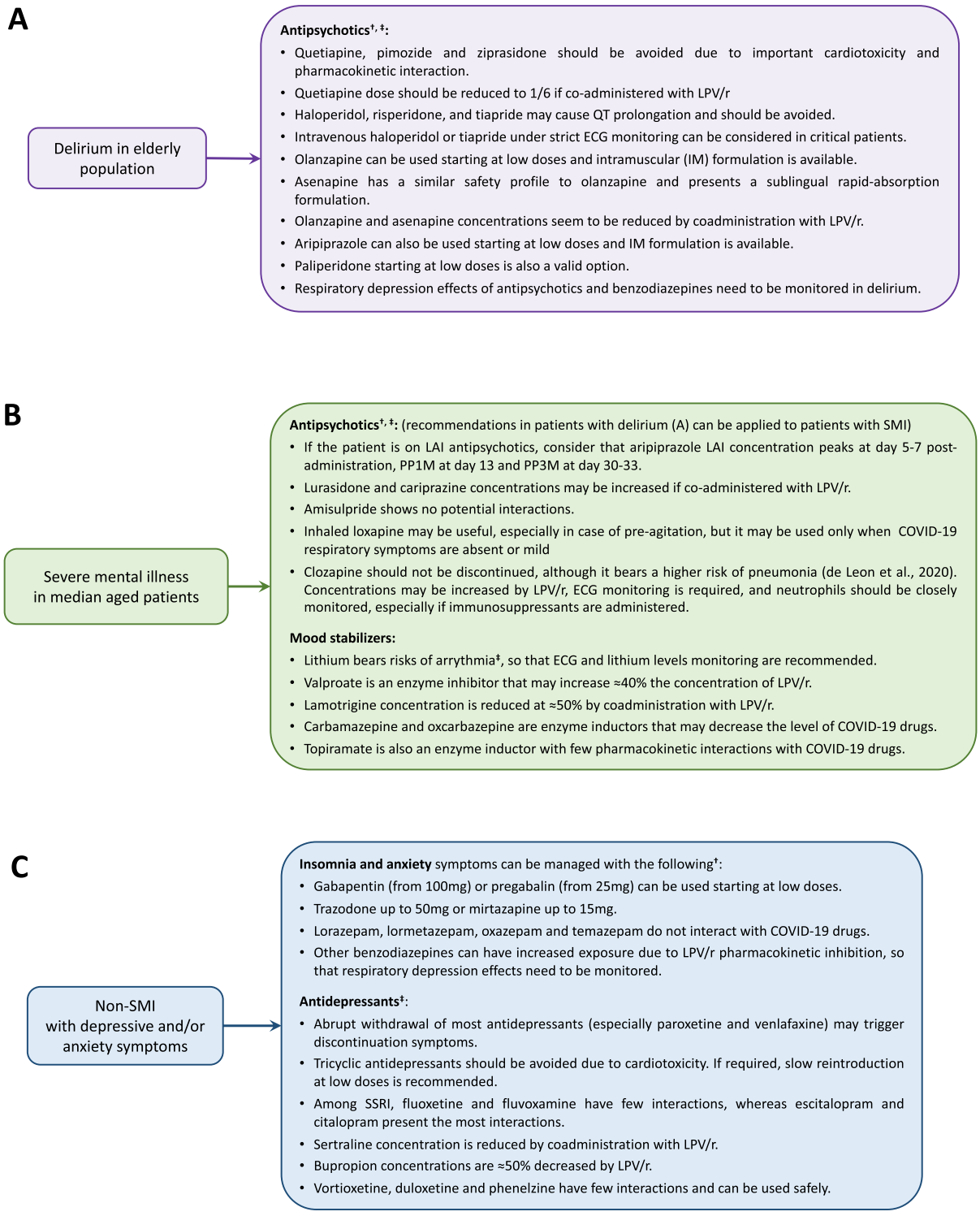

Fig. 1. Personalized treatment recommendations for each presented real-case scenario. (A) Delirium in elderly population. (B) Severe mental illness in median aged patients with few medical comorbidities. (C) Non-SMI with depressive and/or anxiety symptoms.
† Respiratory depression effects of antipsychotics and benzodiazepines need to be monitored, especially in delirium.
‡ Psychopharmacological treatments with risk of cardiotoxic interactions (most antipsychotics and antidepressants, lithium and methadone) should include an ECG evaluation with special attention to QTc interval and consider the presence of drug-inherent cardiac risks and co-existing cardiac risk factors.
Abbreviations: ECG: electrocardiogram; IM: intramuscular; LAI: Long-acting injectable; LPV/r: lopinavir/ritonavir; PP1M: once-monthly LAI paliperidone palmitate; PP3M: once-every-3-months LAI paliperidone palmitate; SMI: severe mental illness; SSRI: Selective serotonin reuptake inhibitors.

and methadone should be around 50% increased. If the psychopharmacological usual doses are in the low-to-median range levels, we do not recommend a dose change during COVID-19 drugs co-administration, but only ECG and clinical monitoring of adverse effects and drug levels if required. Finally, when introducing a psychopharmacological drug with potential interactions, dose titration should be progressive and with ECG monitoring if cardiotoxic interactions are present and, in outpatient consultations, some psychopharmacological

drugs should be avoided in front of alternative treatments that are compatible with a potential treatment for COVID-19.

CRediT authorship contribution statement

G. Anmella: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **N. Arbelo:** Conceptualization, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **G. Fico:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing. **A. Murru:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing. **C.D. Llach:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing. **S. Madero:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing. **S. Gomes-da-Costa:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing. **M.L. Imaz:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing. **H. López-Pelayo:** Conceptualization, Supervision, Validation, Visualization, Writing - review & editing. **E. Vieta:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing - review & editing. **L. Pintor:** Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

Dr. Anmella has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck and Angelini and reports no financial or other relationship relevant to the subject of this article. **Dr. Arbelo** has received CME-related financing and travel grants from Janssen-Cilag and Lundbeck and reports no financial or other relationship relevant to the subject of this article. **Dr. Fico** has received CME-related honoraria, or consulting fees from Janssen-Cilag and Lundbeck. **Dr. Llach** has received CME-related financing and travel grants from Janssen-Cilag and reports no financial or other relationship relevant to the subject of this article. **Dr. Madero** has received travel grants and CME-related honoraria from Janssen-Cilag, Lundbeck, Pfizer and Angelini and reports no financial or other relationship relevant to the subject of this article. **Dr. Gomes-da-Costa** has received CME-related honoraria, or consulting fees from Janssen-Cilag, Lundbeck, Italfarmaco and Angelini and reports no financial or other relationship relevant to the subject of this article. **Dr. López-Pelayo** has received travel grants from the laboratories honoraria and travel grants from Janssen and Lundbeck. None of them has relationship with this research. **Prof. Vieta** has received research support from or served as consultant, adviser or speaker for AB-Biotics, Abbott, Actavis, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sage pharmaceuticals, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Telefónica, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme (ENBREC), and the Stanley Medical Research Institute. All other authors declare no conflict of interests.

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