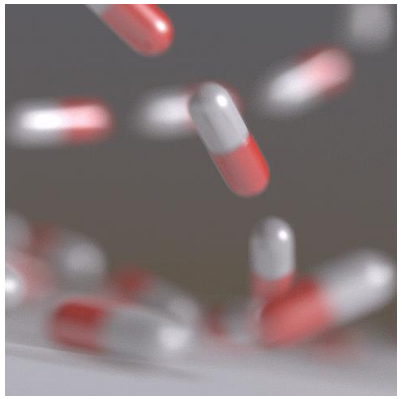
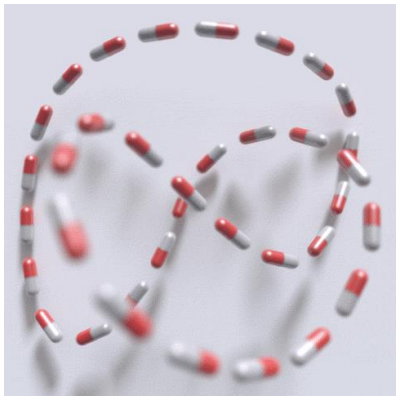
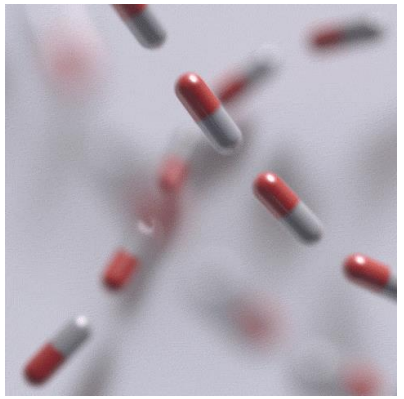
Psychotropic medications and COVID-19

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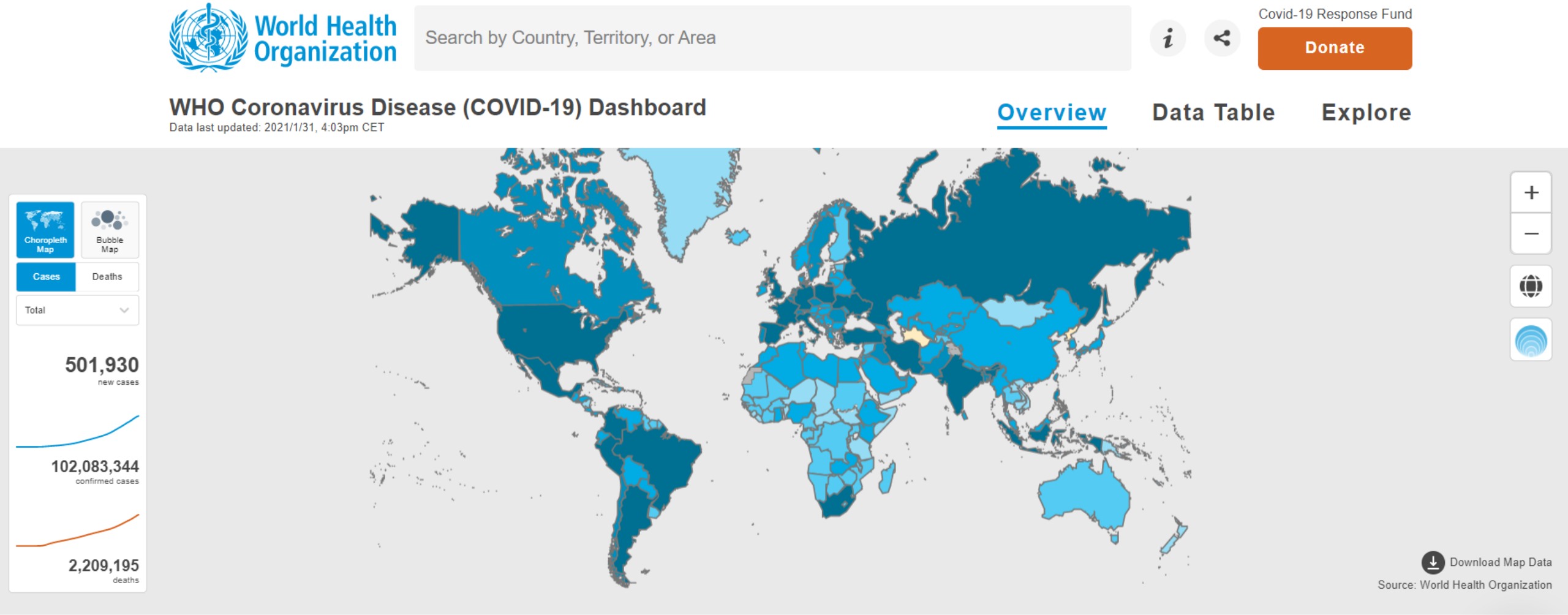
University College Dublin School of Medicine

UCD Child & Adolescent Psychiatry "Covid & Mental Health" Webinar Series

5th February 2021

Global impact of COVID-19



Globally, as of **4:03pm CET, 31 January 2021**, there have been **102.083.344 confirmed cases** of COVID-19, including **2.209.195 deaths**, reported to WHO.

Psychotropic medications and COVID-19

- Psychotropic drugs are commonly used in the general population, including people with higher vulnerability for COVID-19 (i.e. elderly, people with dementia)
- People with COVID-19 often experience psychiatric/neuropsychiatric manifestations because of (a) intense psychological distress; (b) direct neurotropic action of SARS-CoV-2; (c) hyperinflammatory/immunity-mediated damage; (d) anti-COVID-19 medications might trigger/exhacerbate psychiatric symptoms

- Are psychotropic medications associated with an increased vulnerability towards the SARS-CoV-2 infection?
- What is the role of psychotropic medications in managing COVID-related neuropsychiatric manifestations?

COVID-19 prognostic factors

PLOS ONE

OPEN ACCESS

Citation: Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, et al. (2020) Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS ONE 15(11): e0241955. https://doi.org/10.1371/journal.pone.0241955

RESEARCH ARTICLE

Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review

Ariel Izcovich[1]*, Martín Alberto Ragusa[2], Fernando Tortosa[3], María Andrea Lavena Marzio[1], Camila Agnoletti[1], Agustín Bengolea[1], Agustina Ceirano[1], Federico Espinosa[1], Ezequiel Saavedra[1], Verónica Sanguine[4], Alfredo Tassara[1], Candelaria Cid[1], Hugo Norberto Catalano[1], Arnav Agarwal[5], Farid Foroutan[6], Gabriel Rada[7,8,9]

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Risk factors did not include pre-existing diagnosis of **mental disorders** (with the exception of demetia, for which no data were available on the COVID-19 severity) or treatment with **psychotropic drugs**

Risk factors for increased COVID-related **mortality** with HIGH-to-MODERATE certainty (GRADE):

- Any chronic comorbidity (OR 3.3, 95% CI 2.18 to 5)
- Cerebrovascular disease (OR 2.85, 95% CI 2.02 to 4.01)
- Chronic obstructive pulmonary disease (COPD) (OR 2.43, 95% CI 1.88 to 3.14)
- Chronic kidney disease (CKD), (OR 2.27, 95% CI 1.69 to 3.05)
- Coronary heart disease and/or cardiac failure (OR 2.12, 95% CI 1.77 to 2.56)
- Cardiac arrhythmia (OR 2.13, 95% CI 1.72 to 2.65)
- Arterial hypertension (OR, 2.02, 95% CI 1.71 to 2.38)
- Diabetes (OR 1.84, 95% CI 1.61 to 2.1)
- Dementia (OR 1.54, 95% CI 1.31 to 1.81)
- Obesity (OR 1.41, 95% CI 1.15 to 1.74)
- Cancer (OR 1.35, 95% CI 1.17 to 1.55)
- Dyslipidemia (OR 1.26, 95%CI 1.06–1.5).

Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States

QuanQiu Wang[1], Rong Xu[1], Nora D. Volkow[2]

[1]Center for Artificial Intelligence in Drug Discovery, School of Medicine, Case Western Reserve University, Cleveland, OH, USA; [2]National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA

Methods: case-control study using de-identified population-level electronic health records data collected by the IBM Watson Health Explorys from 360 hospitals and 317,000 providers across 50 states in the US, representing 20% of US population

Table 1 Characteristics of the sample

	Study population	With mental disorder (lifetime)	With mental disorder (recent)	With COVID-19	With COVID-19 + mental disorder (lifetime)	With COVID-19 + mental disorder (recent)
Total	61,783,950	11,240,580	1,307,720	15,110	5,450	3,430

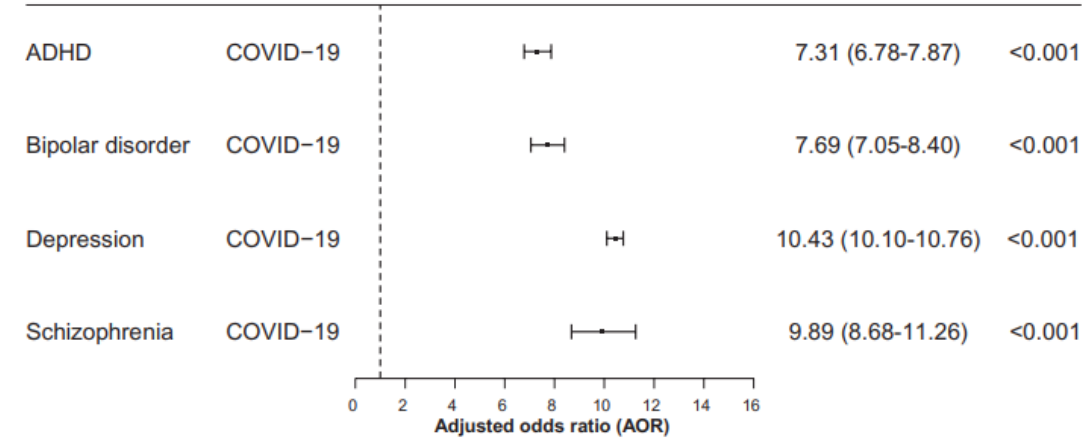


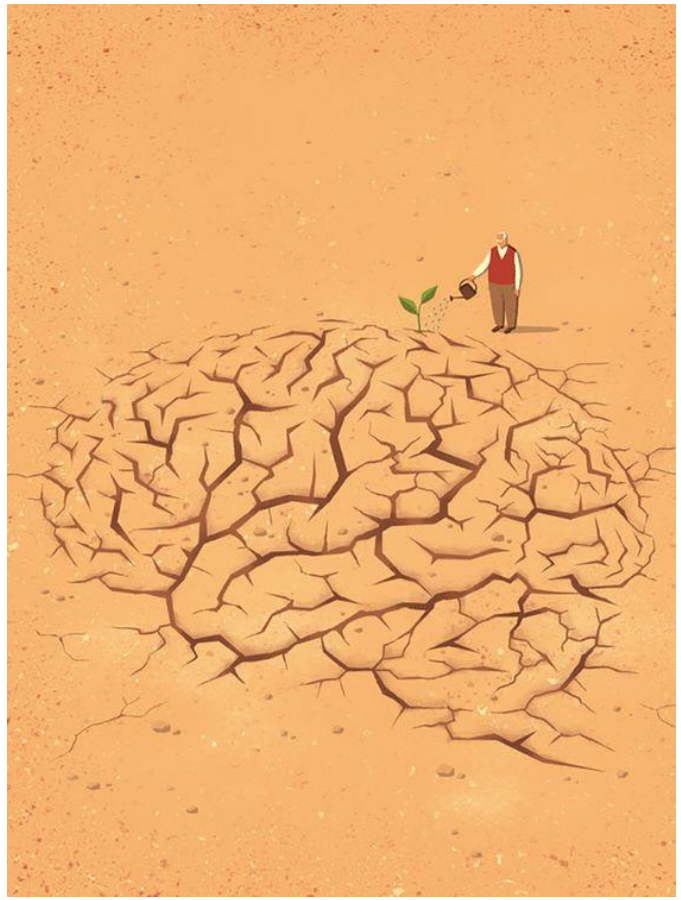
Figure 1 Association of recent (within past year) diagnosis of a mental disorder and COVID-19 infection after adjusting for age, gender and ethnicity. ADHD – attention-deficit/hyperactivity disorder

The trend was similar for patients with a lifetime diagnosis of a mental disorder, but the risk associations were weaker

The death rate for patients with both a recent diagnosis of a mental disorder and COVID-19 infection (8.5%) was higher than for patients with COVID-19 infection but no mental disorder (4.7%) ($p<0.001$)

Available studies did not assess possible associations between the use of **psychotropic drugs**, COVID-19 severity and COVID-related mortality

Managing neuropsychiatric manifestations of COVID-19



Common reasons for psychiatric consultation in people hospitalized for COVID-19

a. Delirium
b. Adjustment disorders
c. Management of psychotropic medications in people without active psychiatric symptoms (e.g. maintenance treatment of depression)
d. Acute/sub-acute exacerbation of pre-existing psychopathology
e. Psychoactive side effects of medical treatments (e.g. chloroquine, interferons, steroids)

Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA

Maxime Taquet, Sierra Luciano, John R Geddes, Paul J Harrison

Methods: We used TriNetX Analytics Network (54 health-care organisations in the USA), which included 62 354 patients diagnosed with COVID-19 (Jan-Aug 2020). We measured the incidence of and hazard ratios (HRs) for psychiatric disorders, dementia, and insomnia, during the first 14 to 90 days after a diagnosis of COVID-19.

	COVID-19	Influenza in matched cohort (n=26 497)		Other respiratory tract infection in matched cohort (n=44 775)		Skin infection in matched cohort (n=38 977)		Cholelithiasis in matched cohort (n=19 733)		Urolithiasis in matched cohort (n=28 827)		Fracture in matched cohort (n=37 841)	
	% (95% CI)	% (95% CI)	p value	% (95% CI)	p value	% (95% CI)	p value	% (95% CI)	p value	% (95% CI)	p value	% (95% CI)	p value
Psychiatric illness	5·8 (5·2–6·4)	2·8 (2·5–3·1)	<0·0001	3·4 (3·1–3·7)	<0·0001	3·3 (3–3·7)	<0·0001	3·2 (2·8–3·7)	<0·0001	2·5 (2·2–2·8)	<0·0001	2·5 (2·2–2·7)	<0·0001
Psychotic disorder	0·1 (0·08–0·2)	0·04 (0·01–0·10)	0·019	0·1 (0·06–0·16)	0·23	0·15 (0·096–0·24)	0·83	0·11 (0·054–0·24)	0·21	0·044 (0·016–0·12)	0·0051	0·16 (0·11–0·24)	0·77
Mood disorder	2·0 (1·7–2·4)	1·1 (0·9–1·3)	<0·0001	1·5 (1·3–1·7)	0·0054	1·7 (1·5–1·9)	0·55	1·6 (1·3–1·9)	0·14	1·2 (1–1·4)	0·00011	1·4 (1·2–1·6)	0·0050
Anxiety disorder	4·7 (4·2–5·3)	2·2 (1·9–2·5)	<0·0001	2·5 (2·2–2·8)	<0·0001	2·4 (2·1–2·7)	<0·0001	2·6 (2·2–3)	<0·0001	1·8 (1·6–2·1)	<0·0001	1·6 (1·4–1·8)	<0·0001
Insomnia	1·9 (1·6–2·2)	0·6 (0·5–0·8)	<0·0001	0·8 (0·7–1·0)	<0·0001	0·89 (0·73–1·1)	<0·0001	1·1 (0·88–1·4)	<0·0001	0·57 (0·43–0·74)	<0·0001	0·7 (0·57–0·85)	<0·0001
Dementia in all participants	0·44 (0·33–0·60)	0·11 (0·06–0·20)	0·00044	0·25 (0·18–0·35)	0·00063	0·28 (0·20–0·39)	0·13	0·24 (0·14–0·38)	<0·0001	0·16 (0·09–0·28)	<0·0001	0·34 (0·25–0·44)	0·14
Dementia (among those ≥65 years)	1·6 (1·2–2·1)	0·66 (0·41–1·1)	0·0043	0·84 (0·61–1·1)	0·00071	0·70 (0·49–1·0)	0·00069	0·58 (0·36–0·94)	<0·0001	0·60 (0·38–0·95)	<0·0001	0·94 (0·68–1·3)	0·0036

p values obtained using a log-rank test. A breakdown of the results for different diagnoses of the anxiety disorders and mood disorders categories is provided in the appendix (pp 26–27).

Table 2: **Estimated incidence of first psychiatric diagnoses during the first 14 to 90 days after a diagnosis of COVID-19 compared with other health events**

Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic

Jonathan P Rogers, Edward Chesney*, Dominic Oliver, Thomas A Pollak, Philip McGuire, Paolo Fusar-Poli, Michael S Zandi, Glyn Lewis, Anthony S David*

Methods: systematic review of case reports, case series, cross-sectional studies, cohort studies including individuals with suspected or laboratory-confirmed coronavirus infection (SARS coronavirus, MERS coronavirus, or SARS coronavirus 2). Also databases of unpublished paper (still to undergo peer-review) were searched (i.e. medRxiv, bioRxiv, PsyArXiv)

	Acute				Post-illness			
	Studies	Cases	Sample size	Prevalence (95% CI)	Studies	Cases	Sample size	Prevalence (95% CI)
Any	1	17	27	63·0% (43·8–80·4)	1	0	4	0 (0·0–39·1)
Insomnia	2	54	129	41·9% (22·5–50·5)	4	34	280	12·1% (8·6–16·3)
Anxiety	2	46	129	35·7% (27·6–44·2)	2	21	171	12·3% (7·7–17·7)
Impaired concentration or attention	1	39	102	38·2% (29·0–47·9)	2	34	171	19·9% (14·2–26·2)
Impaired memory	2	44	129	34·1% (26·2–42·5)	3	44	233	18·9% (14·1–24·2)
Depressed mood	2	42	129	32·6% (24·7–40·9)	5	35	332	10·5% (7·5–14·1)
Confusion	2	36	129	27·9% (20·5–36·0)	1	1	621	0·2% (0·0–0·7)
Emotional lability	1	30	102	29·4% (0·4–7·3)	1	24	102	23·5% (15·8–32·3)
Altered consciousness	1	17	82	20·7% (12·6–30·3)	NA	NA	NA	NA
Pressured speech	1	21	102	20·6% (13·3–29·0)	1	12	102	11·8% (6·1–18·8)
Euphoria	1	8	102	7·8% (3·3–14·0)	1	11	102	10·8% (5·4–17·6)
Aggression	1	2	27	7·4% (0·2–21·1)	1	1	102	1·0% (0·0–4·2)
Irritability	1	5	102	4·9% (1·4–10·1)	3	28	218	12·8% (8·7–17·6)
Auditory hallucinations	2	6	129	4·7% (1·6–9·1)	1	1	102	1·0% (0·0–4·2)
Persecutory ideas	1	4	102	3·9% (0·9–8·7)	1	2	102	2·0% (0·0–5·8)
Visual hallucinations	1	2	102	2·0% (0·0–5·8)	NA	NA	NA	NA
Suicidality	1	2	102	2·0% (0·0–5·8)	1	0	102	0 (0·0–1·7)
Fatigue	NA	NA	NA	NA	4	61	316	19·3% (15·1–23·9)
Frequent recall of traumatic memories	NA	NA	NA	NA	1	55	181	30·4% (23·9–37·3)
Sleep disorder	NA	NA	NA	NA	1	14	14	100% (88·0–100·0)
Psychotic symptoms (unspecified)	NA	NA	NA	NA	1	4	90	4·4% (1·0–9·9)
Self-harm	NA	NA	NA	NA	1	1	102	1·0% (0·0–4·2)

NA=not available.

Table 2: **Prevalence of psychiatric and neuropsychiatric signs and symptoms reported by acute and post-illness studies that used systematic assessments**[39,43,46,48,54,73,83,86,92,93]

Medical treatment of COVID-19

COVID-NMA
COVID-19 OPEN LIVING EVIDENCE SYNTHESIS TO INFORM DECISION

The COVID-NMA initiative

A living mapping and living systematic review of Covid-19 trials

https://covid-nma.com/

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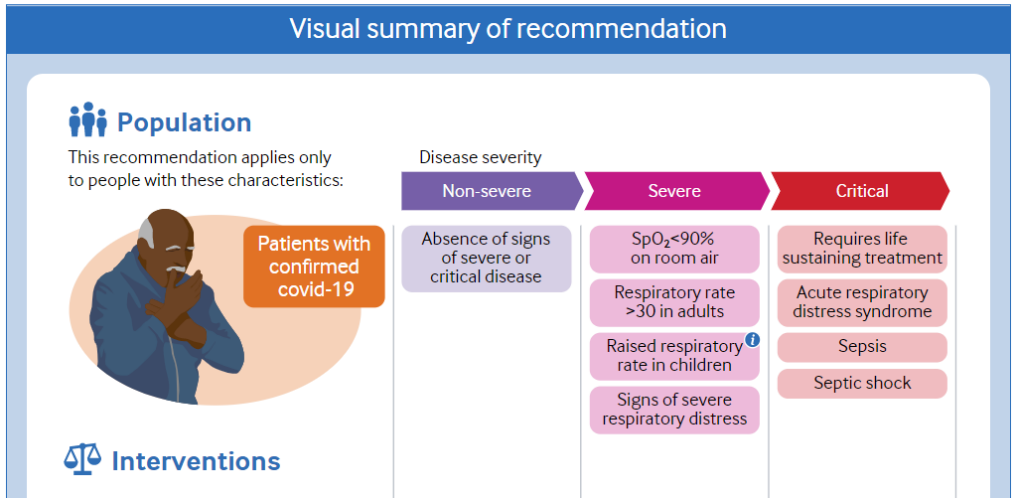
Practice » Rapid Recommendations

A living WHO guideline on drugs for covid-19

BMJ 2020 ; 370 doi: https://doi.org/10.1136/bmj.m3379 (Published 04 September 2020)
Cite this as: *BMJ* 2020;370:m3379



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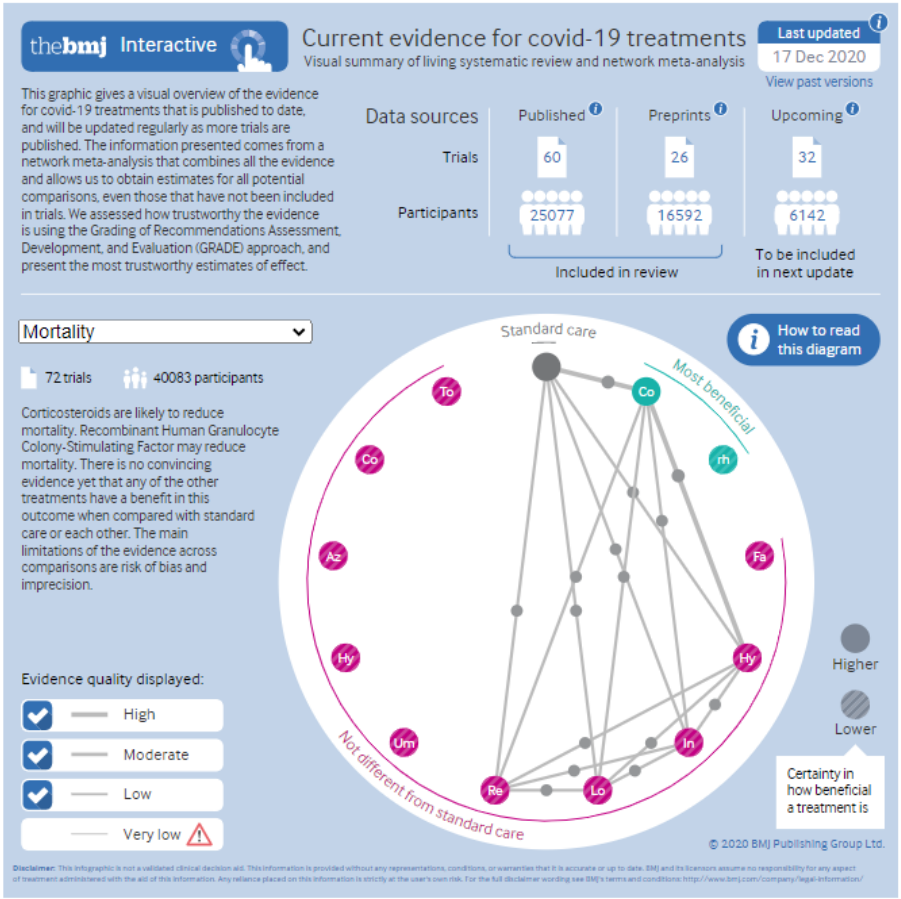
Research

Drug treatments for covid-19: living systematic review and network meta-analysis

BMJ 2020 ; 370 doi: https://doi.org/10.1136/bmj.m2980 (Published 30 July 2020)
Cite this as: *BMJ* 2020;370:m2980

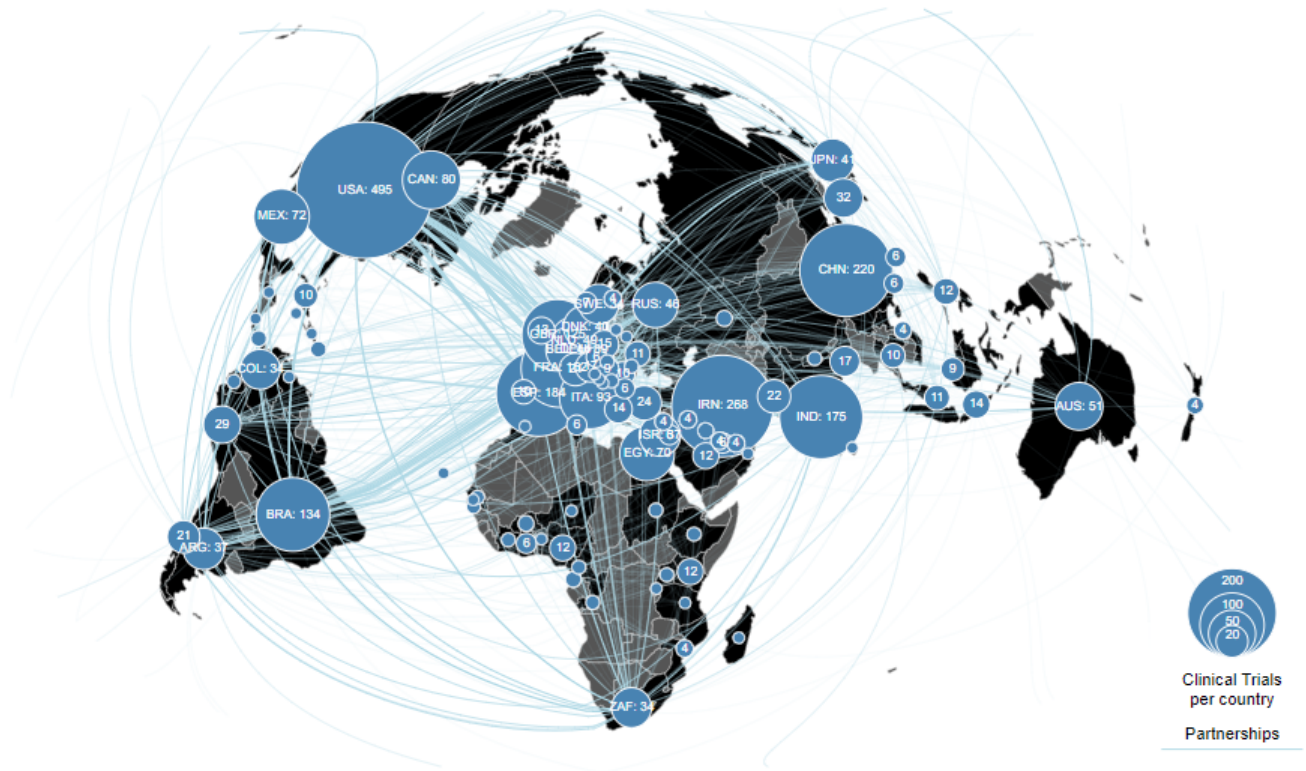


As of **January 29, 2021** the Covid-19 - living NMA initiative collected **2497** studies of treatments from the ICTRP. **1378** of these trials are recruiting patients.

▼ User Guide

- To see how to explore the mapping, check our tutorial.
- Make your browser window as **wide** as possible for a 2-column display.
- Click on the **map** or any of the **graphs** to create filters on the data.
- All the **filters** are applied jointly, refining your selection.
- Click **Reset all** to remove the filters.
- Click on the **arrows** to open or close any section.
- *For any questions or remarks, please contact us.*

▼ Map



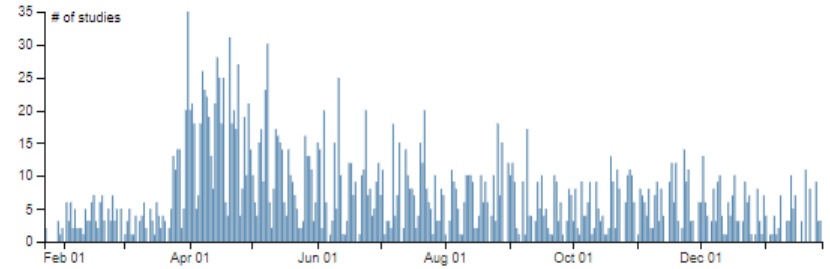
Filters

All trials selected (**2497**) | Reset all

Search...

Ex: Interferon, antiviral, Spain, Assistance Publique, EUCTR2020…

▼ Registration date



To filter by Registration dates, click and drag to create a range.

▼ Recruitment status

- ☑ Recruiting (1,378 studies)
- ☑ Not recruiting (911 studies)
- ☑ Completed (159 studies)
- ☑ Terminated (31 studies)
- ☑ Withdrawn (11 studies)
- ☑ Suspended (7 studies)

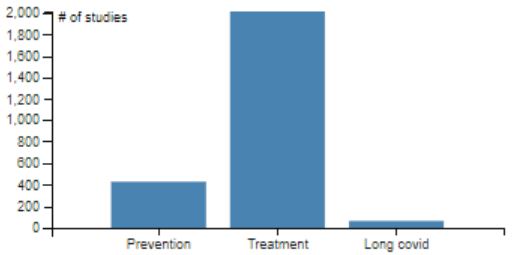
▼ Publication status

- ☑ Not published (2,331 studies)
- ☑ Published (166 studies)

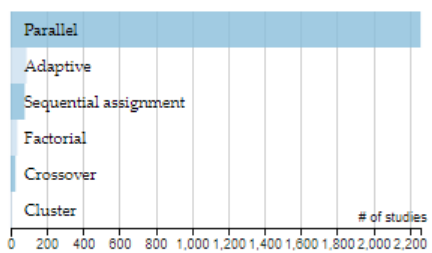
▼ Registry status

- ☑ No results posted (2,480 studies)
- ☑ Results posted in the registry (17 studies)

▼ Study aim



▼ Design



Medical treatments for COVID-19

Candidate treatments

a. Antipyretics; NSAID; opioids; corticosteroids (e.g. dexamethasone)

b. Antivirals: lopinavir/ritonavir, darunavir/cobicistat, other HIV protease inhibitors; remdesivir; ivermectin

c. Antimalarials (chloroquine/hydroxychloroquine)

d. Antibiotics (e.g. azithromycin)

e. Immunomodulators: IL-1 inhibitors (anakinra); IL-6 inhibitors (sarilumab, tocilizumab, siltuximab); interferons (alpha and beta)

f. Venous Thromboembolism Prophylaxis (i.e. low molecular weight heparin)

g. Blood-derived products: convalescent plasma; SARS-CoV-2 immunoglobulins; mesenchymal stem cells; Non-SARS-CoV-2-specific intravenous immunoglobulin

https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/

Ostuzzi et al. BMC Medicine (2020) 18:215
https://doi.org/10.1186/s12916-020-01685-9

BMC Medicine

RESEARCH ARTICLE Open Access

Safety of psychotropic medications in people with COVID-19: evidence review and practical recommendations

Giovanni Ostuzzi[1*], Davide Papola[1], Chiara Gastaldon[1], Georgios Schoretsanitis[2], Federico Bertolini[1], Francesco Amaddeo[1], Alessandro Cuomo[3], Robin Emsley[4], Andrea Fagiolini[3], Giuseppe Imperadore[5], Taishiro Kishimoto[6], Giulia Michencigh[1], Michela Nosé[1], Marianna Purgato[1], Dursun Serdar[7], Brendon Stubbs[8,9], David Taylor[10], Graham Thornicroft[11], Philip B. Ward[12], Christoph Hiemke[13], Christoph U. Correll[2,14,15] and Corrado Barbui[1]

- We followed the process of the World Health Organization (WHO) Rapid Advice Guidelines in the context of a public health emergency
- A multi-disciplinary international working group was established *ad hoc*
- Priority areas regarding the safety of psychotropic medications in people with COVID-19 were defined: (a) drug–drug interactions, (b) respiratory risk, (c) cardiovascular risk, (d) risk of infections, (e) risk of coagulation abnormalities, and (f) risk of delirium.
- We searched for the most updated systematic reviews and meta-analyses including the general population or, if available, people with medical conditions or vulnerabilities similar to those of COVID-19 (e.g. respiratory/cardiovascular diseases, elderly). Quality of studies assessed with the AMSTAR-2.

Drug-drug interactions

Table 2 Clinical risk and actions recommended for selected drug–drug interactions between psychotropic and medical treatments for COVID-19

	Lopinavir/ Ritonavir	*Darunavir/ Cobicistat*	*Remdesivir*	*Chloroquine*	*Hydroxychloroquine*	*Azithromycin*	*Tocilizumab*	*Low-molecular-weight heparin*
Amitriptyline	🟧	🟥	🟨	🟧	🟧	🟧	🟩	🟩
Clomipramine	🟧	🟧	🟨	🟧	🟧	🟨	🟩	🟩
Citalopram	🟧	🟨	🟨	🟥	🟥	🟥	🟩	🟨
Escitalopram	🟧	🟨	🟨	🟥	🟥	🟥	🟩	🟨
Sertraline	🟧	🟧	🟨	🟩	🟩	🟩	🟩	🟨
Paroxetine	🟥	🟥	🟨	🟧	🟧	🟨	🟩	🟨
Fluoxetine	🟥	🟨	🟨	🟨	🟩	🟧	🟩	🟨
Fluvoxamine	🟨	🟨	🟨	🟨	🟨	🟨	🟩	🟨
Venlafaxine	🟧	🟧	🟨	🟧	🟧	🟧	🟩	🟨
Haloperidol	🟧	🟨	🟨	🟥	🟥	🟨	🟩	🟩
Chlorpromazine	🟧	🟩	🟩	🟧	🟧	🟨	🟩	🟩
Clozapine	🟧	🟨	🟨	🟧	🟧	🟧	🟩	🟩
Risperidone	🟥	🟥	🟨	🟧	🟧	🟨	🟩	🟩
Paliperidone	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Olanzapine	🟧	🟨	🟨	🟧	🟧	🟧	🟩	🟩
Quetiapine	🟥	🟥	🟩	🟨	🟨	🟧	🟩	🟩
Aripiprazole	🟧	🟧	🟨	🟨	🟩	🟩	🟩	🟩
Carbamazepine	🟥	🟥	🟩	🟧	🟨	🟨	🟩	🟩
Lithium	🟨	🟩	🟩	🟨	🟨	🟩	🟩	🟩
Sodium valproate	🟧	🟩	🟩	🟩	🟩	🟨	🟩	🟩
Alprazolam	🟥	🟥	🟩	🟩	🟩	🟩	🟩	🟩
Lorazepam	🟨	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Midazolam	🟥	🟥	🟩	🟩	🟩	🟨	🟩	🟩
Diazepam	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟨
Clonazepam	🟧	🟥	🟩	🟩	🟩	🟩	🟩	🟩

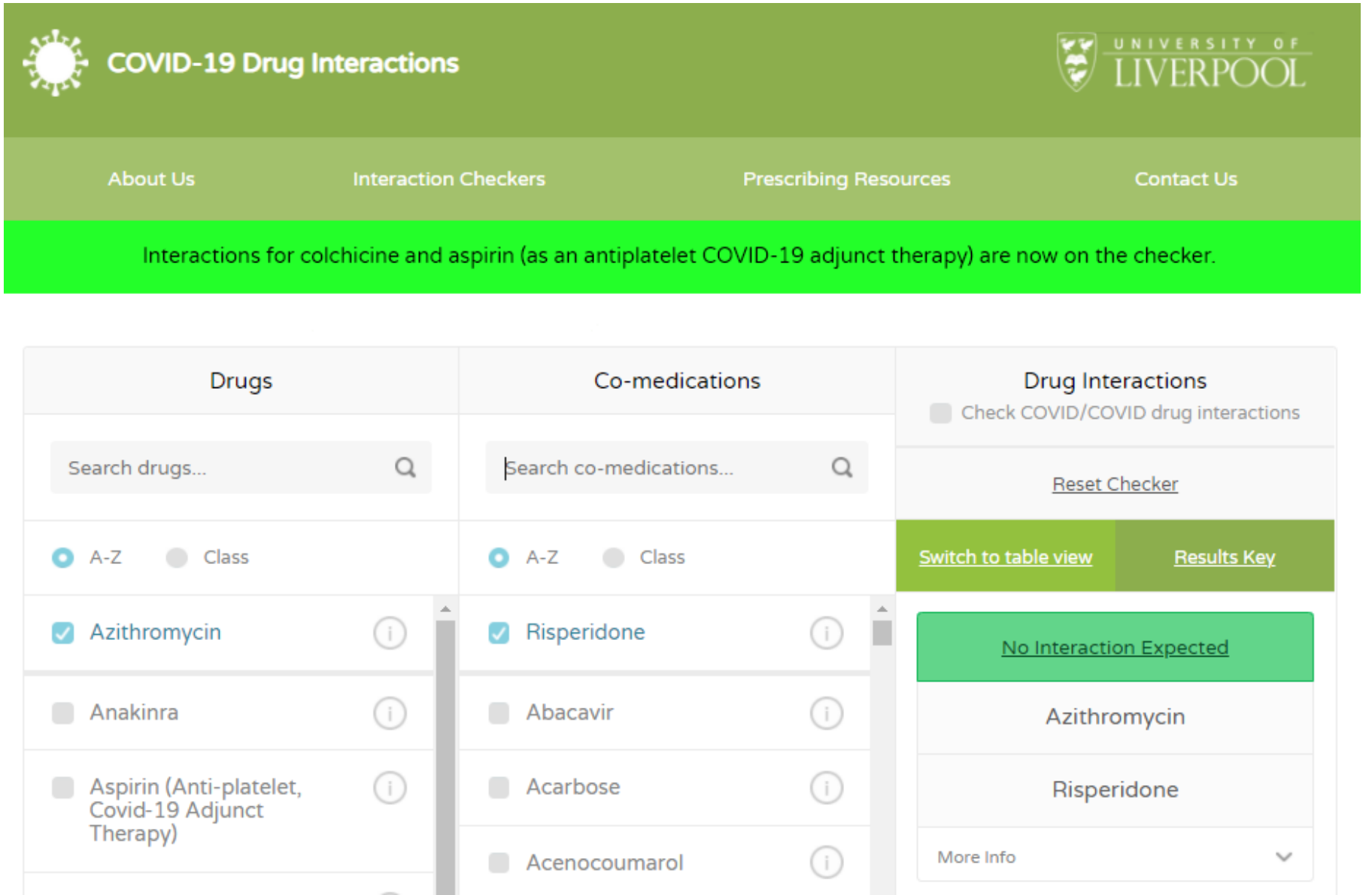
🟥 High risk: the combination should be avoided if possible

🟧 Moderate risk: dose adjustments, psychotropic medication withdrawal, or switch to a safer medication, should be considered

🟨 Low risk: regular monitoring should be provided, and dose adjustments as clinically appropriate

🟩 Very low risk: regular monitoring is suggested

Drug-drug interactions



https://www.covid19-druginteractions.org/checker

Respiratory risk

As a general rule, sedative medications might worsen the respiratory performance, although the evidence is controversial.

BENZODIAZEPINES might impair ventilation centrally (bulbar depression) and periferically (muscular relaxant effect). However, data are lacking and some consider that the use of medications with a short half-life (e.g. lorazepam, oxazepam) «as needed» might be clinically justified.

ANTIPSICOTICS are at higher risk if highly sedative (anti-hystaminergic and anti-cholinergic effect) and used in combination, particularly in people with pre-existing impairment. Extra-pyramidal symptoms and reduced mobility (e.g. rapid sedation of agitated individuals) might worsen the risk or respiratory depression.

ANTIDEPRESSANTS (SSRIs and SNRIs) might worsen COPD-related hospitalization and mortality in older patients taking according to some observational data. However, this is not confirmed by RCTs and guidelines regards them as a safe choice in these patients.

MOOD STABILIZERS have no evidence of risk for respiratory distress.

Wang et al. JAMA psychiatry. 2017;74(3):252-60
Yagmur et al. Pharmacopsychiatry. 2010;43(3):118-9

Cardiovascular risk

People with COVID-19 may have several cardiovascular risk factors, including old age; pre-existing comorbid cardiovascular diseases; use of medical treatments with QTc-prolonging properties, often in combination (e.g., antivirals, chloroquine/hydroxychloroquine, antibiotics, opioids); possible direct cardiotoxic effects of the SARS-CoV-2; electrolyte alterations related to abnormal respiratory gas exchange.

SSRIs are generally considered safe in terms of cardiovascular events, while tricyclic antidepressants **(TCAs)** have been shown to increase the risk of coronary heart disease. TCAs, citalopram and escitalopram and venlafaxine might prolong QTc interval.

ANTIPSYCHOTICS are at risk of QTc prolongation and have been associated with sudden cardiac death, myocardial infarction, and stroke according to large observational evidence.

The risk of arrhythmias is probably very low for **MOOD STABILIZERS** and **BENZODIAZEPINES** (with the possible exception of lithium)

QT-prolonging antibiotics

Macrolides
- Azithromycin
- Clarithromycin
- Erythromycin
  - Desmethyl erythromycin (a metabolite of erythromycin)
- Telithromycin

Quinolones
- Ciprofloxacin
- Gatifloxacin[b]
- Gemifloxacin
- Grepafloxacin[b]
- Levofloxacin
- Moxifloxacin
- Sparfloxacin[b]

Imidazoles/triazoles
- Fluconazole
- Itraconazole
- Ketoconazole
- Voriconazole

Taylor et al. (eds.). Maudsley Prescribing Guidelines 2018
Owens et al. Clinical Infectious Diseases 2006; 43:1603–11

Cardiovascular risk

Risk of QTc prolongation

Antidepressants

Amitriptyline	+++
Bupropion	
Citalopram	+
Clomipramine	+++
Duloxetine	
Escitalopram	+
Fluoxetine	
Fluvoxamine	
Imipramine	++
Mirtazapine	
Nortriptyline	++
Paroxetine	
Sertraline	
Trazodone	+
Venlafaxine	+
Vortioxetine	

Antipsychotics

Aripiprazole	+
Asenapine	+
Brexpiprazole	
Cariprazine	
Chlorpromazine	++
Clotiapine	++
Clozapine	+
Haloperidol	++
Lurasidone	
Olanzapine	+
Paliperidone	+
Pimozide	+++
Promazine	++
Quetiapine	++
Risperidone	+
Tiapride	+

Mood stabilizers

Carbamazepine	
Gabapentin	+
Lamotrigine	
Lithium	+
Pregabalin	+
Sodium Valproate	+

Taylor et al. (eds.). Maudsley Prescribing Guidelines 2018
Stroup et al. World Psychiatry 2018; 17(3)

Risk of infections

Many psychotropic medications have been claimed to interact with the immune system, but the clinical implications are unclear.

ANTIDEPRESSANTS: data are laking on their possible role on systemic infections. TCAs have been associated with blood dyscrasias, including neutropenia.

ANTIPSYCHOTICS have been associated with immunosuppressive proprieties, such as decreased pro-inflammatory cytokine levels, blood dyscrasias, and altered production of antibodies. **Clozapine**-related neutropenia has an overall risk of about 1%. Large observational evidence showed a higher risk of pneumonia for both FGAs and SGAs, and the risk might be particularly high for clozapine. Other contributing mechanisms might include: central cough inhibition, reduced clearance of the airways, impaired chest movements and swallowing due to EPS, sialorrea.

BENZODIAZEPINES might be associated with a higher risk of pneumonia.

MOOD STABILIZERS: Carbamazepine, oxcarbazepine, and, to a lesser extent, sodium valproate, have been associated with an increased risk of neutropenia, while lithium appears to be free from relevant immunological effects.

Szalac et al. Arch Immunol Ther Exp (Warsz) , 67(3), 143-151
Kohler et al. Mol Neurobiol , 55(5), 4195-4206

Risk of coagulation abnormalities

Blood hypercoagulability related to inflammatory endothelial dysfunction has been largely reported in patients with COVID-19, up to life-threatening disseminated intravascular coagulation.

ANTIPSICOTICS have been associated with increased risk of thromboembolism (observational studies), particularly in vulnerable populations with pre-existing risk factors. Differential risk between agents is unclear.

ANTIDEPRESSANTS have been associated with increased risk of severe bleeding at different sites and possibly also thromboembolism (observational studies). The risk of bleeding is arguably higher in vulnerable patients (e.g., old age, pre-existing coagulation abnormalities, anticoagulant therapy, major surgery).

The risk for pro- or anticoagulant effect is likely to be low for **MOOD STABILIZERS** and **BENZODIAZEPINES**.

Risk of delirium

People with COVID-19 have multiple risk factors for delirium → old age, multiple medical comorbidities, pharmacological treatments, dementia, social isolation, ICU admission, mechanical ventilation, direct neurotropic effect of COVID-19 and anti-COVID medications (e.g., antimalarials, antivirals, interferons, corticosteroids)

Furthermore, non-pharmacological strategies (for prevention and treatment) are hardly implemented in COVID-19 settings.

Anticholinergic psychotropics (tricyclic ADs, possibly paroxetine and mirtazapine), **benzodiazepines** (high risk for ICU use of midazolam) and **lithium** might increase the risk.

Reade et al. New England Journal of Medicine. 2014;370(5):444-54
Markowitz et al. Psychiatry (Edgmont). 2008;5(10):29-36
Burry et al. The Cochrane database of systematic reviews. 2019;9(9):Cd011749

Ostuzzi *et al. BMC Medicine* (2020) 18:215
https://doi.org/10.1186/s12916-020-01685-9

BMC Medicine

RESEARCH ARTICLE Open Access

Safety of psychotropic medications in people with COVID-19: evidence review and practical recommendations

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- Most psychotropic medications have possible safety concerns in severely ill people (including COVID-19), however we can hardly describe the **magnitude** of this risk and the risk for **individual** medications
- Recommendations aimed at supporting clinicians in the assessment and management of this risk → in many cases, adjusting the dose of medical or psychotropic medications (or both) is probably a satisfactory and pragmatic safety measure
- Psychotropic drug are generally studied in the general population, and people with medical illness are often excluded
- Limitations: indirectness; WHO Rapid Advice Guidelines approach (no protocol, simplified search process, no formal GRADE assessment, no external review)

Therapeutic Advances in Psychopharmacology Review

Pharmacological treatment of hyperactive delirium in people with COVID-19: rethinking conventional approaches

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- Role of psychopharmacology for treating delirium is debated;
- Guidelines recommend pharmacological treatments only for hyperactive delirium with behavioural issues or in severely distressed patients;
- First-generation antipsychotics (haloperidol or levomepromazine) are recommended to obtain sedation;
- Possible other targets might be: modulation of neurotransmission, neuroinflammation, oxidative stress reduction and cognitive enhancement;
- In people with COVID-19, excessive sedation might impair the respiratory performance, and drug-drug interactions (particularly between QTc-prolonging drugs) are very likely → the use of haloperidol is limited;
- We collected RCTs including people with: (a) delirium in critically ill patients in intensive care units (ICUs); (b) delirium in non-ICU settings; (c) dementia-related agitation or aggressiveness; and (d) psychosis-related agitation or aggressiveness.

Table 1. Clinical elements, evidence of benefit and regulatory information of candidate medications for the treatment of hyperactive delirium in people with COVID-19.

Drugs	Clinical elements				Evidence of benefit				EMA/BNF therapeutic indications			Formulations available				Suggested daily doses
	Sedation	Anti-cholinergic effects	QTc prolongation	COVID-19 drug interactions	DEL ICU	DEL no ICU	DEM	PSY	DEL	DEM	PSY	TAB	DROPS	IM	IV	
ANTIPSYCHOTICS																
Aripiprazole	-	-	+ Ⓦ	++ Ⓦ			■	■		Ⓦ	■	■		■		10–30 mg
Chlorpromazine[a]	+++	++	++ Ⓦ	++ Ⓦ					■	■■ Ⓦ	■	■	■	■	■	25–300 mg (elderly 25–75 mg)
Haloperidol	+	+	++ ⃠	++ ⃠				■	■	■■ Ⓦ	■	■	■	■	■	1–10 mg (elderly 0.5–5 mg)
Olanzapine	++	+	+ Ⓦ	+ Ⓦ				■		Ⓦ		■		■		2.5–5 mg
Paliperidone	+	+	+ Ⓦ	+ Ⓦ						Ⓦ		■				3–6 mg
Promazine[b]	+++	++	++ Ⓦ	++ Ⓦ					■	■■ Ⓦ	■	■	■	■	■	100–200 mg × 4 (elderly 25–50 mg)
Quetiapine	++	+	+ Ⓦ	+++ ⃠	■		■	■		Ⓦ		■				25–50 mg
Risperidone[c]	+	+	+ Ⓦ	++ Ⓦ			■	■		■■ Ⓦ		■	■			0.5–2 mg
Tiapride	++	+	+ Ⓦ	++ Ⓦ					■	■■ Ⓦ		■		■	■	100–400 mg
Ziprasidone	+	-	++ ⃠	+++ Ⓦ				■		Ⓦ		■			■	10–80 mg
Zuclopenthixol	++	++	++ Ⓦ	++ Ⓦ						Ⓦ	■	■		■		20–150 mg (elderly 5–150 mg)
BENZODIAZEPINES																
Lorazepam	++	-	-	+ ⃠				■	■	■	■	■	■	■	■	1–4 mg (elderly 0.5–2)
Midazolam[d]	+++	-	-	++ Ⓦ					■				■	■	■	10–60 mg

(Continued)

Table 1. (Continued)

Drugs	Clinical elements				Evidence of benefit				EMA/BNF therapeutic indications			Formulations available				Suggested daily doses
	Sedation	Anti-cholinergic effects	QTc prolongation	COVID-19 drug interactions	DEL ICU	DEL no ICU	DEM	PSY	DEL	DEM	PSY	TAB	DROPS	IM	IV	
ANTIDEPRESSANTS																
Mirtazapine	+++	+	-	++								■				15–30 mg
Trazodone	+++	+	+ ⓦ	++ ⓦ								■				50–150 mg
OTHER DRUGS																
Dexmedetomidine	+++	-	++	++	■										■	0.2–1.4 mcg/kg/h
Rivastigmine[e]	-	-	+	-						■		■	■			3–12 mg
Donepezil[f]	-	-	+	-						■		■	■			5–10 mg
Sodium valproate	+	-	+	+			■					■	■		■	250–1000 mg

-, no risk; +, low risk; ++, moderate risk; +++, high risk; ⃠, contraindication according to EMA/BNF; ⓦ, special warnings and precautions for use according to EMA/BNF; ■, presence of evidence of benefit, EMA/BNF therapeutic indication, or formulation; BNF, British National Formulary; DEL, delirium; DEM, aggressiveness/agitation/behavioural issues in dementia; DROPS, drops or other oral liquid formulations; EMA, European Medicines Agency; ICU, intensive care unit; IM, intramuscular injection; IV, intravenous infusion; mcg, micrograms; mg, milligrams; PSY, aggressiveness/agitation/behavioural issues in psychosis; QTc, corrected QT interval prolongation; RCT, randomised controlled trial; TAB, tablets or capsules.

Evidence of benefit was reported for treatments showing statistical superiority over placebo at study endpoint according to the most updated meta-analysis of RCTs. If data from placebo-controlled trials were lacking, we considered head-to-head RCTs showing no significant differences against haloperidol and narrow confidence intervals according to the GRADE approach for detecting imprecision, provided that haloperidol was effective *versus* placebo in the same population.

Notes on registered indications: (a) Registered indication (BNF): Psychomotor agitation, excitement, and violent or dangerously impulsive behaviour; (b) Registered indication (BNF): Short-term adjunctive management of psychomotor agitation; Agitation and restlessness in elderly; (c) Registered indication (BNF): Short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological interventions and when there is a risk of harm to self or others; (d) Registered indication (BNF): Adjunct to antipsychotic for confusion and restlessness in palliative care; (e) Registered indication (BNF): Mild to moderate dementia in Alzheimer's disease and in Parkinson's disease; (f) Registered indication (BNF): Mild to moderate dementia in Alzheimer's disease.

Notes on EMA/BFN warnings and precautions: all antipsychotics have a warning for (a) the increased risk QTc prolongation (and for haloperidol and ziprasidone there is contraindication if QTc ⩾500 ms) and (b) the increased risk of death in older people with dementia. Haloperidol is contraindicated in association with other QTc-prolonging medications, including certain antibiotics and chloroquine. The risk of QTc prolongation is likely to be greater with intravenous route. The associations quetiapine + cytochrome P450 3A4 inhibitors (e.g. HIV-protease inhibitors, clarithromycin) and lorazepam + HIV-protease inhibitors are contraindicated. Caution should be observed for any antipsychotic in association with other QTc-prolonging medications, for midazolam in association with HIV-protease inhibitors and macrolide antibiotics, and for trazodone in association with ritonavir and macrolide antibiotics.