دانشگاه علوم پزشکی تهران
Tehran University of
Medical Sciences

انجمن روانپزشکی کودک و نوجوان ایران
Iranian Academy of
Child & Adolescent Psychiatry

Psychiatrist's Role in COVID -19 management

Lessons learned from the COVID-19 Crisis

Psychiatric face of covid-19 in **Medical Setting**

Can children get COVID-19?

UpToDate®

Can children get COVID-19?

- Children of all ages can get COVID-19 .

- In surveillance from various countries children typically account for 1 to 9 percent of laboratory-confirmed cases.

How do children get COVID-19?

- Most cases in children result from household exposure, usually with an adult as the index patient .

Children Hospitalization Rates With COVID

- The hospitalization rate ranged from 2.5 to 4.1 percent.
(CDC reports until May 30, 2020)
- Approximately 33 percent required intensive care and 6 percent required invasive mechanical ventilation.

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Clinical manifestations

- In children of all ages — The symptoms of COVID-19 are **similar** in children and adults.

A multisystem disease?

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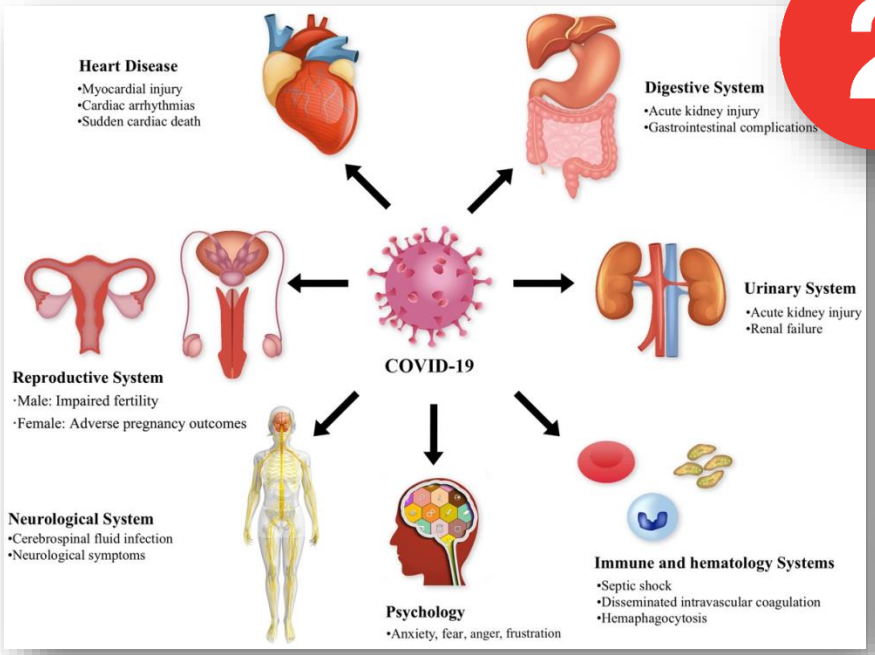

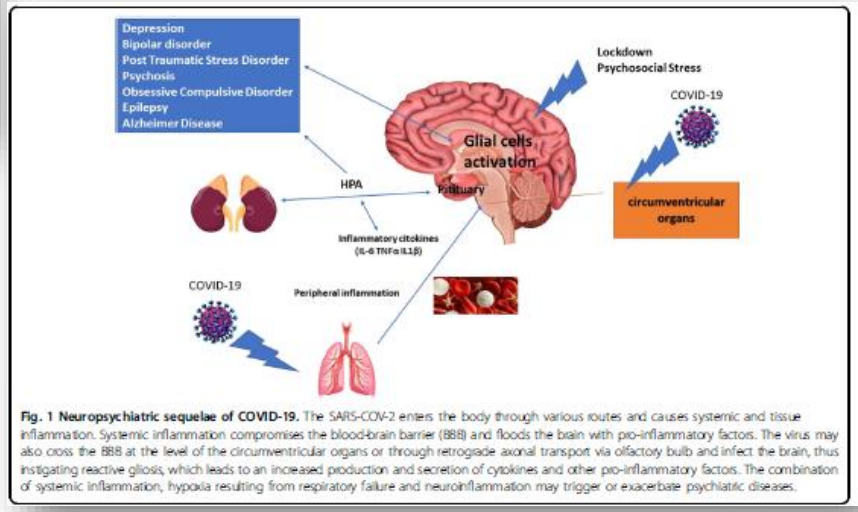

Fig. 1 Neuropsychiatric sequelae of COVID-19. The SARS-COV-2 enters the body through various routes and causes systemic and tissue inflammation. Systemic inflammation compromises the blood-brain barrier (BBB) and floods the brain with pro-inflammatory factors. The virus may also cross the BBB at the level of the circumventricular organs or through retrograde axonal transport via olfactory bulb and infect the brain, thus instigating reactive gliosis, which leads to an increased production and secretion of cytokines and other pro-inflammatory factors. The combination of systemic inflammation, hypoxia resulting from respiratory failure and neuroinflammation may trigger or exacerbate psychiatric diseases.

Neuropsychiatric sequelae of COVID-19

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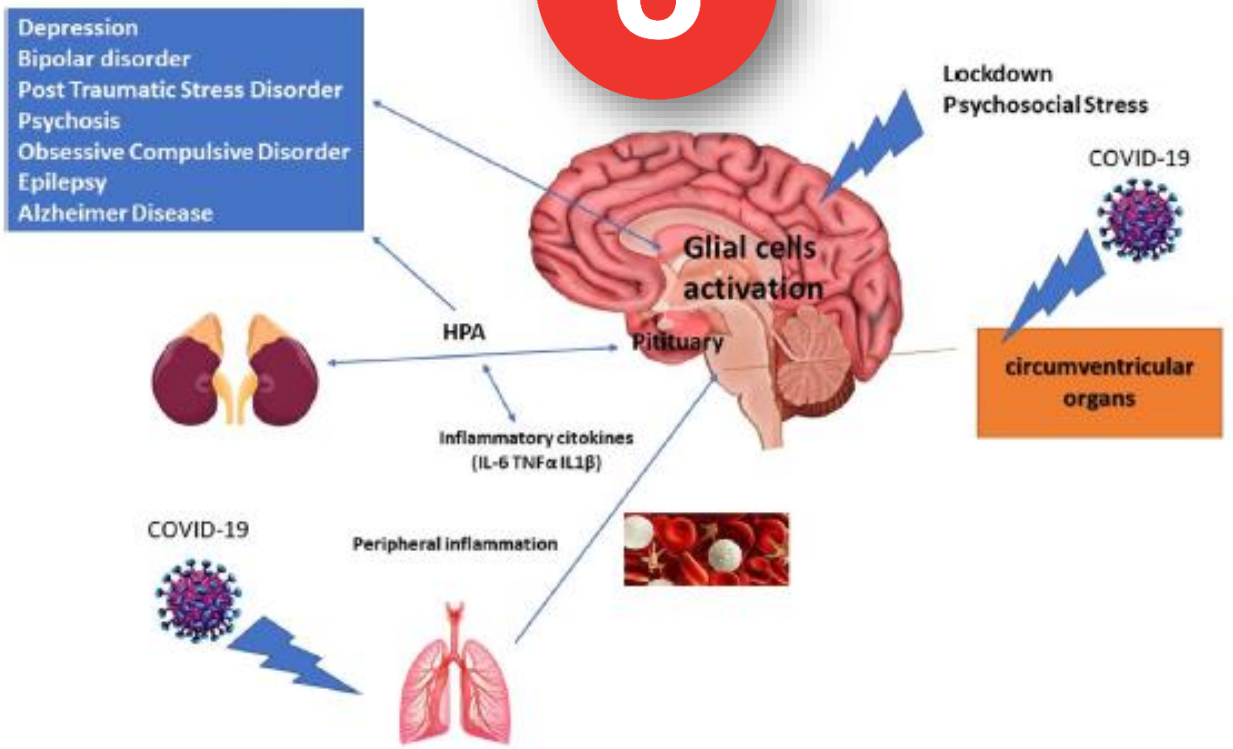

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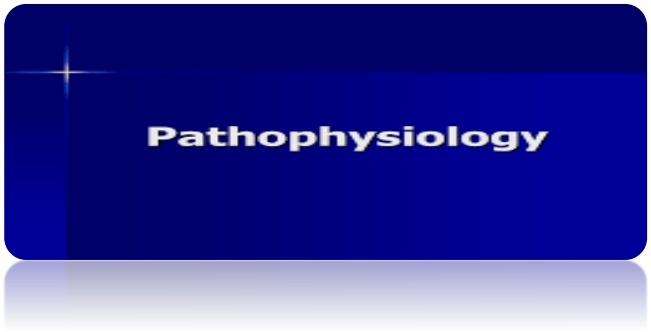
Neuropsychiatric sequelae of COVID-19



- There is a strong association between systemic inflammation and depressive syndromes with infections rising the risk of depressive episodes by ~60%.
- In animal models, injections of cytokines instigates sickness behaviour; which is very similar to a human "flu-like syndrome" manifested by anhedonia, anorexia, fever, fatigue, increased pain, sleep disturbances, and confusion.
- Furthermore, severe respiratory failure accompanying COVID-19 triggers long-lasting hypoxia, which arguably affects the brain and causes neurocognitive alterations.

STEARDO et al-2020

Prevalence of psychiatric and neuropsychiatric signs and symptoms reported by acute and post-illness studies

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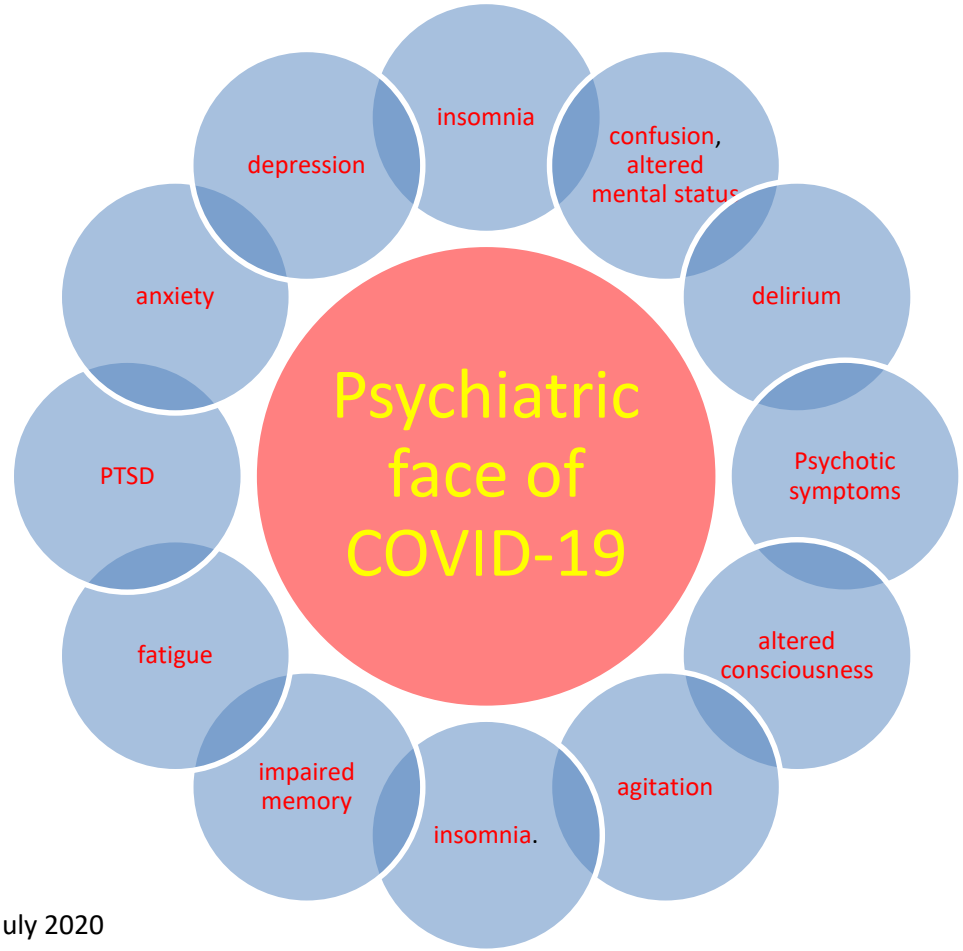


www.thelancet.com/psychiatry Vol 7 July 2020

In the acute illness

- Confusion (27.9%)
- Depressed mood (32.6%)
- Anxiety (35.7%)
- Impaired memory (34.1%)
- Insomnia (41.9%)

[Rogers J et al., 2020]

In acutely ill with severe disease

- Delirium(65%)
- Agitation after withdrawal of sedation (69%)
- Altered consciousness (21%)

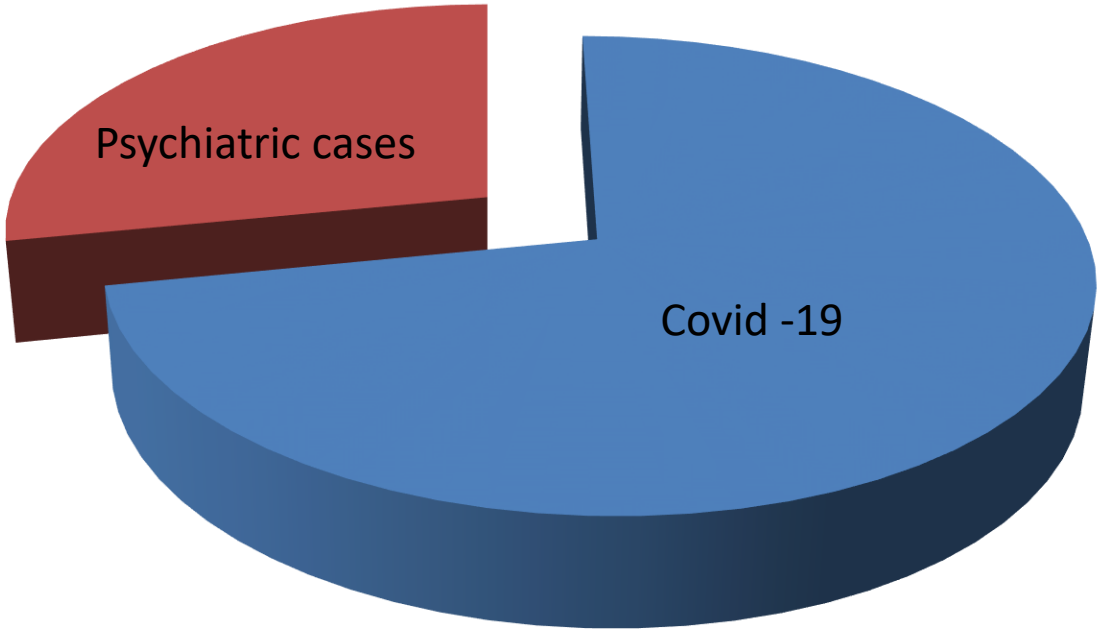
Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic -Jonathan P Rogers*et al, Lancet Psychiatry 2020; 7: 611–27 Published Online May 18, 2020

In the post-illness stages

1. Depressed mood (10.5%)
2. Insomnia (12.1%)
3. Anxiety (12.3%)
4. Irritability (12.8%)
5. Memory impairment (18.9%)
6. Fatigue (19.3%)
7. Traumatic memories (30.4%)
8. Sleep disorder (100%)

[Rogers J et al., 2020]

Nearly 1 in 5 Develop Mental Illness Following COVID-19



4 Clinical scenarios that should prompt psychiatry consultation:

1. Sleep Problems during COVID-19
2. Agitation in the setting of delirium or neurocognitive disorder
3. Assistance with management of mood symptoms
4. New onset psychosis or assistance for patients with acute psychosis
5. Assistance with management of psychotropic medications & Drug – Drug interaction(DDIs)
6. Substance disorder or opioid withdrawal
7. Suicidal ideation or risk of self harm

https://covidprotocols.org/protocols/psychiatry/

Pediatric Consultation-Liaison Psychiatry

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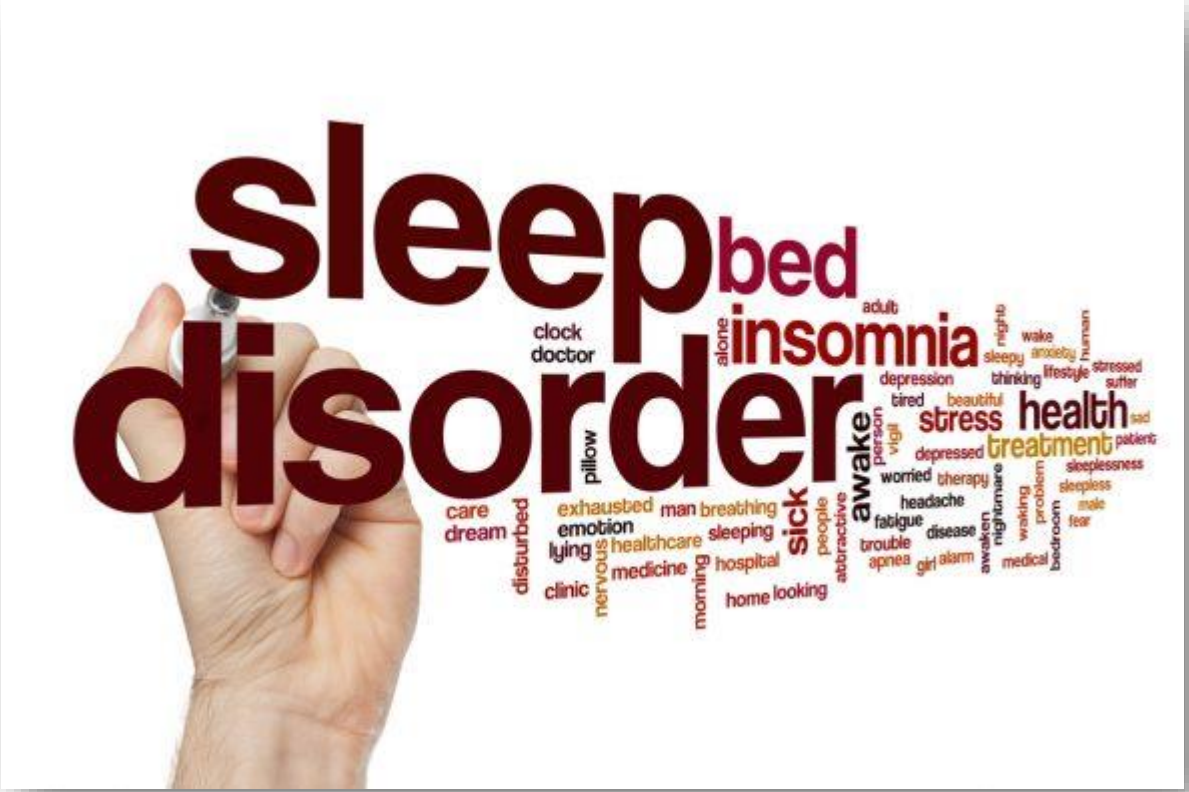
Sleep Problems



Epidemiology of sleep disorders during COVID-19 pandemic

- A total of 78 articles were evaluated, the prevalence of sleeping disorders ranged from 2.3% to 76.6%.

DOI: 10.1101/2020.05.17.20104794

Sleep in the Intensive Care Unit

- Surveys of ICU patients show that self-reported sleep disturbance is common, in some cases being reported by 100% of patients.
- A total of 22 studies were identified, with assessment tools including subjective questionnaires, polysomnography, and actigraphy.

- Subjective questionnaire studies reveal a 50–66.7% (within 1 mo), 34–64.3% (.1–3 mo), 22–57% (.3–6 mo), and 10–61% (.6 mo) prevalence of abnormal sleep after hospital discharge after critical illness.

Sleep in the Intensive Care Unit -Margaret A- 2015

Sleep in the Intensive Care Unit

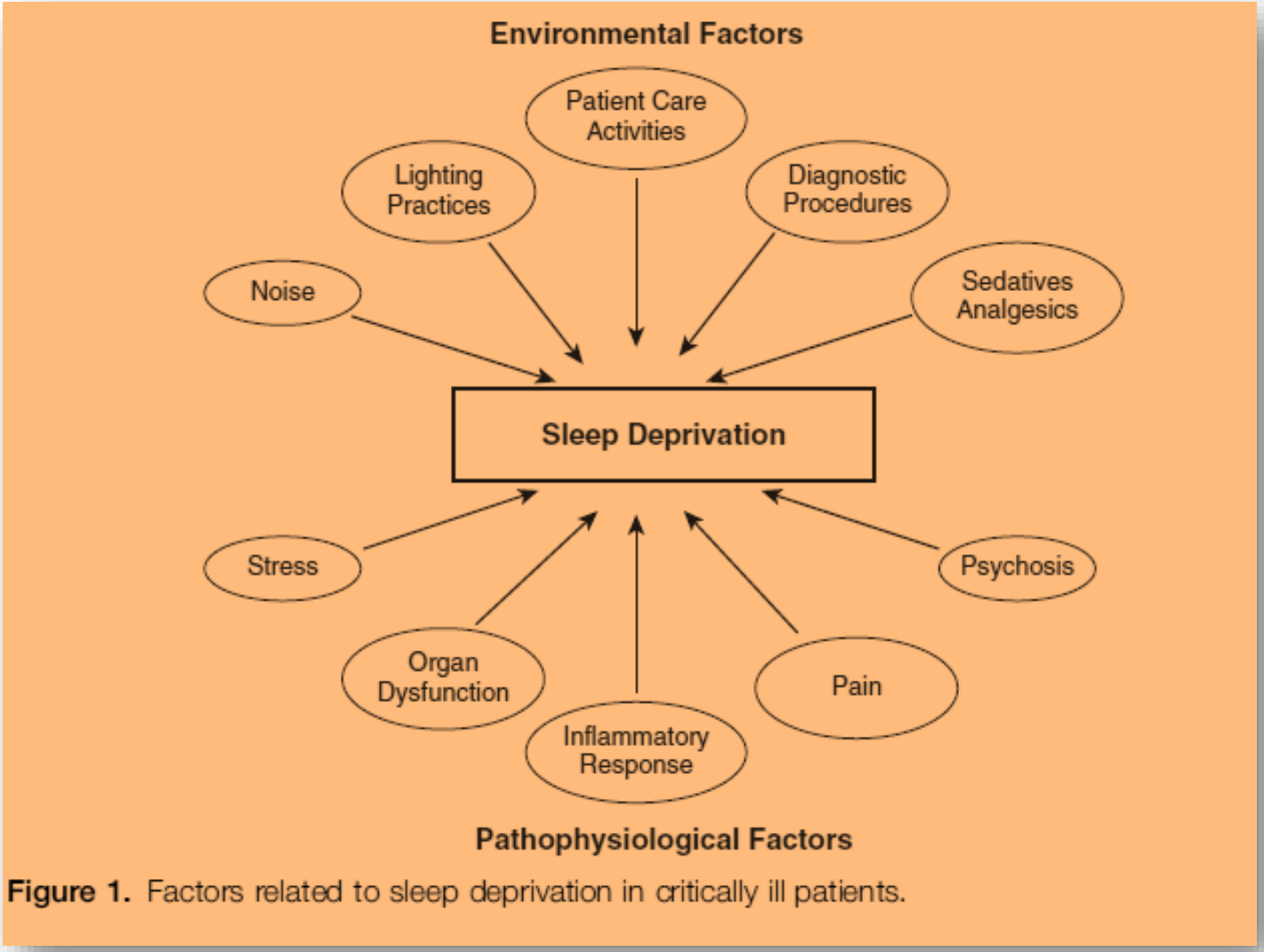


Figure 1. Factors related to sleep deprivation in critically ill patients.

American Journal of Respiratory and Critical Care Medicine Volume 191 Number 7 | April 1 2015

Non-pharmacological strategies to improve sleep in hospitalized patients

Strategy
Ventilator mode (assist-control in preference to pressure support)
Music at sleep time
Reduction of ambient noise
Earplugs
Reduction of ambient light at night
Scheduling of patient care activities during daytime
Tapering of drugs with sedative effects
Daytime mobilisation

ICU Management & Practice 3 - 2018


Covid-19
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Lorazepam 1-2 mg/Oral or parenteral PRN

when benzodiazepine are contraindicated

insomnia

Amitriptyline 25 mg/day

Zolpidem 2.5-5 mg PRN

Quetiapine 25mg /day

Olanzapine 5 mg/DAY

Trazodone 50 mg/ day

Recommended drugs for acute psychiatric conditions in patients with COVID-19

The 2018 PADIS guidelines

Table 2. Drugs to improve sleep

Drug	Suggested dose	Effect on sleep	Known effects on other outcomes
Melatonin	3-10mg	In normal people and people with primary insomnia, reduces time to fall asleep, but no clinically significant effect on time spent asleep. In patients unable to sleep due to a medical cause ("secondary" insomnia), moderate to high quality studies show melatonin has little or no beneficial effect on sleep (Buscemi et al. 2004)	No other benefit has been observed in ICU patients (Devlin et al. 2018)
Ramelteon	8mg	Shortens time to fall asleep and increases total duration of sleep (Neubauer 2008)	Lower incidence and duration of delirium, and fewer nighttime awakenings (Nishikimi et al. 2018)
Dexmedetomidine	0.1mcg/kg/hr	Increases total sleep time and proportion of time spent in N2 (deeper) stage of sleep; reduces proportion of time spent in N1 (lighter) sleep. No change in REM sleep (Wu et al. 2016)	Reduced postoperative delirium, reduced reported pain, improved reported sleep (Su et al. 2016)
Amitriptyline	10-50mg	Shortens time to fall asleep and increases overall sleep time, but reduces REM sleep (Wilson and Argyropoulos 2005)	No benefit has been proven in ICU patients when used for this indication
Mirtazapine	15-30mg	Increases total slow wave sleep and REM sleep, as well as improving insomnia scores (Shen et al. 2006)	No benefit has been proven in ICU patients when used for this indication
Trazodone	50mg	Increases total slow wave sleep but reduces REM sleep. Improves subjective insomnia. No effect on total sleep duration or time to fall asleep (Montgomery et al. 1983)	No benefit has been proven in ICU patients when used for this indication

6

Management of delirium in COVID-19

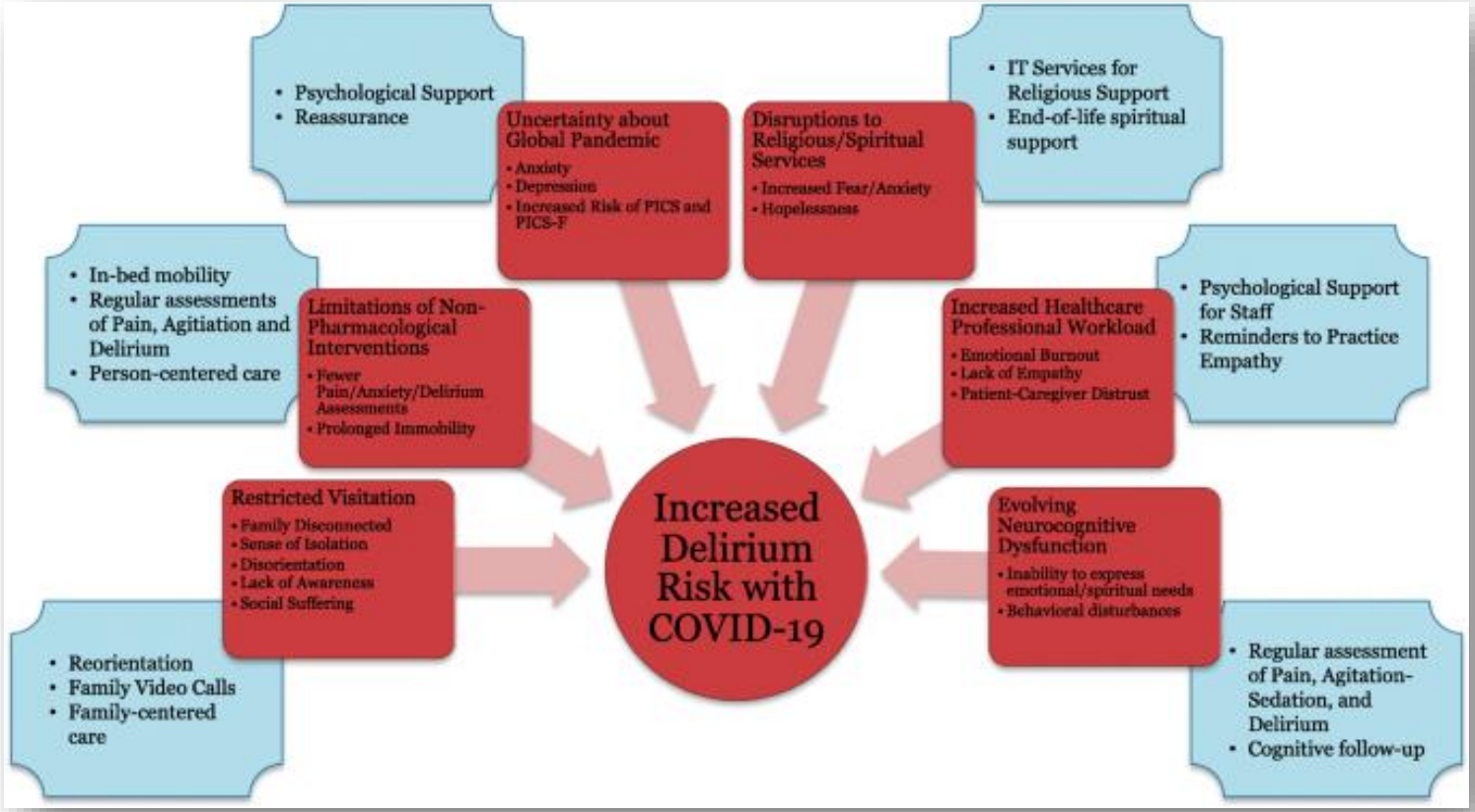
RC PSYCH
ROYAL COLLEGE OF PSYCHIATRISTS

Prevalence of delirium in covid-19

Historically, delirium rates among mechanically ventilated ICU populations were consistently **70–75%**.

Kotfis et al. Critical Care (2020) 24:176

Potential factors contributing to ICU delirium during the SARS-CoV-2 pandemic



Recommendations

- The recommendations follow two key themes:
- First, good general care including prevention, early detection, and non-pharmacological management should be provided as systems allow.
- Second, because of the ease of transmission of COVID-19, the risk of harm to others may exceed risk of harm to the individual and this may necessitate earlier use of pharmacological treatments for potentially risk behaviour.

Recommendations

1. Enhanced implementation of screening for delirium in at risk groups and also regular assessment for delirium using a recommended tool (eg. the 4AT www.the4AT.com1).

2. Reduce the risk of delirium by avoiding or reducing known precipitants.

- Actions include: regular orientation, avoiding constipation, treating pain, identification and treatment of superadded infections early, maintaining oxygenation, avoiding urinary retention and medication review.

Recommendations

3. look for and treat direct causes including pain, urinary retention, constipation, etc. Where these interventions are ineffective or more rapid control is required to reduce the risk of harm to the patient and others, it may be necessary to move to pharmacological management earlier than would normally be considered.
4. In these circumstances we would recommend the guidance provided in the SIGN guidance/ The National Guidelines for – CoV-19

USE OF SEDATING MEDICATION FOR SEVERE AGITATION IN PATIENTS WITH DELIRIUM AND COVID-19

1. Current advice is to start with low dose lorazepam or haloperidol and increase dose and frequency slowly if needed. Be aware that benzodiazepines may cause respiratory depression, and so haloperidol may be preferred in COVID delirium. Prescribe flumazenil if needed.
2. • Stat dosing should be used initially however PRN use may be needed if agitation persists
3. • Antipsychotics should not be used for patients with Parkinson's Disease or Lewy Body Dementia. Quetiapine and clozapine are preferred when psychosis warrants drug treatment. Quetiapine is a safer alternative atypical antipsychotic in PDD and DLB, typically in the dose range of 6.25 mg to 50 mg a day, although higher doses may be used if tolerated and necessary.

Medication	Route	Dose range (mg)	Daily frequency range	Recommended 24 hour max	**If no improvement over 4 days, review diagnosis** Continue to treat underlying medical condition(s) Continue to address common causes of delirium, e.g. constipation, dehydration, urinary tract infection, pain, medication side effects
Lorazepam	PO/IM/IV	0.5-1	OD - QDS	2mg	
Haloperidol	PO/IM/SC (liquid form available)	0.5 – 2	OD - 2-4 hourly	5 mg	
Risperidone	PO (liquid form available)	0.25 – 0.5	OD -BD	2 mg	
Olanzapine	PO/IM (liquid form available)	2.5 - 5	OD - BD	10 mg	
Quetiapine	PO (liquid form available)	12.5 - 50	OD - BD	100mg	

https://www.rcpsych.ac.uk/covid-19-delirium-management-guidance.pdf

https://www.lbda.org/

USE OF SEDATING MEDICATION FOR SEVERE AGITATION IN PATIENTS WITH DELIRIUM AND COVID-19

1. • An ECG should be obtained prior to administering antipsychotics to check QTc (upper limits 440mS in men, 470mS in women)
2. • Haloperidol is not licensed for concomitant use with other QTc prolonging drugs (which include some antimicrobials and antiarrythmics).
3. • If antipsychotics are contraindicated low dose lorazepam can be used, please note lorazepam is not licensed in delirium.
4. • In severe cases both antipsychotics and lorazepam may be needed.
5. • Alternative antipsychotics can be used if needed, but please note they are not licensed for delirium. Risperidone is licensed for use in Alzheimer's dementia for aggression, so can be considered if there is a history of this.

https://www.alzheimers.org.uk/about-dementia/treatments/drugs/antipsychotic-drugs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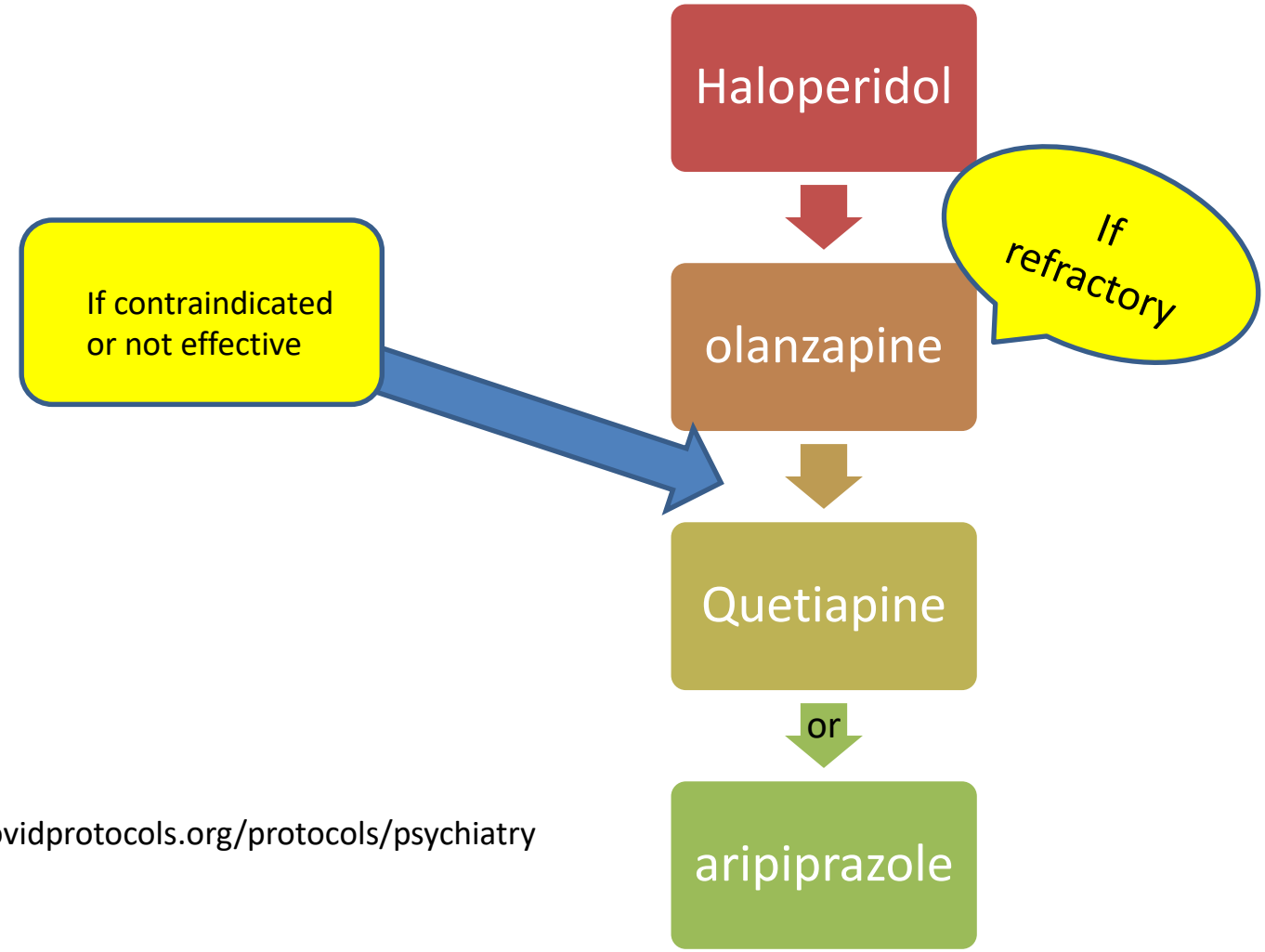
Pharmacological Recommendations for Delirium with COVID-19



https://covidprotocols.org/protocols/psychiatry

Pharmacological Recommendations for Delirium with COVID-19

1. Haloperidol: Mild agitation:0.5-1.0 mg IV or 1 to 2 mg PO q6h and 1-2 mg q2h PRN.; Moderate agitation: 2-4 mg IV; Severe agitation: 4-10 mg Maximum dose: 20 mg / 24 hours
2. If refractory, olanzapine (Zyprexa), 2.5 to 5 mg (PO, SL, or IV) q12 hr and 2.5 mg q4h PRN; Maximum dose: 30mg / 24 hours. **do not combine with parenteral benzodiazepines due to increased risk of respiratory depression**
3. If haloperidol/olanzapine not effective or contraindicated, could try:

- Quetiapine (Seroquel) 12.5-50 mg qHS
- aripiprazole (Abilify) 5 mg PO daily; maximum dose 30 mg daily

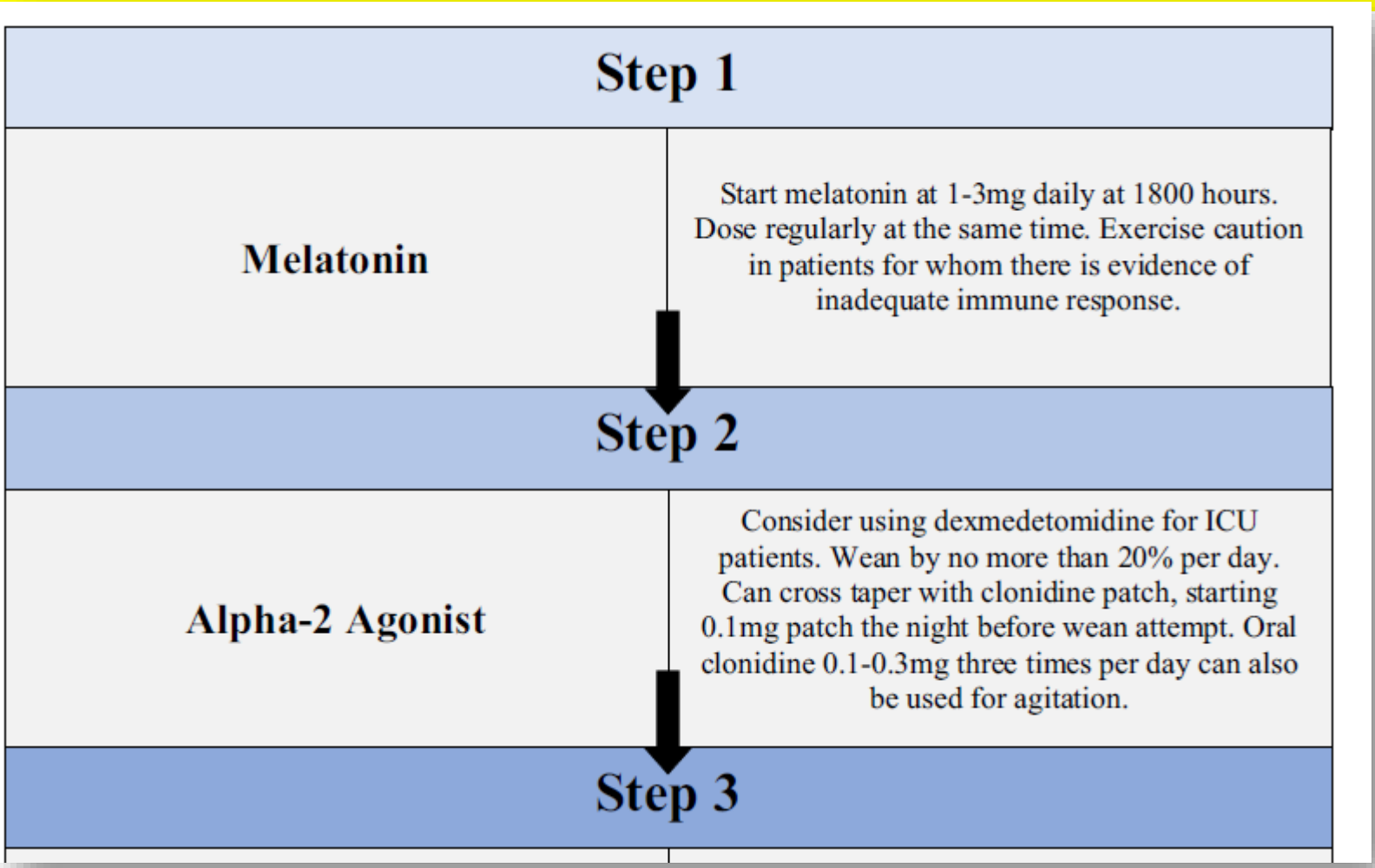
https://covidprotocols.org/protocols/psychiatry/

Medications that may be used in delirium (based on the SIGN guidelines)

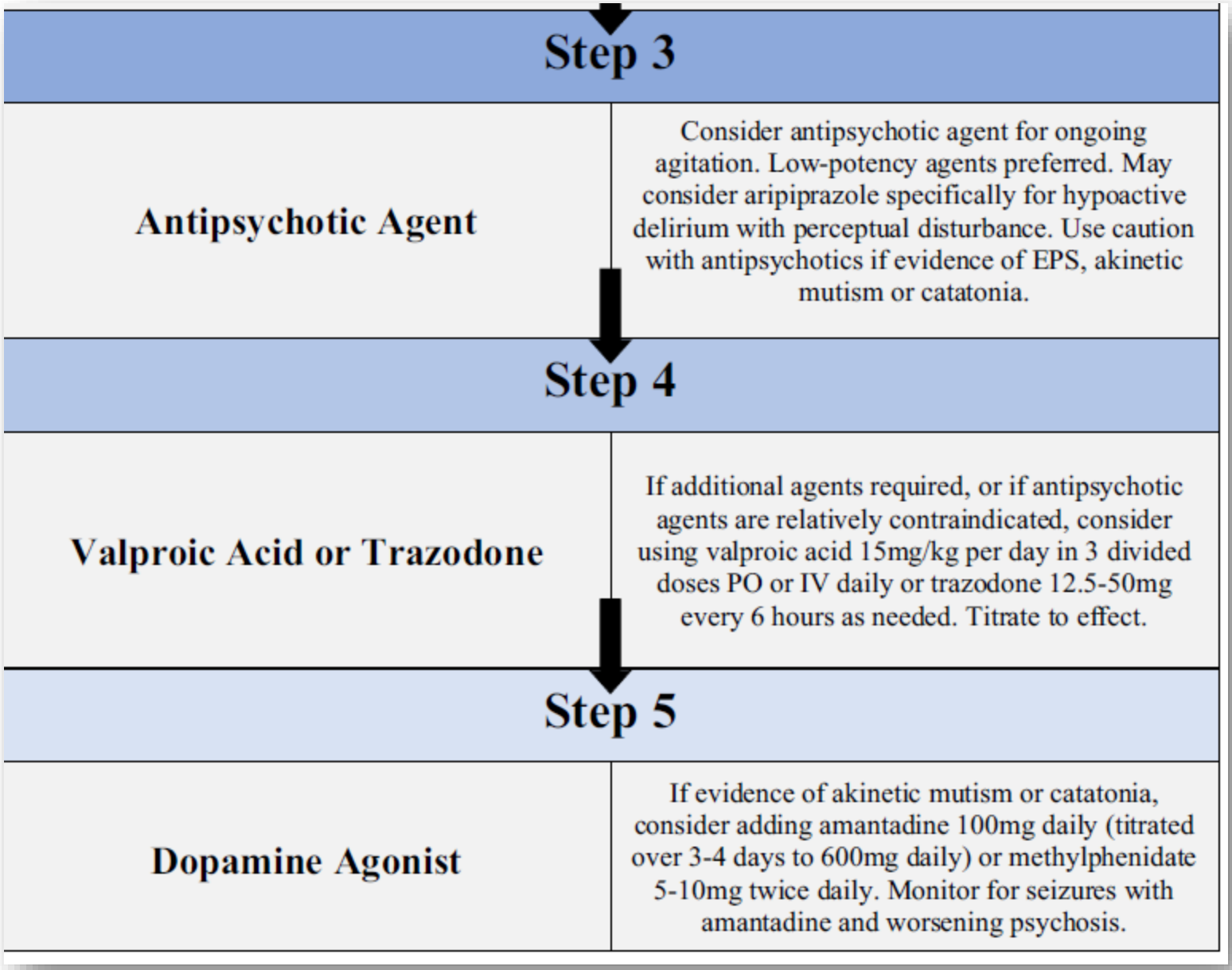
Medication	Single starting dose	Maximum dose in 24 hours*	Cautions/Contraindications
Haloperidol**	0.5mg orally 0.5mg im	2mg orally 2mg im	Prolonged QTc interval in ECG Signs of parkinsonism or lewy body dementia When used with any medication that prolongs QT interval this is off-license
Risperidone	0.25mg orally	1mg in divided doses	Signs of parkinsonism or lewy body dementia Not licensed in delirium
Lorazepam if antipsychotics are contraindicated	0.5mg orally 0.5mg-1mg im	2mg orally 2mg im	Caution in renal impairment Not licensed in delirium

Pharmacologic treatment algorithm.

Medication recommendations were extrapolated from previous delirium literature and adapted for patients with delirium in the setting of COVID-19 based on clinical experience from the Massachusetts General Hospital C-L Psychiatry COVID-19 Workgroup.



Baller et al. Psychosomatics , November/December 2020


Step 3
Antipsychotic Agent
Consider antipsychotic agent for ongoing agitation. Low-potency agents preferred. May consider aripiprazole specifically for hypoactive delirium with perceptual disturbance. Use caution with antipsychotics if evidence of EPS, akinetic mutism or catatonia.
Step 4
Valproic Acid or Trazodone
If additional agents required, or if antipsychotic agents are relatively contraindicated, consider using valproic acid 15mg/kg per day in 3 divided doses PO or IV daily or trazodone 12.5-50mg every 6 hours as needed. Titrate to effect.
Step 5
Dopamine Agonist
If evidence of akinetic mutism or catatonia, consider adding amantadine 100mg daily (titrated over 3-4 days to 600mg daily) or methylphenidate 5-10mg twice daily. Monitor for seizures with amantadine and worsening psychosis.

Special Considerations

Akinetic Mutism and Catatonia

1. Anecdotal reports of catatonia-like syndromes, which are also considered to be low-dopamine states, have been reported in COVID-19 delirium.

2. It remains unclear whether these patients are suffering from catatonia, which may be related to underlying psychiatric illness, delirium, or the infection itself or a related phenomenon, such as akinetic mutism, which may have features overlapping with catatonia.
3. For patients exhibiting alogia, abulia, immobility, and withdrawal , C-L psychiatrists should consider using dopamine agonists and avoiding antipsychotics. Amantadine has been recommended as a third-line agent in catatonia and is also the treatment of choice for akinetic mutism.
4. Benzodiazepines may also be useful in this setting, despite the potential to worsen delirium.

Baller et al. Psychosomatics , November/December 2020

Special Considerations

- Alpha 2 agonists : good option if prolonged QTc:

1. **dexmedetomidine** (Precedex) IV - easily titratability given short half-life.

2. Consider use of **clonidine** 0.1 mg BID (can uptitrate) - available as a transdermal patch as well.

Special Considerations

- **Valproic Acid** (**good option if prolonged QTc**): Start at 125-250mg IV q8h TID, however, COVID patients are seeming to need escalations in doses (up to anti-manic dosing of 15-25 mg/kg) in combination with antipsychotics (i.e. haloperidol or olanzapine as above).

Special Considerations

- For regulation of sleep/wake cycle: Mirtazapine (Remeron): 7.5 mg (can uptitrate, but it is more sedating at lower doses).

Special Considerations

Geriatrics

1. High risk for delirium given restrictive visitor policy, disorienting effect of PPE use by staff, difficulty hearing/identifying caregivers through masks.

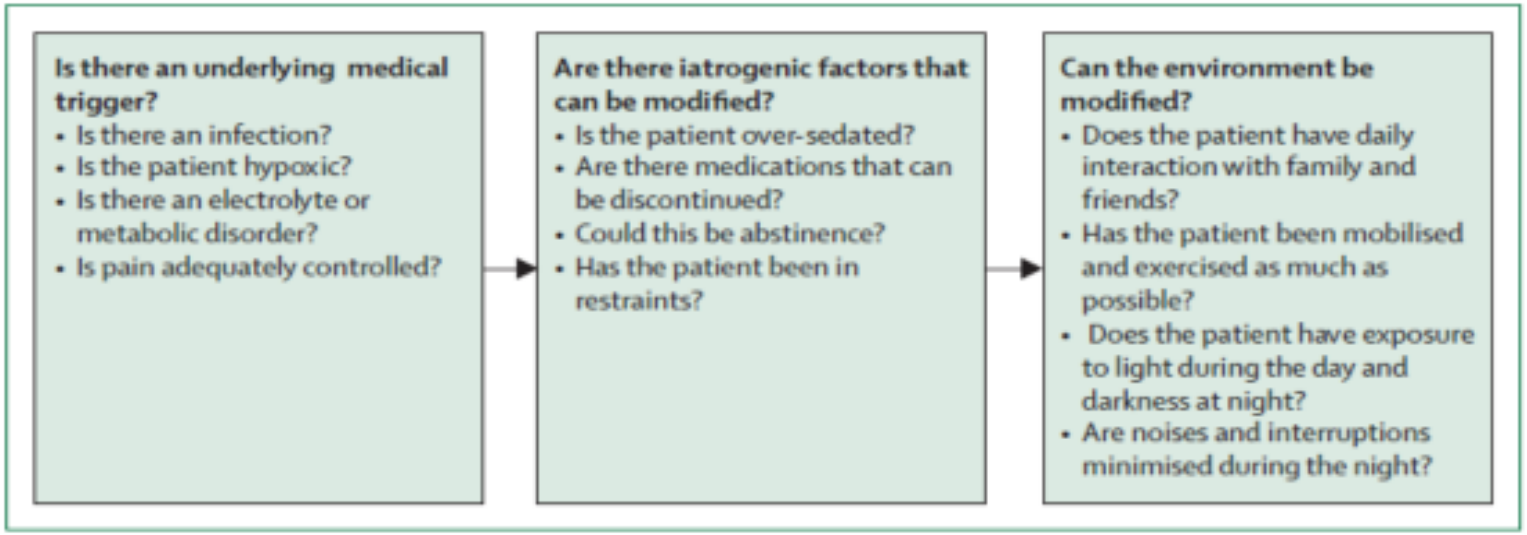
2. Avoid deliriogenic medications such as anticholinergics and benzodiazepines.
3. If acutely agitated, not redirectable by non-pharmacologic means, trial 12.5 mg trazodone x 1 prn, repeat dose x 30 min if no effect.

4. Use of antipsychotics (e.g. haloperidol, olanzapine, quetiapine) **as last resort only, and only if QTc is < 500.**

Special Considerations
Children

Non-pharmacological interventions

- More than **80%** of children with delirium will respond to non-pharmacological interventions.



Drug interactions between commonly used medications in delirium and COVID- 19 drugs

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	NITAZ	RBV	TCZ
Aripiprazole	↑	↑	↔	↔	↔	↔	↔	↔	↔
Haloperidol	↑♥	↑♥	↔	↔	↔♥	↔♥	↔	↔	↔
Olanzapine	↔	↓	↔	↔	↔	↔	↔	↔	↔
Quetiapine	↑♥	↑♥	↔	↔	↔♥	↔♥	↔	↔	↔
Risperidone	↑♥	↑♥	↔	↔	↑♥	↑♥	↔	↔	↔
Diazepam	↑	↑	↔	↔	↔	↔	↔	↔	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Midazolam (oral)	↑	↑	↔	↔	↔	↔	↔	↔	↔
Midazolam (parenteral)	↑	↑	↔	↔	↔	↔	↔	↔	↔
Oxazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zaleplon	↑	↑	↔	↔	↔	↔	↔	↔	↔
Zolpidem	↑	↑	↔	↔	↔	↔	↔	↔	↔
Zopiclone	↑	↑	↔	↔	↔	↔	↔	↔	↔

Key

↑ Potential increased exposure of the co-medication

↓ Potential decreased exposure of the co-medication

⇑ Potential increased exposure of COVID drug

⇓ Potential decreased exposure of COVID drug

↔ No significant effect

♥ One or both drugs may cause QT and/or PR prolongation.

ECG Monitoring is advised if co-administered

Colour Legend

	These drugs should not be co-administered
	Potential interaction which may require a dose adjustment or close monitoring.
	Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required.
	No clinically significant interaction expected

Date: 28th March 2020 Dr Josie Jenkinson, Consultant Psychiatrist for older people, ASPH Psychiatric Liaison services. Adapted for older adults from original guidance compiled by Prof Tayyeb Tahir, Dr Mehrul Hasnain, Dr Ankit Saxena, Dr Radhika Oruganti at University of Wales with reference to the Liverpool Drug Interactions Group, – with grateful thanks. References: SIGN Guideline 157 Delirium 2019, BGS and RCPsych Coronavirus: managing delirium in confirmed and suspected cases 2020, British National Formulary 79 2020, Maudsley Prescribing Guidelines 2018, Clinical guide for the management of palliative care in hospital during the coronavirus pandemic NHS England 2020. This guidance may be amended following further national guidance and development of evidence base.

Key to abbreviations

ATV	Atazanavir	CLQ	Chloroquine
LPV/r	Lopinavir/ritonavir	HCLQ	Hydroxychloroquine
RDV	Remdesivir	NITAZ	Nitazoxanide
FAVI	Favipiravir	RBV	Ribavirin
		TCZ	Tocilizumab

https://www.rcpsych.ac.uk/docs/default-source/members/faculties/old-age/covid-19-delirium-management-guidance.pdf?sfvrsn=2d5c6e63_2

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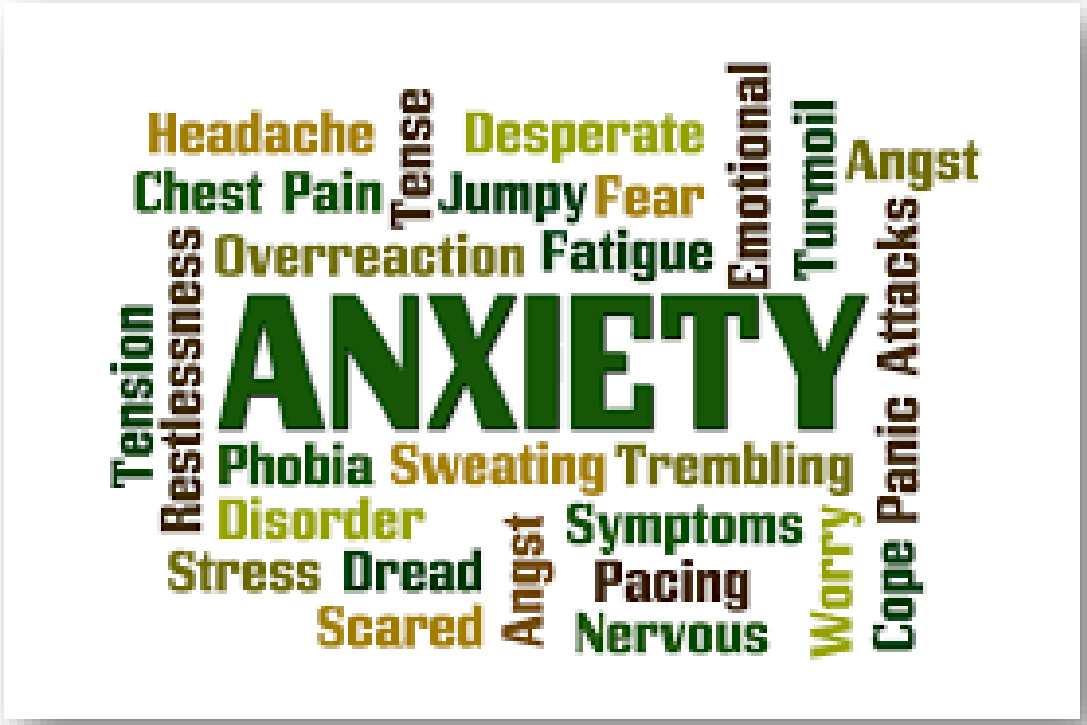

Headache
Tense
Desperate
Emotional
Angst
Chest Pain
Jumpy
Fear
Turmoil
Overreaction
Fatigue
Restlessness
Panic Attacks
Tension
ANXIETY
Phobia
Sweating
Trembling
Disorder
Symptoms
Worry
Cope
Stress
Dread
Angst
Pacing
Scared
Nervous

General Management of Anxiety/PTSD

- Preliminary data from China found that 96.2% of patients hospitalized for COVID-19 reported significant PTSD symptoms prior to discharge from the hospital (Bo et al, Psychol Med, 2020).

- Patients with anxiety or panic-like symptoms can appear agitated and restless. Patient with acute anxiety might develop panic attacks presenting with a sense of impending doom, breathlessness, hyperventilation, sweating, restlessness, irritability and sometimes agitation.

Non-pharmacologic

A. Feelings of uncertainty and fear can fuel anxiety

1. Important to first acknowledge and normalize distress reactions

2. Correct misinformation. Provide accurate information (regarding patient's current medical condition and next steps, regarding hospital protocols and measures being taken for safety).

3. Encourage limiting media exposure.

B. Counseling (Spiritual, Psychocological,Reiki …)

Non-pharmacologic

C-Strategies for reducing distress

I. Restful & comfortable sleep, eating regular meals, exercising

II. Talking to loved ones (via telephone or video chat)

III. Diaphragmatic breathing

IV. Muscle relaxation

Pharmacologic Management

- Continue home psychotropic medication regimen if possible

1-For patient without evidence of delirium
Quetiapine 12.5-25mg TID PRN

Lorazepam 0.5-2 mg PO/SL TID PRN; 0.5-2 mg IV TID PRN

2-For patient with evidence of delirium
Quetiapine 12.5-25mg TID PRN

3-For patient with risk of respiratory depression or history of respiratory illness

4-Buspirone 5-15mg PO TID

https://covidprotocols.org/protocols/psychiatry/

Pharmacologic Management

1. In case of a diagnosable independent anxiety disorder, SSRI's like escitalopram 10-20mg or sertraline 25-100mg can be considered.

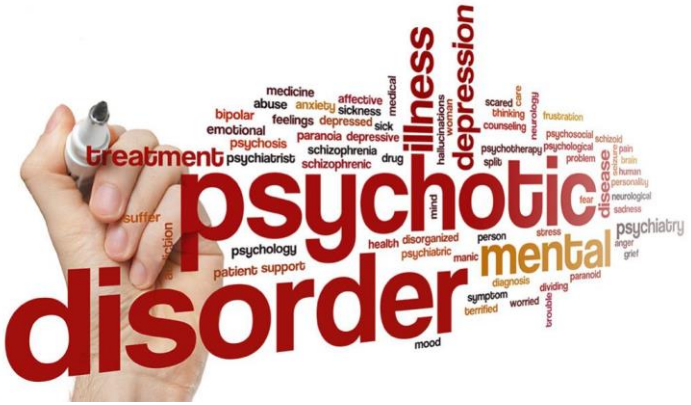
- SSRIs can cause hyponatremia in the elderly.

https://www.mohfw.gov.in/pdf/COVID19Final2020ForOnline9July2020.pdf


bipolar
disorder
illness
depression
mental
anxiety
personality
emotional
stress
psychology

7


DEPRESSION
feelings
worthless
worried
irritable
overeating
mood
disorder
symptom
events
anxious
hopeless
empty
behavior
sad
guilty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psychology
patient
support
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disorganized
psychiatric
manic
person
stress
psychiatry
suffer
mood

Depression

Symptoms: Dysphoric mood, withdrawn, difficulty concentrating, disrupted sleep, decreased appetite, fatigue, tearfulness, worthlessness, hopelessness, helplessness

Non-Pharmacologic

- Physical distancing can worsen depression given increase in isolation.
  - Using safe communication channels between patients and families such as smartphone communication should be encouraged to decrease isolation

- Feelings of guilt and stigma surrounding COVID positivity may also increase symptoms of depression
  - Bring focus to what the patient and family can control going forward and that the appropriate steps to ensure safety are being taken

Pharmacologic

1-Continue home psychotropic medication regimen if possible

2-Depression: Sertraline 50mg daily. If tolerated, can up titration of 50mg every 5-7 days to target symptoms. Max dose 200mg daily Or escitalopram (10-20 mg/day) .

3-Depression with sleep disruption and low appetite: mirtazapine 7.5mg qhs.
Can uptitrate to 30mg qhs as tolerated.

4- Despite the risk of hyponatremia in the elderly and medically ill, it is relatively safe to use. Improvement is expected after a few weeks.

Acute psychosis/mania

1-Atypical antipsychotics like oral risperidone (4-8mg) /olanzapine (10-20mg) are the first-line drugs used in treating acute psychosis and mania.

2· Catatonic symptoms respond to higher dose of IV Lorazepam but should be used with caution in individuals with compromised respiratory status because of the risk of respiratory depression.

3· IV Haloperidol 5-10mg can be used alone or in combination with promethazine (only through intramuscular route) in severe states of agitation as a chemical restraint.


8


addiction
fear
drug abuse
gambling
alcohol abuse
pessimistic
helplessness
risk
habits
impaired control
stress
illnesses
denial
behavior
help
disturbance
substance

Substance disorder or opioid withdrawal

Opioid Use Disorder

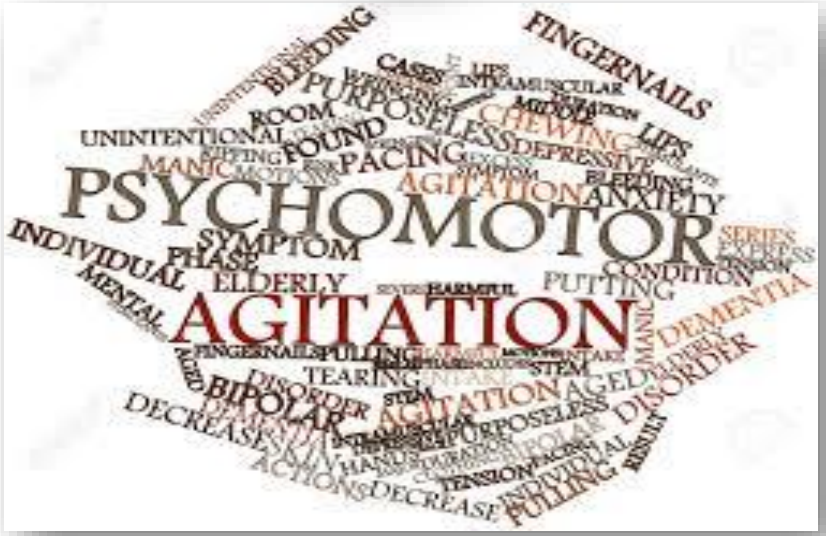
Symptomatic management of withdrawal symptoms:

Symptomatic management of withdrawal symptoms:

1. Hypertension: Clonidine 0.1 mg q8h prn (hold for SBP < 90, HR < 55)
2. Diarrhea: Loperamide 4mg po with 1st loose stool, then 2mg per loose stool. Max of 24 mg per day
3. Nausea: Ondansetron 4-8 mg po/IV q8h prn
4. Pain: Ibuprofen 600 mg or Acetaminophen 650 mg po q4-6h
5. Abdominal cramping: Dicyclomine 20 mg po q4h
6. Nasal congestion: Diphenhydramine 50 mg po q4h
7. Muscle cramps: Methocarbamol 750 mg po q6h
8. Insomnia: Trazodone 50-100 mg po qhs
9. Anxiety: Diphenhydramine 50-100 mg po qhs or Hydroxyzine 25-50 mg qhs

Pregnant women who are opioid dependent should NOT undergo symptomatic withdrawal management due to increased risk of miscarriage or preterm delivery.

9



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Aggression treatment of patients in COVID-19 settings.

- Aggression can be a symptom of bipolar disorder, psychosis, substance use disorders, and delirium.

- In the background of the recommendation of chloroquine as a prophylactic and treatment agent in COVID-19 cases, it is important to note that there are reports of chloroquine induced psychosis.

- Aggression has to be managed systematically, and in a COVID-19 patient, additional precautions have to be taken to prevent the spread of disease to health workers, other patients, and care givers.

Chemical restraints or pharmacological intervention

- If pharmacologic measures are required, the patient should be closely monitored with frequent vital signs and continuous cardiac, pulse oximetry, and capnometry monitoring.

1-If verbal de-escalation fails or cannot be used and with imminent risk of violence, chemical restraint can be used. Informed consent should be taken from the patient or bystander as far as possible.

2· The following agents can be used –Olanzapine, haloperidol, lorazepam, promethazine.

- Oral route is preferred or else, intramuscular-i.m. (haloperidol, promethazine) /slow intravenous i.v. (haloperidol, lorazepam) the route can be used as the second choice.

3· Olanzapine 5mg stat dose may be an oral agent is the patient is willing.

But this strategy **IS INEFFECTIVE IF THERE IS AN IMMEDIATE RISK OF AGGRESSION**.

Benzodiazepines should be used with caution in case of respiratory compromise.

Intervention

1.Verbal de-escalation:

De-escalation is a technique where the health care professional calmly communicates with an agitated patient to understand, manage and resolve his/her concerns.

It should help reduce the patient's agitation and potential for future aggression or violence.

Interview settings:

1· Even though the patient is isolated due to COVID-19, try to ensure privacy during the interview
2· The patient should be under constant observation by keeping the patient near the nursing area
3· There should be a clear exit point for the health care professional
4· Maintain a safe distance of at least two arm distance
5· Never examine a potentially violent patient alone and call for more help when required

Interview technique:

1· Stay calm and listen to the patient carefully.

2· Try to understand his concerns and reasons behind aggression.

3· Talk to the patient softly yet firmly.

4· Stay non-provocative and be non-judgmental.

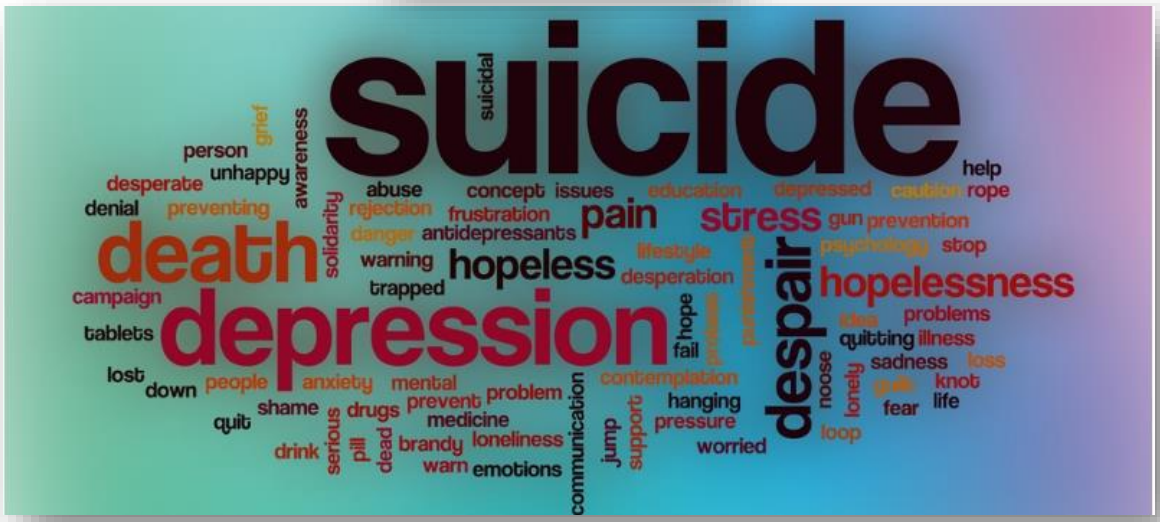
5· Address the patient's concerns that are valid and offer valid solutions.

Mechanical restraint:

- **Mechanical restraint should be used sparingly, never used as the first choice and only used if :**

1. **there is a risk of disruption to life-saving measures**
2. **aggression is present even after adequate sedation or**
3. **if there is a contraindication for chemical restraint.**

10



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Finances
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Economic impact
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Economic crisis

Suicidality in the context of COVID-19

- The ongoing COVID-19 pandemic worldwide has been increasingly associated with suicides.
- Instances of suicide in context of the pandemic have been reported among individuals who have tested positive for COVID-19 infection, those who have suffered severe financial set-backs and those experiencing alcohol withdrawal syndrome.

- The COVID-19 pandemic has led to significantly increased levels of stress at community, family and individual level with a consequent increased vulnerability to suicide.

Initiate high suicidal risk management

1- Constant supervision by staff. The bed should be located close to the nursing station with easy view

2- Scissors, razors and other potentially lethal objects should be removed

3- No medicines with the patient

4-A shatterproof window of the room, windows with mesh, high windows

5- Doors of the room without latches/bolts from inside

6- Risk assessment twice daily-high risk/medium-once daily/low-once weekly

RISK FACTORS for completed suicide

1. Previous suicide attempts
2. Presence of mental disorders
3. History of substance use disorders
4. Family history of suicide
5. Chronic physical illness/terminal illness

Intervention based on level of risk:

Risk Level	Risk	Suicidality	Possible Interventions
High	• Depression or other psychiatric illnesses • Triggering event • Absence of protective factors	• Has made a Lethal attempt • Recent suicidal attempts • Recurring thoughts about suicide	• Admission to a psychiatric set up is recommended • Removal of access to methods • Vigilant supervision by the staff
Moderate	• Multiple risk factors • Few protective factors	• Ideation with plan	• Admission may be necessary • Develop a crisis plan • Frequent observation by staff/family
Low	• Few risk factors • Strong protective factors	• Thoughts of death, • No plan, intent or behaviour	• Outpatient referral to a counsellor or mental health professional recommended

11

Psychological care

Psychological care in severe and critical adult patients with COVID-19

- Psychological and humanistic care should probably be considered for conscious patients with COVID-19.

- Besides experiencing physical impairment and stressful treatments, COVID-19 patients are being subjected to closing monitoring, and are also witnessing various events in the ward such as sudden deterioration of illness, emergency resuscitation procedures and death , all of which could lead to posttraumatic stress disorder, anxiety, and depression according to previous studies.

Psychological care in severe and critical adult patients with COVID-19

- The prevalence of clinician-diagnosed adjustment disorder during hospitalization was 26.7% respectively in 1 study.
- It was reported that 10% to 18% of SARS survivors had symptoms related to posttraumatic stress disorder , anxiety, and depression and that emotional support, such as communication with others and sharing worries could reduce symptom severity .

➢ Psychological implications should not be ignored in coronavirus patients.

❑ Citalopram or Olanzapine should probably be used to improve the psychological symptoms in patients or intervention of the psychologists in the isolation ward who would perform psychological assessment and psychotherapy for patients with new coronary pneumonia.


Covid-19 ?
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Recommended drugs for acute psychiatric conditions in patients with COVID-19

Condition	Recommended drugs
Delirium	Haloperidol 2.5-5 mg PRN Olanzapine 5-10 mg PRN
Acute psychosis/mania	Risperidone 4-8 mg/day* Olanzapine 10-20 mg/day
Anxiety	**For acute anxiety attacks** Lorazepam 1-2 mg PRN
	For long term treatment of anxiety disorders Escitalopram 10-20 mg
Depressive disorder	Escitalopram 10 -20 mg/day Sertraline 50-100 mg/day
Insomnia	Lorazepam 1-2 mg PRN
	When benzodiazepine are contraindicated Zolpidem 2.5-5 mg PRN Amitriptyline 25 mg/day Trazadone 50 mg/day Quetiapine 25 mg/day

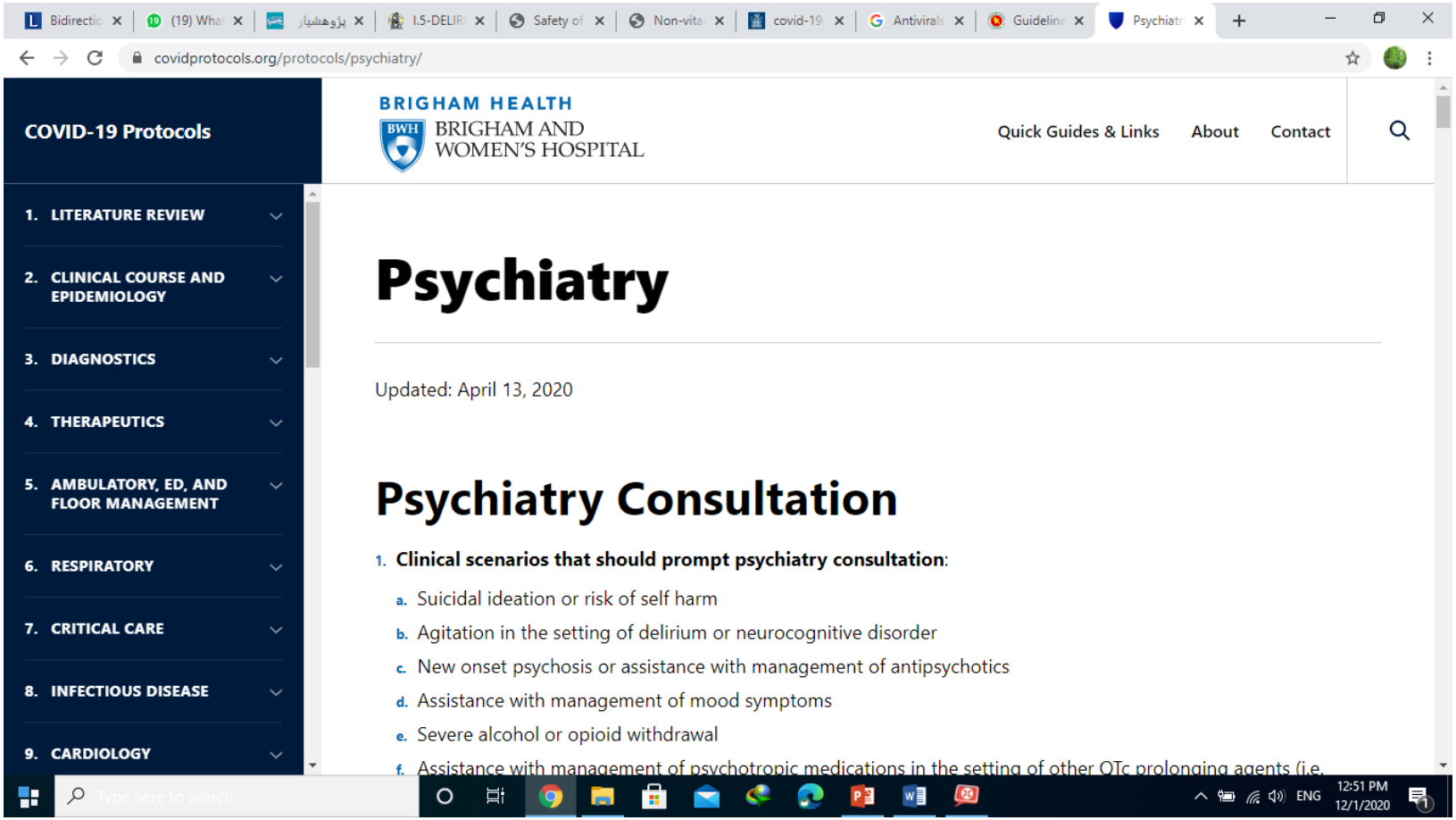
* Trihexyphenidyl may be added to prevent extrapyramidal symptoms

Insomnia and anxiety symptoms can be managed with the following[†]:

- Gabapentin (from 100mg) or pregabalin (from 25mg) can be used starting at low doses.
- Trazodone up to 50mg or mirtazapine up to 15mg.
- Lorazepam, lormetazepam, oxazepam and temazepam do not interact with COVID-19 drugs.
- Other benzodiazepines can have increased exposure due to LPV/r pharmacokinetic inhibition, so that respiratory depression effects need to be monitored.

Antidepressants[†]:

- Abrupt withdrawal of most antidepressants (especially paroxetine and venlafaxine) may trigger discontinuation symptoms.
- Tricyclic antidepressants should be avoided due to cardiotoxicity. If required, slow reintroduction at low doses is recommended.
- Among SSRI, fluoxetine and fluvoxamine have few interactions, whereas escitalopram and citalopram present the most interactions.
- Sertraline concentration is reduced by coadministration with LPV/r.
- Bupropion concentrations are ≈50% decreased by LPV/r.
- Vortioxetine, duloxetine and phenelzine have few interactions and can be used safely.


covidprotocols.org/protocols/psychiatry/
COVID-19 Protocols
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6. RESPIRATORY
7. CRITICAL CARE
8. INFECTIOUS DISEASE
9. CARDIOLOGY
Psychiatry
Updated: April 13, 2020
Psychiatry Consultation
1. Clinical scenarios that should prompt psychiatry consultation:
a. Suicidal ideation or risk of self harm
b. Agitation in the setting of delirium or neurocognitive disorder
c. New onset psychosis or assistance with management of antipsychotics
d. Assistance with management of mood symptoms
e. Severe alcohol or opioid withdrawal
f. Assistance with management of psychotropic medications in the setting of other QTc prolonging agents (i.e.
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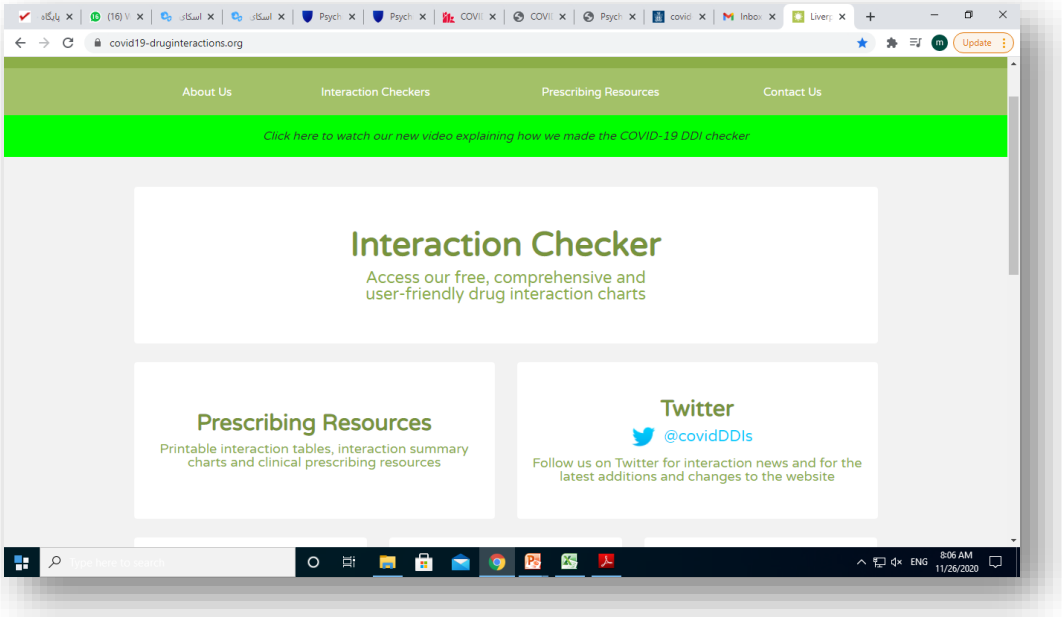
Drug Interactions of Psychiatric and COVID-19 Medications

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

https://reference.medscape.com/druginteractionchecker



1. Drug interactions are major challenge in comorbidity of psychiatric disorders and COVID- 19 infection

2. QTc prolongation is a major concern while using antiviral medications and/or Chloroquine/hydroxychloroquine in combination with many psychotropics. Cardiac monitoring especially in high risk patients is highly recommended.

3. Concomitant use of SSRIs with antiviral medications and/or Chloroquine/hydroxychloroquine increase the risk of hypoglycemia.or Concomitant use of pimozide or midazolam with antiviral medications is contraindicated.

4. Drug induced Psychiatric disorders Such as Hydroxychloroquine-induced acute psychosis.

5. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects such as Fluoxetine , paroxetine as a CYP2D6 inhibitor affect Risperidone , Increased risk of extrapyramidal adverse effects .

QTc prolongation

Table 1
Psychiatric drugs with high risk of QTc prolongation.

First generation antipsychotics:	Thioridazine, Haloperidol, Pimozide, Chlorpromazine.
Second generation antipsychotics:	Quetiapine, Iloperidone, Ziprasidone, Clozapine.
Selective Serotonin Reuptake Inhibitors:	Escitalopram
Tricyclic Antidepressants:	Amitritilline, Nortryptilline, Imipramine, Clomipramine, Imipramine
Serotonin Norepinephrine Reuptake Inhibitor:	Venlafaxine
Other antidepressant:	Mirtazapine

- Olanzapine and aripiprazole are considered to have least QTc prolongation.

- **Baseline ECG to check for QTc is a must in these situations. If QTc is more than 440mSec in males or 470 mSec in females then there is risk of developing cardiac arrythmia.**

Drug induced Psychiatric disorders

Corticosteroid induced psychiatric disorders

https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, **psychiatric effects**, avascular necrosis).

- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 **inducer.** Clinicians should review a patient's medication regimen to assess potential interactions.

Drug induced Psychiatric disorders

- The mechanism of the psychiatric side effects of corticosteroids remains unclear.

- Corticosteroids have been associated with a decrease in serotonin levels, which could contribute to depression.

- Some studies suggest that the steroids increase dopamine concentration in the brain.

Saira Khan-2011

Current Psychiatry. 2017 June;16(6):50-51

Drug induced Psychiatric disorders

- Psychiatric symptoms associated with corticosteroid therapy include mood swings, mania, hypomania, and depression. Mania and hypomania are more common than depression.
- The association of adverse psychological side effects with the use of oral and systemic steroids has been well documented in both the adult and the pediatric populations.

Drug induced Psychiatric disorders

- Lewis and Smith reported a median time to onset of 11.5 days; 39% of cases had onset during the first week and 62% within 2 weeks. Hall et al. noted that **86%** of patients with psychiatric side-effects developed these symptoms within 1 week of starting treatment.

- In most cases, reported symptoms are insomnia, aggressiveness, uninhibited behavior, mania, irritability, and increased energy.
- In most cases, the symptoms resolved after discontinuation of the drug, switching to another drug, or decreasing the dosage.

Drug induced Psychiatric disorders

➢incidence

- In a meta-analysis of 11 uncontrolled studies involving 935 adult patients, Lewis and Smith found incidences of psychiatric reactions ranging from 13% to 62% with a weighted-average incidence of 27.6%.

Drug induced Psychiatric disorders

- Educating patients about potential adverse effects and asking about such effects at each patient encounter can enhance early intervention for adverse corticosteroid-induced psychiatric reactions.

- Patients should be evaluated for any suggestion of suicidality.
  - Among patients with corticosteroid-induced psychosis **33%** experience suicidal ideation.

Bräunig P, Bleistein J, Rao ML. Suicidality and corticosteroid-induced psychosis [letter]. *Biol Psychiatry*. 1989;26:209-210.

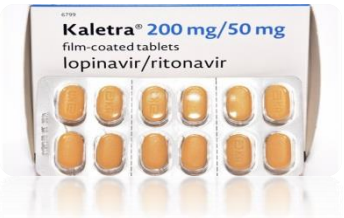
Drug induced Psychiatric disorders

- For patients who cannot tolerate corticosteroid cessation or dose reduction or who suddenly develop psychosis, severe agitation, aggressive behavior, or other intolerable symptom complexes, palliative pharmacotherapy is indicated, even though no definitive treatment has been identified.

- Myriad case reports have shown varying degrees of clinical success with mood stabilizers including lithium, carbamazepine, and valproic acid with selective serotonin reuptake inhibitors (SSRIs) including fluoxetine and sertraline, and with venlafaxine typical antipsychotics, and atypical antipsychotics.

Drug-Drug interactions

Ritonavir/Lopinavir



- Ritonavir/Lopinavir are contraindicated if patient is on Pimozide, as it may cause life threatening cardiac arrhythmias. These protease inhibitors (PI) are potent CYP3A4 inhibitors, so any psychotropic which is metabolized mainly through CYP3A4 (Buspirone, Clonazepam, Carbamazepine, Lurasidone,Quetiapine, Mirtazapine, Trazodone) **should be dose adjusted or stopped.**

- Due to above reason, when administered with midazolam, it can cause prolonged respiratory depression and with sildenafil it can cause persistent erection.

- Also, PIs are themselves substrates of CYP3A, so any psychotropic that inhibits (Fluvoxamine) or induces (Carbamazepine, Topiramate) CYP3A are better replaced with alternative drugs (English et al., 2012).

- Ritonavir/Lopinavir, by inducing glucuronidation in liver reduces serum levels of Valproate and Lamotrigine; so appropriate dose adjustments of these anticonvulsants are required, preferably with serum level monitoring (Sheehan et al.2006).

- FDA recommends reducing the dosage of **Quetiapine to 1/6th** and to monitor for Quetiapine related adverse effects. (Coadministered with strong CYP3A4 inhibitors (ritonavir).

- If the patient is on disulfiram, it can cause disulfiram reaction as the combination oral solution (not capsule) of Ritonavir/Lopinavir contains 42.4 % ethanol (v/v) alcohol . (Cvetkovic and Goa, 2003).

Drug-Drug interactions

Remdesivir

- There is no data regarding its interaction with psychotropics. However,it can cause elevated liver enzymes (FDA, 2020) which means drugs like valproate and benzodiazepines should be used with caution.

- There are no published reports of prolonged QTc, torsades de pointes, or arrhythmias in any database, including the World Health Organization's VigiBase or FDA Adverse Event Reporting System.

Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Remdesivir (GS-5734). FDA website. https://www.fda.gov/media/137566/download. Accessed May 16, 2020.

Drug-Drug interactions
Favipiravir

- FAVI is a weak inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 .
- The QT interval prolongation risk is considered to be low with FAVI.
- Some psychotropic levels are expected be increased due to weak CYP inhibition by FAVI , but since there are no reports of this.
- A dose change may not therefore be required but it is important to be aware of a potential interaction.

Drug-Drug interactions
Famotidine

-ECG changes are seen; prolonged QT interval has been reported in patients with moderate-to-severe renal impairment.

➢The FDA has received reports of torsades de pointes occurring with FAM.

➢ It can very rarely cause psychiatric effects such as depression, anxiety and hallucinations.

-FAM is considered a weak CYP1A2 inhibitor and theoretically, co-administration can lead to increased levels of clozapine, olanzapine and agomelatine as they are predominantly CYP 1A2 substrates.

Selective serotonin reuptake inhibitors(SSRIs)

- Common but relatively mild side-effects include gastritis, diarrhoea, insomnia, and sexual dysfunction. Unusual but notable side effects include the risk of **hyponatremia** and an increase in bleeding tendencies.
- Rare side effects include serotonin syndrome, which occurs when combined with other serotonergic drugs.

Selective serotonin reuptake inhibitors:

- **All SSRIs** are metabolized by cytochrome P450 enzymes and some of them (such as fluoxetine) can inhibit these enzymes. Therefore, SSRIs' interactions with other cytochrome P450 substrates should be considered .

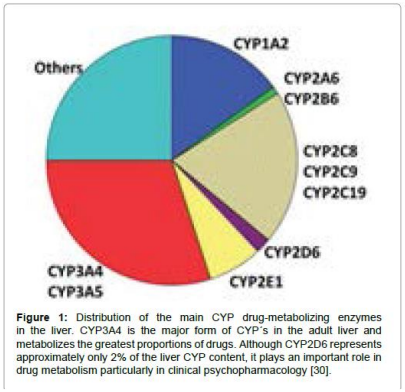


Figure 1: Distribution of the main CYP drug-metabolizing enzymes in the liver. CYP3A4 is the major form of CYP's in the adult liver and metabolizes the greatest proportions of drugs. Although CYP2D6 represents approximately only 2% of the liver CYP content, it plays an important role in drug metabolism particularly in clinical psychopharmacology [30].

Selective serotonin reuptake inhibitors

- Among antidepressants, fluoxetine and paroxetine have the **greatest inhibitory effect on CYP2D6**; fluvoxamine strikingly inhibits CYP1A2 and CYP2C19. Hence, when these medications are prescribed with substrates of the relevant isozymes together, clinically interactions may be anticipated, especially those with a narrow therapeutic range.

- Duloxetine, sertraline, and bupropion inhibit CYP2D6 **moderately**, but sertraline at a high dose may have more potency to inhibit CYP2D6.

- Citalopram, escitalopram, venlafaxine, mirtazapine have a **weak** or negligible inhibitory effect on CYP isozymes in vitro, so significant interactions are less likely to occur with concomitant use of this cytochrome's substrates. (Spina, Santoro, & D'Arrigo, 2008)

Psychotropic Medication	Lopinavir/Ritonavir	Chloroquine/ hydroxychloroquine	Implication
Fluoxetine	↑ risk for serotonin syndrome and hypoglycemia ↑ Ritonavir via CYP2D6 and CYP3A4	Risk of hypoglycemia	Caution in patients with diabetes
Sertraline	↑Sertraline via CYP3A4	Risk of hypoglycemia	Caution in patients with diabetes
Citalopram/Escitalopram		↑QTc	Cardiac monitoring especially in high-risk patients
Paroxetine	↓ Paroxetine via CYP2D6 and protein binding displacement	Risk of hypoglycemia	
Fluvoxamine	↑ Ritonavir via CYP3A4	Risk of hypoglycemia	

Psychotropic Medication	Lopinavir/Ritonavi	Chloroquine/ hydroxychloroquine	Implication
SNRIs		↑ QTc	Cardiac monitoring especially in high-risk patients
TCAs	↑ TCAs via CYP2D6	↑QTc	dose reduction is not necessary,monitor TCA side effects
Bupropion	↓ Bupropion via CYP2B6		Monitor clinical effectiveness of bupropion
Trazodone	↑Trazodone via CYP3A4	↑QTc	Cardiac monitoring especially in high-risk patients Sedation may also occur
Mirtazapine	↑ Mirtazapine via CYP3A4		Use the lowest efficient dose

Psychotropic Medication	Lopinavir/Ritonavir	Chloroquine/ hydroxychloroquine	Implication
Valproic acid	↓ Valproate ↑ Lopinavir		Monitor for lopinavir toxicity and virologic response
Lamotrigine	↓ Lam via UGTs		A dose increase is recommended
Carbamazepine	↓ Lopinavir	↑ Chloroquine	
Lithium			

Psychotropic Medication	Lopinavir/Ritonavir	Chloroquine/ hydroxychloroquine	Implication
Risperidone	↑ Risperidone via CYP3A4 and 2D6		
Aripiprazole	↑ Aripiprazole via CYP3A4 and 2D6		Dose reduction
Olanzapine	↓ Olanzapine via CYP1A2	↑QTc	
Quetiapine	↑ Quetiapine via CYP3A4	↑QTc	Cardiac monitoring
Clozapine	Additive metabolic toxicities	↑QTc	Consider alternative agents
Chlorpromazine		↑QTc	
Pimozide	↑ Pimozide via CYP3A4	↑QTc	**Contraindicated**

Psychotropic medication	Lopinavir/Ritonavir	Chloroquine/ hydroxychloroquine	Implication
Midazolam	↑ Midazolam via CYP3A4		Contraindicated
Diazepam	↑ Diazepam via 3A4		Dose reduction
Alprazolam	↑ Alprazolam via 3A4		Monitor sedation and dose reduction
Triazolam	↓ Triazolam via 3A4		
Zolpidem	↑ Zolpidem via 3A4		Not clinically significant
Buspirone	↑ Buspirone via 3A4		Dose adjustment is not usually necessary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Precautions in COVID-19 patients

- Antivirals tend to increase levels of certain SSRIs (particularly fluoxetine, paroxetine) and may increase the risk of serotonin syndrome.

- Escitalopram and sertraline are safer because of lesser drug interactions and side effects.

Precautions in COVID-19 patients

- There is No interaction between SSRIs and Ribavirin. (Hou, Xu, Wang, & Yu, 2013)
- SSRIs may cause hypoglycemia via different mechanisms

- Hydroxychloroquine Also, chloroquine can induce symptomatic or asymptomatic hypoglycemia in diabetic and nondiabetic patients .

- Thus, one should contemplate further monitoring of glycemic control in patients receiving an agent with blood glucose-lowering effects concurrently with an SSRI and chloroquine or hydroxychloroquine.

Precautions in COVID-19 patients

- Lithium is excreted unchanged in the urine and hence is the least likely to have specific drug interactions with antiviral drugs.

- Valproate level may decrease with Ritonavir but is generally safe with other antiviral drugs. Similarly, lamotrigine levels may decrease with Ritonavir.

Precautions in COVID-19 patients

- Lopinavir and Ritonavir can increase levels of haloperidol, olanzapine, and quetiapine.
- Hence it is imperative to monitor for adverse effects and reduce the dose of the latter if required.

Precautions in COVID-19 patients

- Azithromycin and hydroxychloroquine can cause QTc prolongation which can worsen when combined with haloperidol/quetiapine/ziprasidone.

- They have to be used cautiously, with ECG evaluation, in patients with underlying cardiac conditions.

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

- Non-vitamin K antagonist oral anticoagulants

Precautions in COVID-19 patients
Rivaroxaban

Rivaroxaban is metabolized by CYP3A4,antidepressants that are inhibitors of this isoenzyme, such as fluoxetine ,sertraline, paroxetine and fluvoxamine must be avoided.

- Based on drug interactions in cytochrome p450, the use of escitalopram, citalopram, venlafaxine, mirtazapine would be safer in such patients since these drugs have a minimum CYP 450 inhibition potential.

Common drug interactions with Non-vitamin K Antagonist Oral Anticoagulants (NOACs)

Interacting drug	Pharmacodynamic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Antidepressants					
SSRIs/SNRIs	Increased bleeding risk ***NB**: review if gastro-protection is indicated*	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk *(e.g. Age ≥ 75 years, 30-50 mL/min CrCl, Low body weight (< 50 kg), diseases / procedures with special haemorrhagic risks or*	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk	Monitor for signs of bleeding Review benefits vs. risks, considering other factors contributing to increased bleeding risk

Common drug interactions with NOACs

Interacting drug	Pharmacokinetic interaction	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Carbamazepine	Strong inducers of both CYP3A4 and P-gp[2]	Avoid concomitant use[3]	Avoid concomitant use[7]	Avoid concomitant use[13] ***NB**: SPC notes* *- Prevention of stroke and systemic embolism NVAF and prevention of recurrent DVT and PE: use with caution;* *- Treatment of DVT and treatment of PE: not to be used*[5]	Use with caution[14]
Phenobarbitone	Strong inducers of both CYP3A4 and P-gp[2]	Not documented in SPC[3] Concomitant use should be avoided[2]	Avoid concomitant use[7]	Avoid concomitant use[13] ***NB**: SPC notes* *- Prevention of stroke and systemic embolism NVAF and prevention of recurrent DVT and PE: use with caution;* *- Treatment of DVT and treatment of PE: not to be used*[5]	Use with caution[14]

Interactions between SSRIs, SNRIs and NOACs

Drug	*Rivaroxaban*	*Apixaban*	*Edoxaban*	*Dabigatran*
Fluvoxamine	*NR*	*NR*	*NR*	*NR*
Fluoxetine	*NR*	*NR*	*NR*	*NR*
Paroxetine	*CR[4]*	*NR*	*NR*	*NR*
Citalopram	*NR*	*NR*	*NR*	*NR*
Sertraline	*CR[4]*	*NR*	*NR*	*NR*
Escitalopram	*NR*	*NR*	*NR*	*NR*
Venlafaxine	*NR*	*NR*	*NR*	*NR*
Milnacipran	*NR*	*NR*	*NR*	*NR*
Duloxetine	*NR*	*NR*	*NR*	*NR*

NR-not reported, CR-case report

Curr Probl Psychiatry 2018; 19(4):267-278

Chloroquine Psychosis : A Chemical Psychosis?


Donald J. Trump
@realDonaldTrump
HYDROXYCHLOROQUINE & AZITHROMYCIN, taken together, have a real chance to be one of the biggest game changers in the history of medicine. The FDA has moved mountains - Thank You! Hopefully they will BOTH (H works better with A, International Journal of Antimicrobial Agents).....
9:13 AM · Mar 21, 2020 · Twitter for iPhone
86.4K Retweets
311K Likes
Donald J. Trump @realDonaldTrump · 12h
Replying to @realDonaldTrump
....be put in use IMMEDIATELY. PEOPLE ARE DYING, MOVE FAST, and GOD BLESS EVERYONE! @US_FDA @SteveFDA @CDCgov @DHSgov
13.5K
25.6K
112.9K

Chloroquine Psychosis : A Chemical Psychosis?

- More than **7.1 %** of people who took chloroquine as prophylaxis or for treatment of malaria developed "mental and neurological manifestations" (Bitta et al., 2017).

- Two types of presentation of chloroquine psychosis could be seen:

  - (1) psychic with clear sensorium, mood changes, alteration in motor activity, delusions, and hallucinations.

  - (2) psycho-organic with clouded sensorium, disorientation, and fleeting hallucinations.

- The precise nature of the mechanism of the psychosis is not clear because of the limited number of reported cases.

JOURNAL OF THE NATIONAL MEDICAL ASSOCIATION, VOL. 73, NO. 11, 1981

P.S. Biswas et al. / General Hospital Psychiatry 36 (2014) 181–186

Chloroquine Psychosis : A Chemical Psychosis?

TABLE 1. PSYCHIATRIC MANIFESTIONS OF CHLOROQUINE

Psycho-organic Symptoms	Clouding of sensorium, disorientation, confabulation, fleeting hallucinations
Psychotic Symptoms	Restlessness, agitation, outbursts of violence, depression, suicidal ideas, suicide, delusions of persecution and grandeur, hallucinations (visual and auditory), elation, irritability, perplexity or rapid fluctuation of mood, amok syndrome, irrelevant talk, insomnia, personality change

P.S. Biswas et al. / General Hospital Psychiatry 36 (2014) 181–186

Chloroquine/Hydroxychloroquine

- Hydroxychloroquine is known to cause seizure, neutropenia, and myocardial toxicity. Clozapine also has similar side effect profile (Haas et al., 2007). So, concomitant use of the two can be fatal and best avoided.

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Drug interactions between commonly used medications in delirium and COVID- 19 drugs

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	NITAZ	RBV	TCZ
Aripiprazole	↑	↑	↔	↔	↔	↔	↔	↔	↔
Haloperidol	↑♥	↑♥	↔	↔	↔♥	↔♥	↔	↔	↔
Olanzapine	↔	↓	↔	↔	↔	↔	↔	↔	↔
Quetiapine	↑♥	↑♥	↔	↔	↔♥	↔♥	↔	↔	↔
Risperidone	↑♥	↑♥	↔	↔	↑♥	↑♥	↔	↔	↔
Diazepam	↑	↑	↔	↔	↔	↔	↔	↔	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Midazolam (oral)	↑	↑	↔	↔	↔	↔	↔	↔	↔
Midazolam (parenteral)	↑	↑	↔	↔	↔	↔	↔	↔	↔
Oxazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zaleplon	↑	↑	↔	↔	↔	↔	↔	↔	↔
Zolpidem	↑	↑	↔	↔	↔	↔	↔	↔	↔
Zopiclone	↑	↑	↔	↔	↔	↔	↔	↔	↔

Key

- ↑ Potential increased exposure of the co-medication
- ↓ Potential decreased exposure of the co-medication
- ⇑ Potential increased exposure of COVID drug
- ⇓ Potential decreased exposure of COVID drug
- ↔ No significant effect
- ♥ One or both drugs may cause QT and/or PR prolongation.

ECG Monitoring is advised if co-administered

Colour Legend

	These drugs should not be co-administered
	Potential interaction which may require a dose adjustment or close monitoring.
	Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment unlikely to be required.
	No clinically significant interaction expected

The End

- Comments
- Question and answer
- Thank you!

Tehran University of Medical Sciences