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

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Neuropsychiatric manifestation of the drugs used in the treatment of SARS-2-CoV-2019 (COVID-19) infection and their management: An overview and practice implications

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ABSTRACT

Treatment guidelines for the COVID-19 treatment are still evolving, moreover, the changing variants of the virus with varying virulence, pose challenges for the healthcare professionals (HCP) not only in managing the primary infection but also a myriad of physical and neuropsychiatric complications. The neuropsychiatric adverse consequences associated with the COVID-19 are attributable to the direct effect of the virus, secondary complications, drug-drug interaction, and neuropsychiatric manifestations of drugs used in its treatment. These neuropsychiatric manifestations not only complicate the ongoing treatment but also adversely affect the prognosis. As the treatment guidelines for the management of the COVID are still evolving, the use of non-evidence-based medications, including their off-label use, are rampant that often extend to their non-judicious or irrational use (more than the recommended dose, multiple medications, etc.). Despite the significance of the topic, literature is sparse. Knowing about the risk factors and the potential neuropsychiatric adverse effects with various anti-COVID-19 medications would help HCPs in effectively preventing, early identifying, and promptly managing these neuropsychiatric symptoms. Therefore, this narrative review is aimed to highlight the neuropsychiatric symptoms associated with medications/interventions used in the management of COVID-19 and how to manage them, especially in view of the world facing the third wave of COVID-19.

1. Introduction

Neuropsychiatric (NP) manifestations are common among patients of COVID-19 infection both during the illness and post-recovery, especially in case of severe illness (García et al., 2020; Helms et al., 2020; Mao et al., 2020). Common neuropsychiatric symptoms include anxiety (and related disorders), mood disorders, headache, insomnias, delirium, pain, seizures, movement disorder, suicidal ideations, etc. (Nalleballe et al., 2020). The proposed mechanisms are direct neurotoxicity by the virus, associated psychosocial stressors, the impact of the co-occurring medical or psychiatric comorbidities, COVID-19 treatment-related, etc. Clinical presentation and course of the COVID-19 illness has varied across the first two waves of the pandemic: a higher prevalence of illness among the young, higher secondary infection (e.g., mucormycosis and associated morbidity and mortality) in the second wave (Vs first wave), etc. (Asrani et al., 2021; Conde Cardona et al., 2020).

The COVID-19 infections and associated neuropsychiatric manifestations pose a significant challenge to the healthcare professionals (HCPs). Particularly, immunomodulatory agents (hydroxychloroquine, ivermectin, remdesivir, systemic steroids, etc.) are associated with greater and severe symptoms such as delirium, psychosis, mood symptoms, anxiety, etc. (Jansen van Vuren et al., 2021). Notably, the pediatric population is more likely (than adults) to develop these neuropsychiatric symptoms (Orsini et al., 2020).

The national guideline on the management of COVID-19, based on the severity of the symptoms, recommend various agents such as

Abbreviations: HCP, Healthcare professional; MHPs, mental health professionals; NP, neuropsychiatry; A/E, Adverse event; ADR, Adverse drug reactions; SARS, Severe acute respiratory syndrome.

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antipyretics like acetaminophen; antitussives; ivermectin, hydroxychloroquine/chloroquine, azithromycin, doxycycline; inhalational budesonide, methylprednisolone, dexamethasone; unfractionated heparin or low molecular weight heparin (UF/LMWH); remdesivir, tocilizumab; convalescent plasma, etc. (Clinical Guidance for Management of adult COVID-19 patients, AIIMS Delhi, 2021).

As the treatment guidelines are evolving and efficacy data on these treatments is still scarce, non-judicious use of medications (prednisolone; remdesivir; hydroxychloroquine, immunomodulators, etc.) are rampant (Leroy, 2020; Ved, 2021), resulting in greater neuropsychiatric adverse events (A/Es) among patients.

However, these symptoms, particularly medications-induced neuropsychiatric A/Es, often remain unrecognized; while these symptoms pose significant management difficulties, including higher morbidity and mortality (Nalleballe et al., 2020). Therefore, the clinicians must remain aware of these A/Es, including how to prevent, and identify early, and manage them (Kalil, 2020).

Although there is ample literature on the neuropsychiatric consequences of the COVID-19 infection and its association with comorbid psychiatric illnesses, including drug-drug interaction (psychotropic drugs and COVID-19 medications), data is scarce on COVID-19 treatment-induced neuropsychiatric manifestations. Availability of such literature would guide the clinicians in rational drug prescription, thereby having primary and secondary preventive implications. Moreover, this becomes particularly important when the world is facing the third wave of the COVID-19 pandemic. Therefore, the current review aims to highlight the neuropsychiatric symptoms associated with the medications used in the treatment of the COVID-19 and their management.

2. Material and methods

A literature search was undertaken, including visiting the websites of various international (National Institute of Health, National Institute of Clinical Excellence, Infectious Diseases Society of America) and national agencies (All India Institute of Medical Sciences, Delhi, Indian council of medical research (ICMR), etc.) to enlist the medications commonly used in the treatment of the COVID-19 infections and related complications. Furthermore, drugs that are often used off-label or those approved for compassionate use were also considered.

Keywords/search terms used were drug's name ("Ivermectin", "hydroxychloroquine", "prednisolone", etc.) and "adverse effects"/"neuropsychiatric effects"/"adverse effects in COVID-19" in google scholar and PubMed.

The pharmacological properties of these agents were also reviewed through the published journal articles, standard textbooks, and relevant documents provided by the government bodies (AIIMS Covid Information Portal, n.d.; Indian Council of Medical Research, n.d.) and academic agencies (National institute of Health, 2021; World Health Organization, 2021).

3. Findings

The findings have been described in terms of pharmacokinetics and pharmacodynamics of drugs used in the management of the COVID-19 and its complications, their level of evidence for use in COVID-19 infection, adverse drug reactions (mainly neuropsychiatric symptoms), and management (detail in Table 1). Following this, a general approach to prevent and manage neuropsychiatric A/Es has also been provided (Table 2).

3.1. Medications used in the management of the COVID-19 infections and their neuropsychiatric adverse effects

The medications have been described as per the following pharmacological groups: antimicrobial agents (anti-parasitic, antibacterial, antivirals, antifungals; glucocorticoids; immunomodulators;) and miscellaneous.

3.1.1. Anti-parasitic agents

3.1.1.1. Ivermectin. Evidence for COVID-19 Infection: Because of lack of definitive evidence, the NIH does not recommend or advise against its use in patients suffering from COVID-19 disease (National institute of Health, 2021).

Precautions and Adverse neuropsychiatric Effects: The common neuropsychiatric adverse effects (A/Es) (data from the treatment of helminthic infections) are weakness, increased sleep, headache (10%), dizziness (7.5%)(Chandler, 2018). Additionally, encephalopathies/delirium, psychotic disorders (Mohapatra and Sahoo, 2015), suicidal behavior (Kaur et al., 2017) have been reported with its use (Campillo et al., 2021).

Management of neuropsychiatric A/Es: Given limited efficacy data for ivermectin's role in COVID-19, it should be used only after carefully weighing the risks and benefits, and as per the clinicians' discretion. Although there are no specific guidelines on how to manage the neuropsychiatric symptoms associated with the ivermectin, avoiding this drug in patients with severe headache and dizziness or withholding it if such symptoms pose a significant management challenge. Caution should be exercised in patients with a history of psychiatric disorders (Katzung, 2015).

3.1.1.2. Chloroquine and hydroxychloroquine. Evidence for COVID-19 Infection: These drugs have not yet received Food and Drug Administration (FDA) approval for use in COVID 19; to the extent that NIH recommends against its use (National institute of Health, 2021).

Precautions and Adverse neuropsychiatric Effects: Apart from the common ADR related to gastrointestinal, dermatological, hematological (Katzung, 2015), cardiovascular, endocrinological systems, etc., they could give rise to neuropsychiatric symptoms like confusion; extrapyramidal symptoms like dystonia, dyskinesia, tremors; seizures (Concordia Pharmaceuticals, 2017); and rarely, delusion, hallucinations, mania, affect lability, irritability, and nightmares (The Medical Letter, 2008).

Management of neuropsychiatric A/Es: Literature does not state any specific guidelines to manage the above A/Es. However, risk assessment, avoiding higher than recommended doses, monitoring for the above symptoms, and stopping the drug if any A/Es emerge is important.

3.1.2. Antibiotics

3.1.2.1. Azithromycin. Evidence for COVID-19 Infection: Although, azithromycin is frequently used for its potential role in preventing/treating secondary bacterial infection among COVID-19 patients (Butler et al., 2021), it is not FDA approved for COVID-19, and NIH does not recommend its use in COVID-19 patients (National institute of Health, 2021).

Precautions and Adverse neuropsychiatric Consequences: Macrolides predisposes an individual to develop a series of cardiac problems (QT prolongation, arrhythmia, and death) (Katzung, 2015). They also, though rarely, cause neuropsychiatric symptoms like psychosis, delirium, hallucinations, particularly in elderlies (Skelly et al., 2019; The Medical Letter, 2008). Other rare ADRs include headache, dizziness, sleep disturbances, seizures, choreoathetosis, etc. (Turjanski and Lloyd, 2005).

Management of neuropsychiatric A/Es: Neuropsychiatric A/Es are rare and should be reported if they do occur. Psychiatric symptoms after starting azithromycin should be an indication to stop the drug(Skelly et al., 2019). Management for these symptoms includes decreasing the dose or discontinuation of the drug and administration of the psychotropic medications in severe cases (Turjanski and Lloyd, 2005).

Table 1
Neuropsychiatric manifestations of drugs used in the management of the COVID-19 infection and their management.

Class of drug	MOA	Evidence:	Adverse NP symptoms	Management
Anti-microbial agents				
Ivermectin (IVM) (anti-parasitic agent)	**I**nhibiting the importin α/β rec. responsible for transmitting viral proteins into the host cell nucleus (Heidary and Gharebaghi, 2020)	• No definitive evidence • Clinical trials comparing IVM (vs other interventions or placebo) shows IVM gr. had faster virus clearance, shorter hospital stay, & lesser deaths. • However, there are mixed results & some methodological limitations (low sample size, inadequate randomization, invl'ng mild disease). (National institute of Health, 2021).	Weakness, increased sleep, headache, dizziness, encephalopathies, psychotic disorders, suicidal behavior, delirium (Chandler, 2018)	• No specific guidelines • May try dose reduction or stopping the drug • Cautious use in at-risk individuals or those with psychiatric disorders
Chloroquine (CQ) and hydroxy-CQ	1. Blocks SARS-CoV-2 virus binding to ACE 2 rec., prevents viral entry into the host (Pastick et al., 2020) 2. Raises vesicular pH, thus prevents virus-host cell fusion (Wang et al., 2020) 3. (-) viral genome release by stopping endolysosome maturation (Liu et al., 2020) 4. Immunomodulation	• Lacks evidence • The evidence for CQ/HCQ comes from the SARS-CoV pandemic, which has genetic similarities with SARS-CoV-2 (Pastick et al., 2020). • Notably, clinical studies have shown inconsistent efficacy of these agents in COVID-19 patients. (National institute of Health, 2021).	Impaired hearing, confusion, psychosis, depressed tendon, abnormal nerve conduction, extrapyramidal symptoms like dystonia, dyskinesia, tremors, seizures.	• No specific guidelines • Risk assessment • Avoiding higher than recommended doses, close watch for NP symptoms, & stopping the drug if any adverse effects start appearing
Azithromycin (A macrolide derivative of erythromycin)	**B**inds to the 50s ribosomal unit and prevents bacterial protein synthesis	• Lacks evidence for preventing/ treating COVID-19 infection, rather has a role in secondary bacterial infection. • In-vitro studies: It has antiviral & anti-inflammatory effects (Oliver and Hinks, 2021; Touret et al., 2020).	Headache, dizziness, sleep disturbances, seizures, vertigo, choreoathetosis, psychosis, and delirium	• Decrease the dose or stop the drug • Psychotropics can be used in severe cases
Doxycycline (anti-bacterial, a tetracycline group of drugs)	**B**inds to the 30S subunit of the bacterial ribosome and prevents protein production	• Lacks robust evidence for preventing/treating COVID-19 inf. • Preliminary data suggests it has antiviral & anti-inflammatory properties, thus, have a role in COVID-19 infection (Sodhi and Etminan, 2020; Yates et al., 2020). • Prevent/treats secondary bacterial inf.	Dizziness, vertigo, suicidality, and pseudotumor cerebri	• Decrease the dose or stop the drug • Psychotropics to be used in severe cases • Pseudotumor cerebri and suicidality may require additional interventions.
Remdesivir (a nucleotide analog antiviral drug)	An adenosine nucleotide analog induces lethal mutagenesis & chain termination. Effects are time-dependent & occur early in the viral infectious cycle (Agostini et al., 2018; CHMP, 2016).	• Emergency Use Authorization **(EUA)** by **FDA**	Delirium, agitation, confusion, anxiety, emotional disturbances, neurotoxicity, paresthesia, taste alterations, malaise, headache, myalgias.	• No literature available. • However, lowering the dose or even stopping the drug could be useful strategies.
Lopinavir-ritonavir (Antiviral)	Inhibits protease enzyme required for viral replication Inhibits protease enzyme required for viral replication	• Open-label trial shows its effectiveness in COVID-19. • In vitro-studies have shown its efficacy against **SARS-CoV** and **MERS-CoV**.	–	–
Darunavir (Antiviral)		• Lacks evidence	–	–
Amphotericin B (a systemic antifungal drug derived from Streptomyces nodosus)	Binds to ergosterol in the cell membrane of the fungus, producing pores and cell death.	• Recommended for treating mucormycosis	Headache, anxiety, confusion, sleep issues, weakness, delirium, dizziness, encephal'hy, peripheral neuro'thy, parkinsonism, seizures. Intrathecal use: seizures	• Discontinuation or decreasing the dose of the drug • In a few cases, psychotropics can be used.
Posaconazole (Antifungal)	It is a broad-spectrum antifungal & effective against Mucormycosis	• Recommended for Mucormycosis	Headache, anxiety, dizziness, sleep problems, & weakness	• Discontinuation or decreasing the dose. • Psychotropics use in severe cases.
Glucocorticoids				
Dexamethasone, prednisolone, methyl-prednisolone	Has anti-inflammatory effect. Prevents COVID-19 infection related complications.	• Recommended strongly for hospitalized moderate to severe or critically ill patients for their have significant anti-inflammatory activity (National institute of Health, 2021). • RCTs and meta-analysis support that steroid reduce morbidity, incl. need for mechanical ventilation, and mortality in COVID-19 patients	Insomnias, emotional lability, irritability, pressured speech & euphoria, memory deficits & cognitive impairment, seizures, anxiety, depression, & mood changes, delirium, psychosis	• Should be tapered or stopped • *Mania/ hypomania:* Mood-stabilizers (e.g., Li, Valp, CBZ), atypical AP • Psychosis: atypical AP (e.g., olanzapine) • Depression: SSRIs (fluox. or other drugs like phenytoin, lam., risp, quet, & gabapentin.

(*continued on next page*)

Table 1 (*continued*)

Class of drug	MOA	Evidence:	Adverse NP symptoms	Management
		with moderate to severe ARDS. and mortality (Group et al., 2021; Mammen et al., 2020; Villar et al., 2020).		Avoid TCA
Inhalational budesonide		• Open-label trials support its effectiveness against COVID-19.	Hyperactivity, impaired concentration, mania, & insomnia	• Should be tapered or stopped, if clinically indicated.
Immunomodulators				
Interleukin-6 inhibitors: Tocilizumab (a monoclonal antibody)	Mitigate hyper inflammatory state results from COVID-19 infection or its complications.	• Recommended in hospitalized adults with severe/critical cases with elevated markers of systemic inflammation (Conditional recommendation, low certainty of evidence).	Headache, dizziness, peripheral neur'thy, leukoenc'thy, cognitive impairment, depression demyelinating ds.	• No literature available. • Lowering the dose or stopping the drug can revert symptoms
Neutralizing antibodies: Bamlanivimab & Estesevimb, or Casirivimab & Imdevimab	Target the rec. binding domain of SARS-CoV-2 spike protein.Animal studies: quickly reduce viral load, thereby, reducing the body damage (Bhimraj et al., 2020)	• Recommended in mild-mod cases & those at risk of progressing to sev. Ds. • Sev. ds: Bamlanivimab monotherapy • EUA given for: combination of casirivimab & imdevimab or bamlanivimab & etesevimab	Not reported	–
Janus kinase inhibitor e.g., Baricitinib	Inhibits phosphorylation of key proteins involved in immune reaction	• Recommended with remdesivir and corticosteroids only in clinical trials	Not reported	–
Miscellaneous				
LMWH or unfractionated heparin (anticoagulant)	revents clot formation by inhibiting thrombin, factor 9a, & 10a. PHMWH causes inhibition of all 3 factors, whereas LMWH mainly inhibits factor 10a	• Recommended in hospitalized patients to prevent thrombosis.	Not reported	–
Acetaminophen (a weak COX-1 and COX-2 inhibitor)	Standard antipyretic, rampantly used in COVID-19 infection.	–	At larger dose: dizziness, disorientation, mood symptoms, insomnia, cognitive changes, worsening of psychiatric ds.	• Avoid high doses in at-risk patients.

(-): inhibit, -: data not available, A/Es: adverse effects, Atypical AP: atypical antipsychotics, ACE: Angiotensin-Converting enzyme, ARDS: Acute Respiratory Distress Syndrome, CBZ: cabramezapine, COX: Cyclooxygenase, CQ: Chloroquine, ds.: disorders, EUA: Emergency Use Authorization, FDA: Food and Drug Administration, fluox: fluoxetine, HCQ: hydroxychloroquine, HIV: Human Immune-deficiency Virus, HMW: High molecular weight, incl.:including, inf.: infection, invl'ng: involving, Lam.: lamotrigine, Li:lithium, L/HMWH: Low/high Molecular Weight Heparin, MOA - Mechanism of action, MERS-CoV - Middle East respiratory syndrome coronavirus, quet:quetiapine, RCT: Randomized Controlled Trial, rec.: receptor, risp.: risperidone, SARS-CoV: Severe acute respiratory syndrome coronavirus, SSRIs: selective serotonin reuptake inhibitors, TCAs: Tricyclic Antidepressants,. Valp.: Valproate.

3.1.2.2. Doxycycline. Evidence for COVID-19 Infection: Although doxycycline does not have a direct clinical utility in COVID-19 infection (PRINCIPLE TRIAL, 2021; Robinson, 2021), likewise of azithromycin, it has a role in preventing and treating a secondary bacterial infection (National institute of Health, 2021; Robinson, 2021).

Precautions and Adverse neuropsychiatric Consequences: The most common ADRs are related to the gastrointestinal system (Katzung, 2015). Furthermore, likewise with azithromycin, it can rarely cause suicidality and pseudotumor cerebri among the patients (Skelly et al., 2019).

Management of neuropsychiatric A/Es: Pseudotumor cerebri and suicidality may require stoppage of the implicating agents and addition of other medications if symptoms do not subside (Skelly et al., 2019). General principles of treatment of neuropsychiatric symptoms remain as discussed previously (Turjanski and Lloyd, 2005).

3.1.2.3. Antiviral drugs. Remdesivir, Lopinavir-ritonavir, Darunavir are commonly used antiviral agents in COVID-19 infections.

Evidence for COVID-19 Infection: Remdesivir was issued by the US FDA as an emergency drug to treat hospitalized COVID-19 patients (Rhoades, 2020). The IDSA guideline also recommends it to treat severe COVID-19 in hospitalized patients; however, recommended for a greater level of evidence for its use. Open-label trials have shown, Lopinavir-ritonavir reduces mortality and need for ICU care in SARS-CoV-2 patients; however, there are negative results with Darunavir (Bhimraj et al., 2020).

Precautions and Adverse neuropsychiatric Consequences: There are case reports on Remdesivir-induced delirium in patients suffering from COVID-19 disease (Grein et al., 2020). Agitation, abnormal dreams, confusion, anxiety, emotional disturbances, neurotoxicity, paresthesia, taste alterations, malaise, headache, myalgias have been reported with Lopinavir-ritonavir. Moreover, Lopinavir-ritonavir (and darunavir) are liver enzymes inhibitor, therefore, should be used with caution with psychotropic drugs, as the former can increase the blood levels of the latter, thereby leading to neuropsychiatric symptoms. Particularly, among benzodiazepines, midazolam, triazolam, and diazepam should be avoided; instead, lorazepam and oxazepam can be used if indicated. Also, some of the antivirals can lower the blood levels of some psychotropics like bupropion, lamotrigine, methadone, and olanzapine; hence should be used with caution (Borah et al., 2021).

Management of neuropsychiatric A/Es: Although there is no specific literature on the management of the antivirals-induced neuropsychiatric A/Es, lowering or stopping the implicated agent should be the initial considerations. A milder form of neuropsychiatric symptoms can also be managed by short-term use of benzodiazepines (for anxiety, insomnia) or lithium and atypical antipsychotics (for irritability and restlessness) or SSRIs (for depression), etc.

3.1.3. Antifungals

3.1.3.1. Amphotericin B (AMB). Evidence for COVID-19 Infection: AMB has been recommended for treatment of Mucormycosis in COVID-19

Table 2
Prevention and management of neuropsychiatric adverse events.

- Healthcare professionals (HCPs) should be aware of various neuropsychiatric (NP) manifestations of the COVID-19 infection, particularly its treatment.
- HCPs should remain cautious of the adverse NP events, particularly in at-risk individuals[#].
- When treating COVID-19 patients, health care providers (HCPs) should resist from prescribing off-label medications and drugs with little or no evidence.
- The preventive strategies include:

– using lower doses- and lesser numbers- of medications.
– utilizing non-pharmacological methods, wherever possible.
– assessing various risk factors for the NP A/Es, incl. reducing modifiable risk factors.

- Obtaining adequate medical and psychiatric history and substance use, including the history of any NP events or adverse effects with the medications.
- Sensory stimulation for those in isolation ward/ICUs to prevent NP A/Es.
- Early identification of NP A/Es, establishing the causality, optimizing medications, and effectively treating such conditions would be the cornerstone of management.
- Other potential etiologies: BDZ withdrawal*; symptoms due to abrupt discontinuation of drugs; other physical illnesses** should also be looked for.
- NP symptoms directly related to COVID-19 infection itself and/ or associated complications[##] should be ruled out.
- Decreasing or stopping the offending agent should be the initial management strategy. However, when latter is not possible or in severe cases psychotropics should be used.
- Proper evaluation of these symptoms by the MHPs (through various Consultation-Liaison model) and timely intervention would be crucial if required.
- Pharmacovigilance should be in place in every hospital setup involved in COVID-19 patient care to encourage reporting and enrich the literature.
- Research should be encouraged to investigate the prevalence of-, risk factors for-, and management of- NP A/Es among individuals suffering from the COVID-19 illness.

[#]Such as those with multiple medical comorbidities, past or current history of psychiatric illness, elderlies, and drugs with a higher association with NP events (systematic steroids, immunomodulators, etc.).
*Withdrawal effects benzodiazepines (BZDs), antiparkinsonian medications, antipsychotics, antidepressants, steroids, etc.
**multiple sclerosis, lupus erythematosus, tumors, etc.,
[##]Severe illness or multiple medical morbidities, impaired hepatic or renal function or electrolyte imbalances (including abnormities in SpO2, pH), superimposed infections.
A/Es: adverse effects, ICUs: intensive care units, incl.: including, MHP: mental health professional.

patients (Mucormycosis, World Health Organization, 2021; Mucormycosis in COVID-19 AIIMS Covid Information Portal, n.d.).

Precautions and Adverse neuropsychiatric Consequences: ADRs due to AMB can be immediate (infusion-related toxicity) or delayed (cumulative toxicity). Intrathecal use has been associated with seizures or other neurologic sequelae (Katzung, 2015). Notably, headache is a more common A/E with both types of formulations. Specifically, conventional formulations are associated with neurotoxicity, parkinsonism, and seizures, whereas lipid formulations are associated more with confusion, sleep problems, fatigue, delirium, and dizziness (Ouyang et al., 2013).

3.1.3.2. Posaconazole. It is a new triazole antifungal drug (Katzung, 2015).

Evidence for COVID-19 Infection: Likewise of AMB, posaconazole has been recommend for treatment of Mucormycosis in COVID19 (Mucormycosis, World Health Organization, 2021; Mucormycosis in COVID-19 AIIMS Covid Information Portal, n.d.).

Precautions and Adverse neuropsychiatric consequences: Most common neuropsychiatric side effects are anxiety, dizziness, sleep disturbances, headache, and weakness. Other uncommon A/Es are confusion, seizures, peripheral neuropathy (Ouyang et al., 2013).

Management of neuropsychiatric manifestations of Antifungals: The general principles of management should be followed i.e., discontinuation or decreasing the dose of the drug, or in a few cases, psychotropics may be required (Turjanski and Lloyd, 2005).

3.1.4. Glucocorticoids

Drugs used from this group include dexamethasone, prednisolone, methylprednisolone, and inhalational budesonide.

3.1.4.1. Systemic glucocorticoids. Evidence for COVID-19 Infection: The Infectious Disease Society of America (IDSA) guideline panel strongly recommends oral/parenteral dexamethasone 6 mg (or equivalent doses of other glucocorticoids) for hospitalized severe or critically ill COVID-19 positive patients.

Precautions and Adverse neuropsychiatric Consequences: Systemic corticosteroids are known to cause neuropsychiatric A/Es. Usually, in COVID-19 illness, following a short course of high-dose corticosteroid treatment (> 20 mg/day prednisone for three months), delirium and mood changes (manic/hypomanic episodes > depression) have been reported (with prevalence as high as 52%) (Fardet et al., 2007). Memory deficits, cognitive impairment, agitation, and anxiety are other notable ADRs (Borah et al., 2021; Ou et al., 2018); they can also trigger seizures (Jarrahi et al., 2020; van Campen et al., 2018). Literature from the SARS-virus pandemic (2005) reports that corticosteroids account for 29.9%, 2.9%, and 18% of variances in anxiety, depression, and psychosis, respectively (Sheng et al., 2005). Furthermore, higher doses of steroid use have been associated with an increased incidence of psychotic symptoms among individuals suffering from the COVID-19 (Brown et al., 2020).

In previous reports of acute SARS-CoV-2 infection, mania and psychosis were found to occur only in a small minority (0.7%), but it was almost entirely associated with the use of exogenous corticosteroids. However, reduced sleep, emotional lability, irritability, pressured speech, and euphoria were more commonly reported instead of a full-fledged picture of mania (Rogers et al., 2020; Sheng et al., 2005).

Management of neuropsychiatric A/Es: Patients with COVID-19 receiving corticosteroids, especially in high doses and for long-duration, should be strictly monitored for these symptoms. Literature suggests that neuropsychiatric symptoms associated with the corticosteroids disappear after the tapering or stoppage of the drugs (Kahn et al., 1988; Wada et al., 2001). Whenever required, mood-stabilizers, such as lithium and valproic acid, or atypical antipsychotics like olanzapine, etc. should be used (Zagaria, 2016). Notably, carbamazepine induces steroids metabolism, thereby reducing the neurotoxic effects of the latter (Hall et al., 1978).

Corticosteroid-induced depressive episodes respond better to selective serotonin reuptake inhibitors, such as fluoxetine, or other drugs like lamotrigine, risperidone, quetiapine, and gabapentin, however, tricyclic antidepressants may worsen it (Wada et al., 2001; Wyszynski and Wyszynski, 1993).

3.1.4.2. Inhalational steroid. Evidence for COVID-19 Infection: The Steroids in COVID-19 (STOIC) trial, a phase 2, open-label trial (Active arm received budesonide (800 μg) in divided doses; controlled arm received treatment as usual) reported an early administration of budesonide significantly reduce the likelihood of COVID-19 related urgent medical care and also decreased time to recovery (Ramakrishnan et al., 2021).

Precautions and Adverse neuropsychiatric Consequences: There are some case reports of hyperactivity, impairment in concentration, mania, and insomnia, particularly in the pediatric population, with the use of budesonide (Connett and Lenney, 1991; Lewis and Cochrane, 1983). Literature involving the pediatric population found about 15% of their samples experienced some neuropsychologic A/Es (Hederos, 2004). These symptoms are more frequent in female adolescents (vs. males) and were dose-dependent (Hergüner et al., 2006).

Management of neuropsychiatric A/Es: The neuropsychiatric A/Es often occur within the first few days of starting inhalational budesonide, and get resolved upon tapering or discontinuing the drug (Alotaibi and Alshammari, 2012).

3.1.5. Immunomodulators

3.1.5.1. Interleukin-6 inhibitors

3.1.5.1.1. Tocilizumab. Evidence for COVID-19 Infection: IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) among hospitalized adults with progressive severe or critical COVID-19 illness (Bhimraj et al., 2020).

Precautions and Adverse neuropsychiatric Consequences: Headache, dizziness, peripheral neuropathy, leukoencephalopathy, cognitive impairment, demyelinating disorders, depression have been reported with the use of tocilizumab in chronic inflammatory conditions (Borah et al., 2021). Reports on adverse neuropsychiatric symptoms in COVID-19 with its use are, however, lacking; in contrast, tocilizumab has been found to improve cognition in individuals suffering from schizophrenia (Miller et al., 2016). Slow titration of the dose of the tocilizumab can be a preventive strategy against the development of neuropsychiatric A/Es.

Management of neuropsychiatric A/Es: Decreasing the dose or stopping it, whenever required, could revert these symptoms. Furthermore, a low dose of psychotropic medications for a shorter duration can be used to treat these symptoms, particularly when stopping the drug is not possible.

3.1.5.2. Neutralizing antibodies and Janus kinase inhibitor

3.1.5.2.1. Bamlanivimab/etesevimab, casirivimab/imdevimab; and baricitinib. Evidence for COVID-19 Infection: The IDSA guideline panel recommends bamlanivimab/etesevimab or casirivimab/imdevimab in ambulatory patients with mild to moderate COVID-19 illness who are at high risk for progression to severe disease. It also strongly recommends against bamlanivimab monotherapy in hospitalized patients with severe COVID-19. The combination of casirivimab and imdevimab and bamlanivimab and etesevimab have been approved by the FDA while bamlanivimab monotherapy has been revoked. IDSA also recommends baricitinib plus remdesivir plus corticosteroids for hospitalized patients (Bhimraj et al., 2020).

Precautions and Adverse neuropsychiatric consequences: There is no reported neuropsychiatric adverse effect with these agents.

3.1.6. Miscellaneous

3.1.6.1. Low molecular weight heparin (LMWH) or unfractionated heparin. Evidence for COVID-19 Infection**:** Severe COVID-19 illness results in a hypercoagulable state and is associated with a poorer prognosis (Tang et al., 2020), therefore, heparin is usually recommended among hospitalized COVID-19 patients (Gozzo et al., 2020).

Precautions and Adverse neuropsychiatric Consequences: Although heparin, per se, does not cause neuropsychiatric symptoms, it can have significant pharmacokinetic interaction with the psychotropic agents, particularly with the SSRIs, latter can cause platelet dysfunction, thereby may worsen the risk of bleeding (Taylor et al., 2018).

Management of neuropsychiatric A/Es: A clinician should be cautious while using psychotropic medications with heparin; may consider switching to other psychotropic agents that have lesser interaction with the heparin.

3.1.6.2. Acetaminophen. Precautions and Adverse Neuropsychiatric Consequences: At the usual dose, it is well tolerated. At higher doses, it may cause dizziness, excitement, and disorientation (Katzung, 2015). Although neuropsychiatric A/Es are rare with acetaminophen (and with other Nonsteroidal anti-inflammatory drugs, mood symptoms, sleep problems, cognitive changes, worsening), or in some cases, precipitation of psychiatric conditions including psychosis have been reported (Gupta and Chadda, 2016; The Medical Letter, 2008).

Management of Neuropsychiatric A/Es: Avoiding the higher dose of acetaminophen, particularly in at-risk patients, including those with a history of psychiatric illness or on hepatotoxic drugs such as valproate, carbamazepine, chlorpromazine, etc. (Onder et al., 2004).

A newer modality of treatment such as plasma therapy has been recommended for patients having severe illness and requiring ICU care. Though data is not available on their neuropsychiatric A/Es, pharmacovigilance and mandatory reporting must be exercised to identify them.

3.2. Prevention and management of neuropsychiatric adverse events

To prevent the development of medications-induced the neuropsychiatric A/Es among COVID-19 patients, healthcare professionals (HCPs) must remain aware of these potential neuropsychiatric A/Es (details in Table 2). One needs to be vigilant, particularly while dealing with the at-risk individuals (with multiple medical comorbidities, past or current history of psychiatric illness, elderlies) and while using systematic steroids, immunomodulators, etc. (Gupta and Chadda, 2016). Rational use of evidence-based medications is crucial concerning this. Likewise, early identification and prompt management of these conditions are vital.

Whenever neuropsychiatric A/Es emerge, identifying the offending agent is of foremost importance. Considering biological plausibility and establishing the temporality between the initiation of a particular medication and appearance/worsening of neuropsychiatric A/Es would be key steps. Also, monitoring the course of these neuropsychiatric A/Es after decreasing the dose/ stopping the concerned medication (the neuropsychiatric symptoms should improve following this) or rechallenging (worsening of the neuropsychiatric symptoms) can confirm the association.

Additionally, other causes such as individuals with severe illness or multiple medical morbidities, impaired hepatic or renal function or electrolyte imbalances (including abnormities in SpO2, pH), superimposed infections, etc. must be ruled out. Furthermore, neuropsychiatric A/Es could be the withdrawal effects of sudden discontinuations of drugs like benzodiazepines, antiparkinsonian drugs, steroids, antidepressants, or antipsychotics, etc. Similarly, physical illnesses like multiple sclerosis, lupus erythematosus, tumors, etc., can themselves lead to various neuropsychiatric symptoms (Tango, 2003). Hence, these differentials must be considered before concluding medication-related neuropsychiatric A/Es.

The prevention of the emergence of medication-induced neuropsychiatric A/Es can be ensured by using lower doses or fewer numbers of medications, utilizing non-pharmacological methods wherever possible (sleep hygiene for insomnia, reorientation therapy for the disorientation, relaxation exercise for the anxiety symptoms, etc.), and identifying and managing various risk factors, including reducing modifiable risk factors.

In contrast, various treatment-related factors may predispose an individual for these A/Es: using higher than recommended drug doses, multiple medications, particularly those having pharmacological interactions, rapid escalation in dose/s, and using drugs having narrow safety margin. The parenteral route of drug administration (Intravenous or intrathecal) is more likely to be associated with medication-related neuropsychiatric A/Es. (Gupta and Chadda, 2016).

There could be patient-related factors that give rise to various neuropsychiatric A/Es such as personal or family history of mental illness, deranged metabolic profile, elderly or young age, and long hospital stay, with poor sensory stimulation (isolation ward/room, Intensive Care Unit, etc.) (Tango, 2003). Hence, obtaining adequate medical, including psychiatric history, drugs use history, and a history of neuropsychiatric A/Es with any medications along with rational use of the medications, correcting underlying metabolic abnormalities, and proper sensory stimulation are critical in preventing adverse neuropsychiatric events.

Concerning the management of neuropsychiatric A/Es, decreasing, or stopping the medication, if possible, are useful considerations. However, when symptoms are severe or where the concerned

medication cannot be replaced, the addition of psychotropics medications would be useful. A proper evaluation and continued care by the mental health professionals (MHPs) under the consultation-liaison model should be exercised and encouraged.

Given COVID-19 infections independently causing neuropsychiatric symptoms, and evolving treatment guidelines, including the use of off-label drugs, above mentioned strategies can have a huge role in the prevention and management of such A/Es, thereby, significantly reducing morbidity and mortality in patients with COVID-19.

Moreover, pharmacovigilance and future research must be undertaken in this area to enrich our knowledge and understanding of this problem.

4. Conclusion

Neuropsychiatric manifestations are common among the patients suffering from the COVID-19 and represent a cluster of symptoms that can adversely influence the treatment and prognosis. Often, these occur as A/Es of the medications used for COVID-19 infections. Individuals with severe illness, medical comorbidities, on multiple medications, having personal or family history of psychiatric illnesses are particularly prone to experience these symptoms. Non-evidence-based medical practice, including off-label and non-judicious use of medications (particularly systemic steroids, and immunomodulators), are important contributory factors. HCPs need to be adequately sensitized and trained in this context. A liaison with the MHPs and robust pharmacovigilance system in the hospital, and more research on this topic are required.

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SG: Methodology, Writing – original draft, Writing – review & editing.

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