REVIEW ARTICLE

Post-COVID-19 Depressive Symptoms: Epidemiology, Pathophysiology, and Pharmacological Treatment

Mario Gennaro Mazza[1,2,3] · Mariagrazia Palladini[1,2,3] · Sara Poletti[1,2] · Francesco Benedetti[1,2]

Abstract

The Coronavirus Disease 2019 (COVID-19) pandemic is still spreading worldwide over 2 years since its outbreak. The psychopathological implications in COVID-19 survivors such as depression, anxiety, and cognitive impairments are now recognized as primary symptoms of the "post-acute COVID-19 syndrome." Depressive psychopathology was reported in around 35% of patients at short, medium, and long-term follow-up after the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. Post-COVID-19 depressive symptoms are known to increase fatigue and affect neurocognitive functioning, sleep, quality of life, and global functioning in COVID-19 survivors. The psychopathological mechanisms underlying post-COVID-19 depressive symptoms are mainly related to the inflammation triggered by the peripheral immune-inflammatory response to the viral infection and to the persistent psychological burden during and after infection. The large number of SARS-CoV-2-infected patients and the high prevalence of post-COVID-19 depressive symptoms may significantly increase the pool of people suffering from depressive disorders. Therefore, it is essential to screen, diagnose, treat, and monitor COVID-19 survivors' psychopathology to counteract the depression disease burden and related years of life lived with disability. This paper reviews the current literature in order to synthesize the available evidence regarding epidemiology, clinical features, neurobiological underpinning, and pharmacological treatment of post-COVID-19 depressive symptoms.

Key Points

Post-COVID-19 depressive symptoms have been reported in around 35% of patients at short, medium, and long-term follow-up after infection.

The psychopathological mechanisms of post-COVID-19 depressive symptoms are mainly related to the peripheral immune-inflammatory response triggered by the viral infection.

Conventional antidepressants have proved to be effective in treating post-COVID-19 depression.

✉ Mario Gennaro Mazza
  mazza.mariogennaro@hsr.it

1 Psychiatry and Clinical Psychobiology, Division of Neuroscience, IRCCS Scientific Institute Ospedale San Raffaele, San Raffaele Turro, Via Stamira d'Ancona 20, 20127 Milan, Italy

2 Vita-Salute San Raffaele University, Milan, Italy

3 PhD Program in Cognitive Neuroscience, Vita-Salute San Raffaele University, Milan, Italy

1 Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic started in China in December 2019 and, at over 2 years from its outbreak, it is still spreading around the world. According to the World Health Organization (WHO), the coronavirus disease 2019 (COVID-19) pandemic has affected almost 500 million people around the world, with more than 6 million deaths [1].

Most SARS-CoV-2-infected patients are asymptomatic or experience mild symptoms [2]. However, one in five SARS-CoV-2-infected patients presents with severe acute clinical manifestations characterized by acute respiratory distress syndrome (ARDS), severe immune response leading to an inflammatory and procoagulant state, and death [2]. Furthermore, after the acute phase of COVID-19, persistent and prolonged symptoms have been observed in several patients irrespective of the severity of the disease [3]. Persisting symptoms such as lung dysfunction, psychopathological complaints, and cognitive impairments have been reported to continue over months after acute COVID-19 [4, 5]. The National Institute for Health and Care Excellence (NICE) has termed these long-lasting symptoms after infection "post-COVID-19 syndrome," defining it as new and/or

persistent signs and symptoms more than 12 weeks following SARS-CoV-2 infection [6].

Since the pandemic spread, psychopathological implications have been reported during acute infection and in the post-COVID-19 phase in COVID-19 survivors. Confusion, delirium, depression, anxiety, and sleep disturbances have been observed during acute viral infection [7]. Apart from acute infection, as previously observed in the SARS and the Middle East Respiratory Syndrome (MERS) outbreak, long-term neuropsychiatric sequelae of COVID-19 are now listed as the main symptoms of the post-acute COVID-19 syndrome [3]. The most prevalent long-term neuropsychiatric sequelae have been depressive symptoms, anxiety, and cognitive impairments [8]. Clinically significant depressive psychopathology was reported in approximately 30–40% of patients at 1-, 3-, 6-, and 12-month follow-up after SARS-CoV-2 infection [9–13]. Depression, characterized by depressed mood, diminished interest, and cognitive impairment, negatively influences everyday life. Both pre-existing depression and COVID-19-related depressive symptoms were found to affect SARS-CoV-2 infection outcome, being associated with higher infection rate, hospitalization, intensive care unit admission, and mortality [14, 15]. The mechanisms underlying the COVID-19 psychiatric consequences are mainly related to the immune inflammatory response to the viral infection and subsequent potential neuroinflammation and to the psychological stressor induced by SARS-CoV-2 infection [16, 17].

Given this background, there is a need to describe, diagnose, and treat post-COVID-19 depressive symptoms. In this paper, we review the available literature in order to (i) investigate the epidemiology of post-COVID-19 depressive symptoms through a revision of published meta-analyses, (ii) describe the clinical features of post-COVID-19 depressive symptoms, (iii) revise the neurobiological underpinning of post-COVID-19 depressive symptoms, (iv) synthesize the available literature reporting potential pharmacological treatment for post-COVID-19 depressive symptoms, and (v) finally delineate future research needs.

2 Epidemiology of Post-COVID-19 Depressive Symptoms

Medical databases including PsycINFO and PubMed were searched using relevant keywords to obtain published studies up to 21 January 2022 reporting meta-analytic evidence about the epidemiology of depressive symptoms among COVID-19 survivors. We performed an independent multi-step search entering the following search terms: depress*, COVID-19, SARS-CoV-2, prevalence, incidence, epidemiology, rate, and meta-analysis. Search phrases were adapted to the rules of the databases used.

The initial set of searches yielded 133 records, among which 14 overlapped. After the removal of duplicates, 119 meta-analyses titles and abstracts were preliminarily screened according to the eligibility criteria by two independent researchers (MGM and MP) to avoid biases. The full texts of the studies were further assessed for a final decision on their relevance to the topic of post-COVID-19 depressive symptomatology. Any incongruence in the screening process and eligibility was solved by discussion between all the authors. Inclusion criteria were: (i) research design: meta-analyses were considered; (ii) population: people from the general population who contracted the SARS-CoV-2; (iii) outcome: COVID-19-related depressive symptomatology and its associated risk factors. Overall, six meta-analyses fulfilled the criteria for the review [8, 18–22]. Among them, five were rated between Low and High quality according to the AMSTAR-2 checklist and were included in the present study [8, 18–20, 22], while one was rated as Critical Low and was then excluded [21] (Table 1).

Our inspection revealed that the prevalence of clinically relevant depressive symptoms among COVID-19 survivors mainly ranged from 21% [8] up to 45% [18]. The predominant screening tool for assessing depressive symptomatology in COVID-19 cohorts was the Patient-Health-Questionnaire-9 (PHQ-9), which was implemented by 38 primary studies across all the meta-analyses. Deng et al. found an effect of the screening tools used on depressive symptom prevalence. The highest occurrence of depressive psychopathology was recorded through the PHQ-9 and the Zung Self-Rating Depression Scale (ZSDS) (47–52% and 52–53% respectively). On the other hand, estimates produced by the Hospital Anxiety and Depression Scale (HADS-depression subscale) and Symptom Checklist-90 (SCL-90) were found to be around 20–22% [18]. Additionally, from a methodological point of view, two meta-analyses exploring the frequency of COVID-19 survivors' clinical depressive symptoms according to different study designs revealed an impressive rate of this psychiatric outcome in single-arm cohort studies (values of 74–88%) in comparison with cross-sectional investigations (values of 34–44%) [18, 20].

Sub-group analyses yielded a more precise list of factors facilitating the development of depressive symptoms in the post-COVID-19 stages. According to the existing evidence, female patients are likely to experience a higher prevalence of depressive symptoms (pooled prevalence between 46% and 50%) compared to male counterparts (pooled prevalence between 32% and 39%) [18, 20]. In addition, the severity of COVID-19 affected the depressive symptom rate. Deng and colleagues found an increased frequency of depressive symptoms among hospitalized patients (48%) compared with the outpatient population (35%) [18]. Dong et al. showed a greater proportion of detectable depressive symptoms

Table 1 Characteristics and key findings of the included meta-analyses. Heterogeneity between studies included in each meta-analysis was expressed in I^2

Original meta-analysis	Number of studies included	Total sample size	Diagnostic tool	Heterogeneity %	Overall prevalence % (95% CI)	Subgroup analyses	Subgroup analyses findings	AMSTAR-2
Dong et al., 2021 [19]	27	6,002	PHQ-9; SDS; HADS; SCL-90; HAMD; PHQ-2	I^2=98	38 (29–46)	COVID-19 severity	Combined prevalence for patients clinically stable was 31% (7–55, 95% CI) while combined prevalence for severe patients was 66% (16–117, 95% CI). Combined prevalence for discharged patients was 52% (25–79, 95% CI)	Low
Liu et al., 2021 [20]	20	3,834	PHQ-9; HADS-D; SDS; BDI; SCL-90; DASS-21	I^2=98	38 (25–51)	Sex	Combined prevalence was higher in female (46%, 95% CI 32–60) than in male patients (32%, 95% CI 17–47)	Moderate
						Country	Compared to other Countries (e.g., China, India, South Korea, Iran, Ecuador, Jordan; Turkey), Italy showed the lowest pooled prevalence of depression 11% (6–18, 95% CI)	
						Study design	Single-arm cohort studies showed higher pooled prevalence of depression 88% (44–100, 95% CI)	
						Severity of depressive symptoms	The pooled prevalence of mild depression (29%, 95% CI 24–34) was higher than both that of moderate depression 17% (11–22, 95% CI) and severe depression 10% (2–20, 95% CI)	
						Disease stage	The pooled prevalence of depression among undergoing COVID-19 patients (42%, 95% CI 29–56) was higher than that in those who were in the recovery stage (14%, 95% CI 0–48)	
Deng et al., 2020 [18]	23	4028	PHQ-9; SDS; HADS-D; SCL-90	I^2=96	45 (37–54)	Sex	Combined prevalence was higher in female (50%, 95% CI 38–62) than in male patients (39%, 95% CI 26–53)	High
						Country	Compared to other countries (e.g., China, Ecuador, Iran), Italy registers the lowest rate of depression in COVID-19 infected people, with a pooled prevalence of 38% (29–47, 95% CI)	
						Hospitalization	The pooled prevalence of depression for inpatients was 48% (35–61, 95% CI) while the pooled prevalence of depression for outpatients was 35% (22–48, 95% CI)	

Table 1 (continued)

Original meta-analysis	Number of studies included	Total sample size	Diagnostic tool	Heterogeneity %	Overall prevalence % (95% CI)	Subgroup analyses	Subgroup analyses findings	AMSTAR-2
						Severity of depressive symptoms	The pooled prevalence of mild depression was 33% (26–39, 95% CI), for moderate depression was 14% (11–16, 95% CI), and for severe depression was 7% (4–10, 95% CI)	
						Study design	The pooled prevalence of depression for cohort-studies was 74% (62–83, 95% CI) was significantly higher than the pooled prevalence of cross-sectional studies 44% (36–53, 95% CI)	
						Screening Tools	Studies that used HADS-D and SCL-90 showed lower prevalence of depression (respectively 20% and 19%), on the contrary studies that used PHQ-9 and ZSDS show higher prevalence (respectively 52% and 53%)	
Wu et al., 2021 [22]	4	480	WHO-5; BDI-II; CES-D; DASS-21	I^2=90	42 (26–58)	Target population	Compared to quarantined persons, general population, students, physician and nurses, non-medical staff, COVID-19 patients show the greatest pooled prevalence of depressive symptoms, that is 42% (26–58, 95% CI)	Moderate
Khraisat et al., 2021 [8]	20	7994	Validated Questionnaire	I^2=97	21 (16–28)	NA	NA	Low

AMSTAR Assessment of multiple systematic reviews, *BDI* Beck Depression Inventory, *CES-D* Center for Epidemiology Scale for Depression, *CI* confidence interval, *COVID* Coronavirus Disease 2019, *DASS-21* Depression Anxiety and Stress Scale-21, *HADS* Hospital Anxiety and Depression Scale, *HAMD* Hamilton Depression Scale, *NA* not available, *PHQ-9* Patient Health Questionnaire, *SCL-90* Symptoms Checklist Revised-90, *SDS* Self-Rating Depression Scale, *WHO-5* WHO-Five Well-Being Index

among severely ill patients (66.3%) compared with those who were clinically stable (30.9%) [19].

Moreover, Dong and colleagues furnished a detailed narrative synthesis of risk factors for depressive symptoms pointing out that both socio-demographic and physiological features may promote depressive psychopathology in COVID-19 survivors [19]. Among those, the lack of social support along with forced isolation after virus clearance, low levels of education or high educational qualification seemed to increase the likelihood of depressive symptoms post-infection significantly. Interestingly, wide exposure to media in an attempt to gather information about the virus spread also negatively influenced depressive symptoms. Likewise, abnormal baseline levels of inflammatory markers such as C-reactive protein (CRP), interleukin (IL) 1-β, and cortisol made COVID-19 patients more vulnerable to depressive symptoms in the sub-acute stages of the illness, thus suggesting an underlying immune-related contribution [19].

When considering the epidemiological burden of post-COVID-19 depressive symptomatology in different stages of the disease, the included meta-analyses provide unstable estimates, with percentage of affected discharged patients oscillating between 14 and 52% [19, 20]. Further examinations on COVID-19 survivors who received a specific follow-up psychiatric assessment report depressive symptoms rates ranging between 21 and 33.7% [8, 19].

With respect to depressive manifestation estimates according to severity, two meta-analyses consistently reported an elevated incidence of mild (rates of 29–33%), followed by moderate (rates of 14–17%) and severe depressive symptomatology (rates of 7–10%) [18, 20].

Notably, those who were infected with SARS-CoV-2 were more susceptible to developing depressive symptoms (pooled prevalence of 41.7%) than healthcare workers (pooled prevalence of 31%) and the general population (pooled prevalence of 31.5%) during the COVID-19 outbreak [22]. Moreover, the prevalence estimates indicate a remarkable boost in the burden of depressive psychopathology in COVID-19 survivors compared to the pre-pandemic rates of depressive symptoms among both hospitalized and non-hospitalized patients affected by other medical illnesses [23, 24].

The emerging framework must be interpreted in light of some limitations. Notwithstanding the huge number of primary studies and the extensive sample size included in each meta-analysis, a noticeable heterogeneity was detected throughout the meta-analyses. The use of different survey scales, research designs, and inclusion criteria most likely contribute to the discrepancy in the prevalence estimates [18, 20, 22]. Finally, the lack of a systematic approach in defining a time-point follow-up for the evaluation of depressive

symptoms in COVID-19 survivors makes it challenging to draw more definite conclusions.

These weaknesses, however, do not bias the main finding that the burden of post-COVID-19 depressive symptoms substantially exceeds the pre-pandemic epidemiology of this adverse psychopathological condition [11, 22, 25]. Here, we identified vulnerable groups to whom clinicians should pay special attention, such as females, critically ill patients, and those who perceive themselves as having low social support [18–20]. Despite most COVID-19 survivors experiencing mild and moderate levels of depressive symptomatology as previously reported [18, 20], the extensive progression of people experiencing depressive symptoms represents a serious phenomenon that deserves to be addressed by mental health services. Quantitative synthesis of post-COVID-19 occurrence focusing on specific time points after the infection need to be produced to provide a more detailed and time-oriented epidemiological framework.

3 Clinical Features of Post-COVID-19 Depressive Symptoms

Patients with post-COVID-19 depressive symptoms share psychopathological symptoms, as rated on validated rating scales (see section 2.2), brain-imaging correlates [26], and negative thinking styles [27], as core features observed in Major Depressive Disorder (MDD), fostering the experience of negative emotions. Depressive symptoms have been associated with poor neurocognitive functioning, sleep disturbances, increased fatigue, and reduced quality of life in post-COVID-19 syndrome.

Two independent studies based on 226 COVID-19 survivors at 3 months' follow-up [10] and 120 survivors at 4 months' follow-up [28] showed that depressive symptomatology negatively influenced neurocognitive performances. Moreover, a machine-learning analysis suggested that depressive symptomatology was the main factor affecting cognitive functioning among a large set of clinical and socio-demographical predictors [29]. Consistently, in a sample of 100 patients, cognitive complaints at 1 month after hospitalization for COVID-19 were explained only by depressive symptom severity and older age [30]. The most affected performances were selective attention and processing speed, immediate recall in verbal memory, and visuospatial abilities [10, 28, 29]. Interestingly, COVID-19 survivors showed similar performance to patients with MDD regarding verbal fluency and executive functions [29]. At both 1 ($n = 402$) and 3 ($n = 226$) months' follow-up post-COVID-19 infection, cognitive impairment as well as post-COVID-19 depressive symptoms were found to be predicted by systemic inflammation [10, 13]. This connection is consistent with the previously observed association between depressive

symptoms, cognitive impairments, and systemic inflammation (mainly revealed by the elevation of IL-1β, IL-6, IL-18, TNF-α, and soluble interleukin-2 receptors) found in MDD episodes [31–33].

Further, self-rated depressive symptoms are positively associated with post-COVID-19 fatigue. A significant association was found between fatigue severity and depressive symptomatology in COVID-19 survivors both during acute disease in 90 patients ($r = 0.71$, $p < 0.001$) [34] and at 1-year follow-up in 192 patients ($r = 0.56$, False Discovery Rate corrected p-value < 0.05) [9]. Moreover, in a preliminary investigation based on elastic-net penalized regression we found that among a large set of demographic, clinical, and psychopathological predictors only depressive symptomatology significantly predicted the presence of fatigue 6 months after infection in a sample of 122 patients [35]. Consistently, Townsend et al. in a sample of 128 patients, 10 weeks after initial COVID-19, found a significant association between pre-existing diagnosis of depression and the presence of post-COVID-19 fatigue ($X^2 = 5.18$, $p = 0.02$) [36]. It seems that somewhat independent of the clinical severity of acute COVID-19, depressive psychopathology is associated with persistent fatigue, thus worsening the long-term clinical outcome [34]. Notably, a recent meta-analysis reported that a significant proportion of COVID-19 survivors showed persistent fatigue and cognitive impairment following resolution of acute COVID-19 [37]. Interestingly, in a subset of studies with available inflammatory data, fatigue and cognitive impairments were associated with higher pro-inflammatory markers, suggesting potential shared neurobiological underpinnings [37].

In addition to fatigue, post-COVID-19 depressive symptomatology was found to also be associated with an increased risk of some persistent physical symptoms, including pain and dyspnea [38]. In a sample of 84 patients, post-COVID-19 depressive symptoms at 1 month significantly interacted with the presence of pain at 1 month in predicting the presence of pain at 3 months (odds ratio (OR): 1.60, 95% confidence interval (CI): 1.02–2.51, $p = 0.039$), with a similar trend for dyspnea (OR 1.51, 95% CI 0.99–2.28, $p = 0.052$) [38].

Depressive symptomatology also affected COVID-19 survivors' quality of life, placing additional burden on the survivors' global functioning. Babicki et al. found a significant correlation between depressive symptoms and impaired quality of life in both the first ($n = 2457$, $r = 0.63$, $p < 0.001$) and second wave ($n = 1626$, $r = 0.71$, $p < 0.001$) of the COVID-19 pandemic [39]. Poletti et al. found a significant interaction between depressive symptoms and verbal memory ($\lambda = 0.58$, $p < 0.001$), working memory ($\lambda = 0.17$, $p < 0.001$), psychomotor coordination ($\lambda = 0.47$, $p < 0.001$), verbal fluency ($\lambda = 0.73$, $p < 0.001$), and executive functions

($\lambda = 0.50$, $p < 0.001$) on quality of life in a cohort of 312 COVID-19 survivors [29].

The investigation of the brain underpinnings of depressive symptoms in 42 patients at a mean follow-up of 3 months (90.59 ± 54.66 days after COVID-19) showed an association between higher depressive symptoms and lower gray matter volume in the anterior cingulate cortex and insula, and with a lower white matter microstructure [26].

As largely demonstrated in MDD, we could consider post-COVID-19 depressive symptoms part of a syndrome characterized by cognitive and physiosomatic correlates affecting the quality of life. The reported evidence suggests a central role of depressive psychopathology, which seems to be one of the most relevant predictors of both cognitive impairment and fatigue, which persist over time in almost a third of COVID-19 survivors [37].

4 Neurobiology of Post-COVID-19 Depressive Symptoms

4.1 Pathophysiology of COVID-19

The pathogenesis of the neuropsychiatric manifestations of COVID-19 has been suggested to be mainly a result of central nervous system (CNS) indirect immune-inflammatory-mediated damage and, hypothetically, a potential consequence of direct viral neuroinvasion [16, 40].

SARS-CoV-2 spike glycoprotein binds to the angiotensin 2 converting enzyme (ACE2). After binding, the virus enters the host cell and releases RNA, replicates, and leads to host cell death [41]. The antigen-presenting cells recognize the viral antigens and activate the local immune response, first recruiting macrophages and monocytes that release cytokines and induce T- and B-cell responses. The binding of the SARS-CoV-2 spike glycoprotein to ACE2 itself is able to amplify the systemic inflammation by reducing the bioavailability of angiotensin (1–7) and its anti-inflammatory activity [42]. After the activation of the immune response, there is an increase in the production of T-helper(Th)-1 cytokines, including IL-1β, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, C-X-C motif chemokine ligand 10 (CXCL10), and C-C Motif Chemokine Ligand 2 (CCL2), and Th-2 cell-related cytokines, including IL-4 and IL-10 [43, 44]. The overexpression of cytokines also affects the hypothalamic-pituitary-adrenal (HPA) axis, leading to additional compromising immune response and immunocompetence [45]. The peripheral inflammatory mediators such as cytokines, chemokines, and acute-phase protein reach the CNS passing through a disrupted blood-brain barrier (BBB) [16, 46]. When entering the CNS, peripherally generated inflammatory mediators may activate the microglia, inducing its transition from quiescence to a "primed" state.

The primed microglia in turn release TNF-α, IL-6, IL-1β nitric oxide, prostaglandin E2, and free radicals in the brain, thus potentially increasing the neuroinflammation [47]. Pro-inflammatory cytokines also increase oxidative stress, which damages cellular membranes [48]. Inflammation induces BBB disruption, leading more peripheral inflammatory factors to enter the CNS and release even more cytokines from the microglia into the CNS [49, 50].

Neurons suffer during acute COVID-19, as shown by high circulating levels of neurofilament light chain (NfL), a cytoskeletal intermediate filament protein of central and peripheral neurons that has been validated as a nervous system damage biomarker in a variety of neurological diseases [51]. Accordingly, several months after recovery, axial diffusivity of water in the CNS, which is associated ith the microstructure of axons and myelin sheaths within white matter tracts, is still negatively influenced in the whole brain normal-appearing white matter by the intensity of systemic inflammation observed during the acute phase of COVID-19 [26].

Apart from indirect damage of the CNS mediated by peripheral immune activation, a few preliminary studies have suggested that SARS-CoV-2 could enter the CNS [52, 53]. Neuroinvasion could be mediated by ACE2, which is highly expressed on neuronal cells [54] and by the membrane protein neuropilin-1 [55]. It has also been speculated that SARS-CoV-2 can retrogradely migrate to the CNS through the olfactory, respiratory, and enteric nervous system pathway [52, 56–58]. However, analysis of cerebrospinal fluid from living patients with neuropsychiatric manifestations has failed to detect viral RNA [59]. SARS-CoV-2 direct neuroinvasion is therefore not well understood, and the presence or the absence of SARS-CoV-2 in the CNS is still a topic of debate.

In conclusion, notwithstanding possible brain infiltration, the indirect CNS immune-mediated damage seems to be the primary pathogenic mechanism of neuropsychiatric COVID-19-related symptoms. SARS-CoV-2 infection shifts the immunological milieu toward a systemic pro-inflammatory status. Peripheral inflammation may reach and influence the brain mainly through the disrupted BBB, and through the trafficking of immune cells into the brain possibly leading to neuroinflammation. In this context, neuroinflammation and subsequent BBB disruption, neurotransmission impairment, HPA axis dysfunction, microglia activation, and indoleamine 2,3-dioxygenase (IDO) induction, all represent interaction pathways between SARS-CoV-2 infection and psychopathological mechanisms underpinning depressive disorders [60–62].

4.2 Pathophysiological Mechanisms of Post-COVID-19 Depressive Symptoms

The mechanisms underlying the COVID-19 depressive symptoms seem to be mainly related (i) to the systemic immune-inflammatory response induced by SARS-CoV-2 infection, and (ii) to the psychological stressors induced by SARS-CoV-2 infection.

4.2.1 Immune-Inflammatory Response Induced by SARS-CoV-2 Infection

Immunologic dysregulations entailing inflammatory processes have been widely implicated in mood disorders [63–66]. In fact, the activation of innate immunity and the associated inflammation is considered one of the main pathological underpinnings of MDD [67]. Notably COVID-19 patients show the same molecular inflammatory pathways both in severe and non-severe infection, suggesting a common outcome between depression and SARS-CoV-2 infection for innate immune activation and increased pro-inflammatory markers. Peripheral inflammatory markers such as TNFα, IL-1β, and IL-6 increase the permeability of the BBB by affecting the endothelial cells [68]. The weakened BBB may, in turn, facilitate the potential entry of microorganisms and other inflammatory mediators into the brain. Once in the brain, cytokines can cause several changes in brain neuro-circuits and neurogenesis compromising the functioning of regions of the limbic system, thus leading to symptoms of depression [69]. These changes are associated with different mechanisms including alterations affecting neurotransmission, microglia, oxidative stress, and the HPA [60–62].

Changes in the metabolism of neurotransmitters have been widely associated with depressive psychopathology [70–72]. The neurotransmitters more affected by inflammation are serotonin, dopamine, and glutamate, with alterations in their synthesis, release, and reuptake. Inflammatory cytokines can influence the synthesis of serotonin through the activation of IDO, an enzyme that converts tryptophan into kynurenine. Tryptophan is needed to make serotonin, and its conversion into kynurenine may deplete the availability of serotonin in the brain [73]. Increases in kynurenine and decreases in tryptophan have been observed in patients with MDD episodes [74, 75]. The kynurenine to tryptophan ratio was higher in COVID-19 patients than in healthy controls ($n = 394$, mean $= 0.05$, CI $= 0.03$–0.10 vs. $n = 239$, mean $= 0.03$, CI $= 0.02$–0.03; $p < 0.0001$), and correlated positively with disease severity [76], but its role has not yet been investigated in the pathogenesis of post-COVID-19 depression. Inflammatory cytokines may also directly influence glutamate signaling by stimulating the release of glutamate from astrocytes [77] and by decreasing its uptake, reducing the astrocytic expression of glutamate transporters [78].

Moreover, when inflammation reaches the brain, it can modify the activity of microglia and astrocytes. Whereas under physiological conditions, microglia monitor the integrity of synapses [79], remove apoptotic and necrotic cells,

and promote the maintenance of homeostasis [80], activated microglia in turn release pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-12, and IL-23, and increase the production of reactive oxygen (ROS) and nitroxygen species (RNS) [81]. Accordingly, increased microglial activation in association with high levels of IL-6 and TNF-α have been observed in MDD episodes [82], whereas microglia activation has been implicated in both acute and chronic neurological complications of COVID-19 [83], and increased microglial activation has been demonstrated in post-mortem neuropathological analysis of brain samples from COVID-19 patients [58, 84]. Brain cells are particularly vulnerable to oxidative stress [85], and low levels of antioxidants together with high levels of oxidative stress biomarkers have been consistently reported in MDD [86]. Similarly, inflammation induced by COVID-19 can also increase the production of free radicals and decrease the level of antioxidants like glutathione, a pattern that has been previously detected in patients with MDD [87].

Interestingly, a bidirectional relationship exists between the HPA axis and the immune system. On one side the HPA axis and glucocorticoids regulate the immune response, on the other, cytokines can promote the activation of the HPA axis by ultimately increasing the release of glucocorticoids through the adrenal cortex [88]. In response to pro-inflammatory cytokines, endothelial cells and microglia synthesize prostaglandin E2 (PGE2), which acts on neurons secreting the corticotropin-releasing factor in the hypothalamus, thus promoting the synthesis and release of glucocorticoids. Glucocorticoids then act as negative feedback on the inflammatory response [89] to avoid the deleterious effects of excessive production of inflammatory mediators. However, high levels of glucocorticoids may, in the long term, cause resistance to glucocorticoid feedback on the HPA axis, thus allowing pro-inflammatory signaling pathways to avoid normal feedback inhibition [90]. Accordingly, increased cortisol levels that are resistant to regulatory feedback by the HPA axis have been reported in patients with depression [91]. In addition to these mechanisms, in COVID-19 a downregulation of hypothalamic ACE2 levels has been suggested as a potential mechanism by which the coronavirus induces hyperactivity of the HPA axis [88].

Finally, under physiologic conditions, cytokines contribute to neurogenesis, synaptic scaling and remodeling, and long-term potentiation, thus playing a central role in learning and memory [92, 93]. However, in case of peripheral and central inflammation in which brain levels of cytokines are increased, synaptic plasticity, learning, and memory are inhibited [94], also because of a reduction of the brain-derived neurotrophic factor by pro-inflammatory cytokines, which is responsible for structural and functional cellular support. These changes have been widely reported in depression and have been suggested to underlie the behavioral and mood changes observed in the disorder [95]. Moreover, several cytokines, including TNF-α, IL-8, and IFN-γ, have been associated with changes in white matter microstructure in mood disorders, possibly by directly affecting oligodendrocyte homeostasis [96], and this effect could further contribute to the association of brain microstructure with depression as observed in magnetic resonance imaging [26].

4.2.2 Psychological Stressor Induced by SARS-CoV-2 Infection

Apart from a direct effect of SARS-CoV-2 infection, significant psychological stressors may play a major role in the development of psychopathological outcomes in COVID-19 patients. Social isolation, quarantine, uncertainty about the future, wide exposure to media, and survivor guilt experienced by infected patients may induce depressive symptoms following the infection [97, 98]. During the COVID-19 pandemic, people have been forbidden to visit affected relatives during hospital stays, thus enhancing the feeling of isolation, loneliness, boredom, and fear about an uncertain future. Moreover, quarantine for infected patients also leads to loneliness and social isolation [99, 100]. Evidence from animal models has shown that social isolation alters activity, neurochemical function, and the neuroendocrine system, inducing pathological behavior and symptoms of anxiety, depression, and memory loss [101]. Psychological stress is known to activate the HPA axis and sympathetic nervous system (SNS), notably associated with mental health conditions including anxiety and depression [102]. Sustained psychological stress induces changes in levels of hormones and responsiveness of neurons and HPA to glucocorticoids [91, 103], thus affecting mood through immune modulation in the CNS [104]. Moreover, psychological stress may induce a proinflammatory microglia phenotype, contributing to neuroinflammation [105]. From a clinical point of view, exposure to early or recent stress is associated with a higher risk of an MDD episode [106], also affecting the brain structure and functional connectivity [107, 108], cognitive impairment [109], and incidence of suicidality [108].

Taken together, immune-neuroendocrine mechanisms directly induced by SARS-CoV-2 infection and by COVID-19-related psychological stressors could explain depressive symptomatology.

4.3 Inflammatory Markers of Post-COVID-19 Depressive Psychopathology

Current knowledge of immunopsychiatry suggests that SARS-CoV-2 infection-triggered dysregulation of the immune-inflammatory system could foster depressive psychopathology. In this context, a few preliminary studies investigated the potential association between inflammatory

biomarkers and COVID-19-related depressive symptomatology. We searched for original articles published up to 24 January 2022 on PubMed and PsycINFO reporting data about the association of inflammatory biomarkers and post-COVID-19 depressive symptoms. The search was restricted to articles written in English. The search strategy consisted of the following keywords: depress*, COVID-19, SARS-CoV-2, neutrophil, lymphocyte, c-reactive protein, monocyte, leukocyte, interleukin, blood count, platelet, systemic immune inflammation index, leukocyte, and biomarker. Search phrases were adapted according to different database rules. In addition, the reference lists from selected articles were also screened.

Two independent researchers (MGM and MP) screened the literature and performed data extraction. Our search identified 144 studies, 16 of which met the inclusion criteria for the review. A detailed description of the included study is reported in Table 2. The quality of included studies was rated using a modified version of the Newcastle-Ottawa scale for single-arm cohort studies [18] based on the following criteria: sample representativeness, sample size, comparability between patients with and without depression for sociodemographic factors, ascertainment of depression, and adequacy of descriptive statistics. Studies scoring ≥ 3 were regarded as low risk of bias, while studies scoring < 3 were regarded as high risk of bias (Table 2). The most investigated inflammatory markers were readily available routine biomarkers of inflammation, especially CRP [10, 13, 26, 34, 98, 110–115] and neutrophil/lymphocyte ratio (NLR) [10, 13, 110, 112, 114–117]. Among cytokines, the most investigated were IL-6 [34, 111–115, 118, 119], IL-10 [34, 111, 112, 120], and TNF-α [111, 112, 118, 120]. Finally, two studies investigated T-cell subpopulations [111, 120]. Among the included studies, 13 studies [10, 13, 26, 34, 98, 111–113, 115–117, 119, 120] found a significant association between inflammatory markers and COVID-19-related depressive symptoms, while three studies did not find any statistical association [110, 114, 118]. Specifically, post-COVID-19 depressive symptoms were found to be associated with NLR in four studies [112, 115–117], with CRP in four studies [34, 98, 113, 115], with systemic inflammation index (SII) in three studies [10, 13, 26], with the neutrophil count in two studies [115, 117], and with IL-6 in two studies [34, 113]. Inconsistent findings were reported regarding T-cell subpopulations. He and colleagues found in a sample of 77 adults that patients with moderate depression had significantly (p < 0.05) higher CD8 counts and lower CD4/CD8 ratios than patients with non-moderate depression (27.6, CI 24.4–32.2 vs. 21.9, CI 16.1–27.5 and 1.6, CI 1.2–1.9 vs. 2.2, CI 1.7–2.9, respectively) [111]. Hoswever, Wu et al. in a sample of 57 patients found that the CD4 lymphocytes (r = 0.378, p = 0.004) and CD4/CD8 ratios (r = 0.264 p =

0.047) positively correlated with the severity of depressive symptoms [120].

Single studies reported a positive association between white blood count [119], IL-1β [112], and IL-10 [112] and post-COVID-19 depressive symptoms. Finally, one study found a lower lymphocyte count in patients with depression when compared to patients without depression [119]. Interestingly, two studies found that reducing inflammatory markers over time predicted improvement of depressive symptoms at follow-up [10, 98]. SII was also found to be associated with cognitive impairment and brain-imaging abnormalities [10, 26].

The effect of confounding variables known to affect inflammation response and depressive psychopathology must be considered when interpreting the reported findings. Firstly, we expect to find an immune-inflammatory signature depending on the COVID-19 stage with a mixed innate and adaptive response in the acute phase also characterized by the cytokine storm and, on the contrary, a low grade chronic inflammatory status at longer follow-up. Moreover, sex affects both inflammatory status and depressive psychopathology. We have to consider that while males are at higher risk of COVID-19 severe outcome and related higher inflammatory response [121], females have a higher risk of developing depression than males [122]. Moreover, males tend to express a stronger age-dependent activation of the innate pro-inflammatory pathways [123], leading to higher chronic subclinical systemic inflammation than that observed in females [124]. Thus, accounting for this variable is of primary importance when searching for an inflammatory biomarker.

In conclusion, evidence from the literature suggests that easily available biomarkers of innate inflammatory response such as CRP, NLR, and SII are associated with post-COVID-19 depressive symptoms. CRP, NLR, and SII are cheap, available in a real-life clinical setting, and reproducible markers of the systemic inflammation, which can be derived from a routine blood cell essay. To date, several studies have proven their utility as inflammatory biomarkers of MDD episodes [125, 126].

5 Potential Treatment for Post-COVID-19 Depressive Symptoms

The large number of people infected with SARS-CoV-2 and the high prevalence of post-COVID-19 depressive symptoms may contribute to the emergence of a serious global problem and significantly increase the pool of people suffering from depressive disorders. Untreated depression is independently associated with severe outcomes in pneumonia and respiratory diseases [127–129]. Even in COVID-19, meta-analytic evidence suggested that comorbid depression was

Table 2 Characteristics of the included studies in the revision

Original study	Sample size	Age in years	Males, %	Time of depressive symptoms assessment	Time of inflammatory marker assessment	Diagnostic tool for depressive symptoms	Inflammatory markers	Findings	Modified Newcastle Ottawa Scale
Ahmed et al., 2021 [110]	182	> 18	46	Six months' follow-up	Hospital admission	SCL90 depression subscale	WBC, LYM, NEU, MON, PLT, NLR, CRP, and ferritin	NEU, PLT, and NLR were not significantly associated with SCL90 subscale for depression score	Low risk of bias
Benedetti et al., 2021 [26]	42	> 18	67	Three months' follow-up	Emergency department admission	ZSDS	CRP and SII	SII measured in the emergency department, significantly predicted worse self-rated depressive symptoms ($\beta = 0.411$, Wald = 9.02, $p < 0.001$), widespread lower diffusivity along the main axis of WM tracts, and abnormal functional connectivity among resting state networks	Low risk of bias
Garcia et al., 2021 [118]	27	> 60	70	Acute COVID-19	During hospitalization	GSD	IL-6, IL-1β, and TNF-α	No significant correlation between IL-6, IL-1β, and TNF-α and GDS scale scores was found	High risk of bias
Gonzales et al., 2022 [113]	1851	> 18	59	Acute COVID-19	Hospital admission	Clinical interview according to ICD-10 criteria	IL-6 and CRP	IL-6 serum levels were significantly higher in the group of patients with depressive symptoms than in patients without, even after adjusting for several confounders (114 ± 225 pg/mL vs. 86 ± 202 pg/mL, $p = 0.02$). Similar results were obtained for CRP (102.14 ± 3.93 mg/L vs. 90.79 ± 2.32 mg/L, $p = 0.01$)	Low risk of bias
Guo et al., 2020 [98]	103	> 18	57	Acute COVID-19	At hospitalization admission and ± three days of fulfilling the on-line survey	PHQ-9	WBC, LYM, NEU, MON, PLT, CRP, and ESR	Levels of CRP correlated positively with the PHQ-9 total score of patients who presented symptoms of depression ($r = 0.37$, $p = 0.003$). Moreover, the change of CRP level from baseline inversely correlated with the PHQ-9 total score ($r = -0.31$, $p = 0.002$), indicative of improvement of depression symptoms	Low risk of bias
He et al., 2021 [111]	77	> 18	49	Acute COVID-19	During hospitalization	PHQ-9	IL-2, IL-4, IL-6, IL-10, TNF-α, IFN, CD3+T, CD4+T, CD8+T, CD4+/CD8+, WBC, LYM, NEU, PLT, ESR, and HS-CRP	Patients with moderate depressive symptoms had higher CD8+counts [27.6 (24.4–32.2) vs. 21.9 (16.1–27.5)] and lower CD4+/CD8+ratios [1.6 (1.2–1.9) vs. 2.2 (1.7–2.9)] than patients with non-moderate depressive symptoms ($p < 0.05$)	High risk of bias

Table 2 (continued)

Original study	Sample size	Age in years	Males, %	Time of depressive symptoms assessment	Time of inflammatory marker assessment	Diagnostic tool for depressive symptoms	Inflammatory markers	Findings	Modified Newcastle Ottawa Scale
Hu et al., 2020 [112]	70	> 18	51	Acute COVID-19	During hospitalization within 1 week of the date on which the questionnaire was completed	PHQ-9	IL-1β, IL-6, IL-8, IL-10, TNF-α, CRP, WBC, LYM, NEU, and NLR	PHQ-9 score for depression was significantly related to the level of IL-1β (r=0.50, p<0.001) and to NLR (r=0.36, p<0.01). A multivariate regression model showed that result showed that sex ($\beta = 0.31$, $p < 0.01$), IL-1β ($\beta = 0.41$, $p < 0.001$), and self-perceived illness severity ($\beta = 0.39$, $p < 0.001$) were related to the PHQ-9 score	Low risk of bias
Al-Jassas., 2022 [34]	60	25–59	100	Acute COVID-19	During hospitalization	HDRS	CRP, IL-6, and IL-10	The HDRS scores showed positive significant associations with CRP ($r = 0.547$, $p < 0.001$), IL-6 ($r = 0.480$, $p < 0.001$), and IL-10 ($r = 0.532$, $p < 0.001$)	Low risk of bias
Huarcaya-Victoria et al., 2021 [116]	318	> 18	61	Three months' follow-up	At the beginning of hospitalization	PHQ-9	NLR and MLR	NLR was significantly higher in patients with clinically relevant symptoms of depression (11.4, 95% CI 8.8–14.1 vs. 8.52, 95% CI 7.62–9.42; $p = 0.041$)	Low risk of bias
Kahve et al., 2021 [114]	175	> 18	61	Acute COVID-19	The day of hospitalization or the next day	BDI	ESR, CRP, NLR, IL-6, and ferritin	No significant relationship was found between ferritin, ERS, CRP, IL-6, NLR levels and depressive symptoms severity	Low risk of bias
Li et al., 2021 [117]	66	> 17	42	Acute COVID-19	During hospitalization	ZSDS	WBC, LYM, NEU, and NLR	NEU (2.91, 95% CI 2.36–3.44 10^9/L vs. 3.34, 95% CI 3.22–4.69 10^9/L; $p = 0.028$) and NLR (1.74 ± 0.52 2.22 ± 0.91; $p = 0.043$) were increased in the group with depressive symptoms. Correlation analysis indicated that Self-Rating Depression Scale score was positively related to NEU count and NLR (respectively $r = 0.366$, $p = 0.016$ and $r = 0.330$, $p = 0.031$)	High risk of bias
Mazza et al., 2020 [13]	402	> 18	66	One month's follow-up	Emergency department admission	ZSDS	CRP, NLR, MLR, and SII	SII, which reflects the immune response and systemic inflammation based on peripheral lymphocyte, neutrophil, and platelet counts, positively associated with scores of depressive symptoms at follow-up ($\beta = 0.411$, $F = 5.18$, $p = 0.023$)	Low risk of bias

Table 2 (continued)

Original study	Sample size	Age in years	Males, %	Time of depressive symptoms assessment	Time of inflammatory marker assessment	Diagnostic tool for depressive symptoms	Inflammatory markers	Findings	Modified New-castle Ottawa Scale
Mazza et al., 2021 [10]	226	> 18	66	Three months' follow-up	Emergency department admission	ZSDS	CRP, NLR, MLR, and SII	SII predicted self-rated depressive symptomatology at 3 months' follow-up ($\chi2$=42.417, p<0.001); and changes of SII predicted changes of depression during follow-up (Wald = 6.881, $p = 0.009$)	Low risk of bias
Wu et al., 2021 [120]	57	> 18	35	Acute COVID-19	During hospitalization	PHQ-9	INF-γ, TNF, IL-10, IL-5, IL-4, IL-2, CD3+, CD4+, CD8+, and CD4+/CD8+	The counts of CD4+T lymphocytes and CD4/CD8 significantly correlated with the PHQ-9 scores ($r = 0.378$, $p = 0.004$). After 2 weeks of treatment, significant associations remained ($r = 0.644$, $p = 0.002$) between the changes in the level of CD4+ T lymphocytes and PHQ-9 scores in the patients with depression and anxiety	Low risk of bias
Yuan et al., 2020 [115]	96	> 18	50	One week after negative virus test	During hospitalization	ZSDS	WBC, NEU, LYM, MON, NLR, HS-CRP, and IL-6	The results suggested that patients with self-reported depression exhibited increased immune response, as indicated by increased WBC ($6.0 \pm 1.5 \ 10^9$/L vs. $6.7 \pm 1.5 \ 10^9$/L; $p = 0.016$), NEU ($3.3 \pm 0.9 \ 10^9$/L vs. $4.1 \pm 1.2 \ 10^9$/L; $p < 0.001$), NLR (1.8 ± 0.6 vs. 2.4 ± 0.9; $p < 0.001$), and CRP (0.1 ± 0.1 mg/dL vs. 0.2 ± 0.3 mg/dL; $p = 0.035$)	Low risk of bias
Zhou et al., 2021 [119]	65	> 21	48	Acute COVID-19	During hospitalization	ZSDS	LYM and IL-6	There was significant statistically lower LYM in the patients with relevant depressive symptoms when compared to patients without (1.43 vs. 1.79, $p = 0.01$)	Low risk of bias

BDI Beck's Depression Inventory, *CD* Cluster of Differentiation, *COVID* Coronavirus Disease 2019, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *HDRS* Hamilton Rating Scale for Depression, *ICD* International Classification of Diseases, *IFN* interferon, *IL* interleukin, *LYM* lymphocyte, *MLR* monocyte/lymphocyte ratio, *MON* monocyte, *NEU* neutrophil, *NLR* neutrophil/lymphocyte ratio, *PHQ-9* Patient Health Questionnaire-9, *PLT* platelet, *SII* Systemic Immune-Inflammatory Index, *TNF* tumor necrosis factor, *WBC* white blood cell count, *ZSDS* Zung Self-Rating Depression Scale

associated with increased risk of hospitalization, intensive care unit admission, and mortality [14, 15]. Considering the new threat posed by the COVID-19 pandemic, we should improve our clinical practice to counteract its consequences. Current evidence suggests assessing psychopathology in COVID-19 survivors in order to quickly diagnose emergent depressive psychopathology, and to treat it as soon as possible with the aim of reducing the disease burden and related years of life lived with disability. Unfortunately, very few studies are available about the efficacy of pharmacological interventions for post-COVID-19 depressive symptoms.

5.1 Conventional Antidepressants

Interestingly, increasing clinical data suggest that the use of antidepressants might be associated with a reduced risk of clinical deterioration in SARS-CoV-2-infected patients [130, 131]. To date, three independent clinical trials reported that early treatment with the selective serotonin reuptake inhibitor (SSRI) fluvoxamine could prevent clinical deterioration and hospitalization rates in adults with COVID-19 [132–134]. Moreover, our recent meta-analytic evidence showed a higher risk of COVID-19 severe outcome in mood disorders while pre-existing antidepressant treatment was not significantly associated with a worse prognosis after the adjustment for age, sex, and other covariates [14]. Anti-inflammatory and antiviral properties of conventional antidepressants are suggested to mainly mediate their beneficial effect on COVID-19 outcomes [130, 131]. Some SSRIs, such as fluvoxamine, sertraline, fluoxetine, and citalopram, have a high to moderate affinity for sigma-1 receptor (S1R) [135]. SSRI activation of the S1R is associated with an anti-inflammatory action through the downregulation of cytokine production including IL-6, IL-8, IL-1β, and IL-12 [136, 137]. Furthermore, antidepressants such as fluoxetine, sertraline, paroxetine, and amitriptyline may directly interfere with the viral cell invasion through inhibition of acid sphingomyelinase activity [138]. Functional inhibitors of acid sphingomyelinase (FIASMAs) block the conversion of sphingomyelin to ceramide, thus complicating the SARS-CoV-2 entry to the host cell [139]. Preclinical studies also suggest that antidepressants may exert antiviral effects on SARS-CoV-2 via lysosomotropic properties [140]. Cationic amphiphilic drugs such as fluvoxamine and fluoxetine tend to accumulate in the lysosomes, preventing mature viruses from escaping the host cell using lysosomes. Moreover, SSRIs like fluvoxamine have been shown to reduce loading of serotonin into platelets thus inhibiting platelet activation and aggregation [141]. In so doing, SSRIs may prevent the risk of inflammatory thrombosis and hyperserotonergic state leading to acute respiratory distress [142]. Finally, some SSRIs may increase plasma levels of melatonin by inhibition of cytochrome P450 enzyme CYP1A2, thus enhancing the anti-inflammatory, immunomodulatory, and antioxidant mechanisms of melatonin [143–145].

While growing evidence supports the promising role of SSRIs as effective repurposed drugs against a COVID-19 severe outcome, to date, to the best of our knowledge, only one study has investigated the efficacy of conventional SSRIs in treating post-COVID-19 depressive episode [146]. In 60 patients who presented with a depressive episode in the 6 months after COVID-19, we observed a rapid antidepressant response (50% HDRS reduction) in 55 patients after SSRIs treatment. Specifically, 89% and 95% of patients, respectively, with or without a previous psychiatric history completely responded to SSRI treatment, thus suggesting that first and recurrent depressive episodes triggered by COVID-19 share the same good antidepressant response. From pre-treatment to the 4-week follow-up, a significant decrease over time of depressive symptoms as rated on the Hamilton Depression Rating Scale (HDRS) was reported (baseline HDRS = 23.37 ± 3.94, post-treatment HDRS = 6.71 ± 4.41, $F = 618.90$, p < 0.001) irrespectively of sex, previous psychiatric history, and SSRI type. We hypothesize that SSRIs' serotoninergic and anti-inflammatory properties can be particularly effective in counteracting post-COVID-19 depressive episode triggered by SARS-CoV-2 infection-related systemic inflammation. Antidepressants may decrease peripheral markers of inflammation including IL-6, IL-10, TNF-α, and CCL-2, notably associated both with COVID-19 and with depression severity [137, 147]. Furthermore, in the CNS, SSRIs inhibit microglial activation and decrease cytokine production by these cells [148]. Moreover, SSRIs could directly neutralize the IDO-mediated detrimental effects of inflammation by potentiating serotonin neurotransmission, modulating tryptophan metabolism, and reducing the excitotoxic quinolinic acid [149]. In line with these hypotheses, an observational study found that COVID-19 inpatients under pre-existing antidepressant treatments ($n = 34$) had a lower ARDS incidence than patients not taking an antidepressant ($n = 402$) (20.6% vs. 43.2%, $p < 0.02$) coupled with lower blood levels of IL-6 (12.1 vs. 25.4, $p < 0.001$) [150]. Accordingly, we have previously found a protective effect of the IL-1β and IL-6 receptor antagonist (anakinra and tocilizumab) against post-COVID-19 depressive symptoms possibly associated with their effect in dampening SII [151]. This suggests that modulation of IL-6 may restore the prolonged systemic inflammation that could lead to the development of persistent depressive psychopathology.

Given this background, we suggest routinely monitoring psychopathology status after COVID-19 to treat as soon as possible emergent depressive symptoms in order to reduce the risk of a vicious cycle of infection, persistent sub-chronic inflammation, and structural and functional brain

abnormalities [26] leading to subsequent treatment-resistant depressive symptomatology.

5.2 Other Interventions

When considering post-COVID-19 depressive symptoms, to date, only scarce research has investigated the use of different molecules known to target shared immunological pathways in depressive psychopathology and COVID-19.

Melatonin as well as SSRIs was found to be effective in reducing susceptibility, need for hospitalization, length of hospital stay, and symptoms of acute COVID-19 [152–154]. Melatonin supplementation is known to restore the night–day circadian rhythm typically disturbed in depressive episodes [155, 156]. Moreover melatonin increases heme oxygenase-1 (HO-1), thus enhancing its anti-inflammatory activity [157]. In animal models, melatonin has been shown to relieve a depressed behavioral state in mice as well as stimulating neurogenesis in the hippocampus [158, 159]. The melatonin receptor agonist agomelatine, which is already approved for treating MDD episodes [155, 160], is known to reduce plasma and brain IL-1β, IL-6, and CRP levels, and prevents microgliosis and astrogliosis in rat models [161–163]. Therefore, even if no studies are yet available, melatonin as well as agomelatine could prove beneficial in the treatment of post-COVID-19 depressive symptoms, due to its antioxidant, anti-inflammatory, and antiapoptotic properties [157, 161–163].

Pharmacological blockade of cytokines involved in the COVID-19-induced cytokine storm suggested a protective effect of IL-1 and IL-6 antagonism on hyper-inflammation and progression to respiratory failure [164, 165]. Given the central role of IL-1 and IL-6 in depressive psychopathology, we explored the effect of IL-1 and IL-6 blocking on depressive symptoms [151]. Eighty-four male COVID-19 survivors who during hospitalization had treatment as usual (n = 55) or combined with a cytokine blocking agent (n = 29) were prospectively evaluated 1 and 3 months after discharge. We observed a protective effect of treatment with cytokine-blocking agents (anakinra and tocilizumab) in early phases of COVID-19 against the later onset of depressive symptoms (Time × treatment interaction: $F = 3.96$, $p = 0.0228$). Specifically, clinical depressive symptoms at 3 months' follow-up was found in 9/55 (16.4%) patients treated without and 1/28 (3.6%) treated with cytokine blockers. This preliminary finding, suggesting a potential antidepressant effect of cytokine-blocking agents, needs to be replicated in a larger population in order to possibly identify new therapeutic strategies for treatment-resistant depressive symptomatology [166].

Lithium salts classically belong to the pharmacological class of mood stabilizers; moreover, antidepressant and anti-suicidal effects have been proven for lithium itself [167–169]. Among the immune-inflammatory mechanisms of action, lithium has shown an anti-apoptotic effect on T-lymphocytes [170] and anti-inflammatory effects by reducing the cyclooxygenase-2 expression, IL-1β and TNF-α [171]. Moreover, lithium salt seems to have direct antiviral properties by competing with magnesium that represent an essential cofactor for enzymes that are needed for the replication of viral proteins and nucleosides [172]. In this context, lithium was found to reduce COVID-19-related inflammation and immune response in six patients when compared to patients not treated with lithium [173]. Specifically, lithium significantly reduced CRP and NLR while promoting T-cell proliferation. Interestingly, lithium influences T-cell proliferation and differentiation via a GSK3 pathway, and promotes white matter integrity in mood disorders by enhancing axial diffusivity, which is reduced by COVID-19 [174, 175]. These preliminary findings encourage a possible evaluation of lithium as a potential treatment for severe cases of COVID-19 infection, and given its parallel anti-inflammatory and anti-depressive efficacy, in post-COVID-19 depressive symptoms.

Finally, in order to bolster both the inflammatory response related to SARS-CoV-2 infection, as well as treat post-COVID-19 depressive symptoms, the use of transcranial direct current stimulation (tDCS), ayurveda, curcumin, and oxytocin have been considered, but not yet adequately tested. A single case report documented successful treatment of post-COVID-19 depressive and anxiety symptoms using tDCS [176]. tDCS is a promising nonpharmacological intervention for treating depressive psychopatology [177], potentially able to modulate the levels of IL-1β, IL-6, and TNF-α [178]. Ayurveda, proposed by the Indian government during the COVID-19 crisis, could positively influence immunity with possible direct effects on symptoms of depression or anxiety [179]. A potential modulation of monoamine function, stress axis response, and autonomic activity, paired with a reduction of anxiety and depressive symptomatology, has been postulated to be associated with ayurveda traditional practices [180]. Therefore, such a traditional practice could be beneficial both in terms of psychological effect and in terms of moderating the risk or severity of SARS-CoV-2 infection, and its safety and efficacy should be tested in future studies [181]. Curcumin is known for an antiviral activity against many types of enveloped viruses, including SARS-CoV-2 [182], by modulating NF-κB, inflammasome, IL-6 trans signal, and HMGB1 pathways [183]. Moreover, curcumin 1 g/day exhibits antidepressant activity, and improves cognitive/mood function [182], thus offering a promising option for treating post-COVID-19 depressive symptoms. Oxytocin is a peptide characterized by a well-known anti-inflammatory, anti-oxidant, and immune-modulator activity [184] with possible efficacy in attenuating COVID-19 pathogenesis [185]. Considering that oxytocin

has proven to be effective for stress, anxiety, and depression [184], its activity could be useful in treating post-COVID-19 depressive symptoms, maybe as add-on therapy.

All these mechanisms could potentially target the neuroinflammation triggered by SARS-CoV-2 associated with post-COVID-19 depressive symptoms, and its detrimental effects. However, despite the impressive rates of affected patients, no report is available about the efficacy of pharmacological treatment of post-COVID-19 depressive symptoms. Given the alarming prevalence of post-COVID-19 depressive symptomatology, further investigations are needed to explore the efficacy and tolerability of all these potential pharmacological interventions.

6 Future Research Needs

Scientific evidence on post-COVID-19 depressive psychopathology is still limited. Further research might increase our knowledge on how the immune-inflammatory response translates from organic to psychiatric illness, potentially providing some valuable insight into the etiopathogenetic underpinnings of depressive psychopathology and its therapeutic management.

Findings from different independent meta-analyses consistently showed a high prevalence of post-COVID-19 depressive symptoms (see Table 1); however, to date there is still high heterogeneity that needs to be addressed in order to identify risk and protective factors. Several factors, such as social isolation, psychological stress, medical comorbidity, and COVID-19 severity, are known to possibly increase the risk of presenting post-COVID-19 depressive symptomatology by interacting with the neuro-immune pathway. Although it is reasonable that all these factors contribute to a higher risk of post-COVID-19 depressive symptoms, no clear answers have been provided from research apart from female sex and positive previous psychiatric history. Clarifying the underlying biological and psychological variables associated with post-COVID-19 depressive symptomatology will provide new clinical insights to tailor effective and personalized treatments.

A growing literature is exploring the efficacy of antidepressants for treating acute SARS-CoV-2 infection [130, 131]. In this context, we recommend all clinical trials of serotonergic compounds repurposed against COVID-19 to assess depressive symptomatology at baseline and follow-up in order to explore whether the direct antidepressant effect could reduce the risk for a vicious cycle of infection, inflammation, depression, hospitalizations, and poor prognosis.

To date there are very few available studies that tested the efficacy and tolerability of conventional antidepressant and other pharmacological treatment on post-COVID-19 depressive symptoms; furthermore these preliminary findings were based on single-case, case series, or small sample size studies. High-quality clinical trials investigating different drugs are needed to assess their efficacy for treating post-COVID-19 depressive symptoms. In this context, future pharmacological research is needed to investigate whether the antidepressant efficacy would be paired with a reduction of inflammation, thus reversing the inflammation triggered by the infection. Anti-inflammatory drugs and immunomodulators that are currently being tested for treatment-resistant MDD and that have proved efficacious in reducing depressive symptoms in patients with inflammation could prove useful for inflammation-induced depressive episodes both as prevention and as a treatment strategy [186]. Moreover, the potential effect of non-pharmacological interventions such as light therapy, non-invasive somatic stimulation, horticultural therapy, and nutraceuticals should be explored [187–189].

The available literature suggests that routine biomarkers of innate inflammatory response are associated with post-COVID-19 depressive symptoms (see Table 2); however, larger studies are needed to replicate these preliminary findings. Therefore, we suggest all future investigations of post-COVID-19 depressive symptomatology should explore the potential association of depressive symptomatology with routine biomarkers of inflammation. Moreover, future research needs to improve the in-depth immunophenotyping of post-COVID-19 depressive psychopathology by implementing cytokine assessment and T-cell subpopulation study. This approach could identify at-risk populations and possible new specific targets for the treatment of inflammation-related depressive conditions.

6.1 Limitations

The main limitation of the present review deals with the small number of available studies exploring the biomarkers of post-COVID-19 depressive psychopathology and investigating the pharmacological treatment of post-COVID-19 depressive symptoms that meant we had to conduct a narrative review without a quantitative approach. Moreover, in the majority of reviewed studies, psychopathological evaluation was based on self-assessment questionnaires in the absence of psychiatric interviews, thus allowing us to consider only depressive symptoms and preventing us from dealing with a diagnosis of a MDD episode. This limitation clearly affects the prevalence rate, the pathophysiology, and potentially the treatments.

7 Conclusion

In conclusion, considering the alarming prevalence of post-COVID-19 depressive symptoms and its impact on global functioning, according to current literature [3], follow-up

services for COVID-19 survivors should be implemented in order to monitor mental health and provide early treatment. From a clinical perspective, we suggest that routine assessment of psychopathology of COVID-19 survivors will be critical for the rapid diagnosis and treatment of emergent depressive symptomatology, thus reducing the high disease burden typically associated with psychiatric conditions.

Declarations

Funding None.

Conflict of interest MGM, MP, SP, and FB declare that they have no conflicts of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions MGM supervised the entire process, MGM and MP performed the literature search. MGM, MP, and SP drafted the manuscript. All authors critically revised the work. All authors have read and approved the final submitted manuscript, and agree to be accountable for the work.

References

1. Organization WH. WHO Coronavirus (COVID-19) Dashboard. 2022. p. https://covid19.who.int/.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
3. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601–15. https://doi.org/10.1038/s41591-021-01283-z.
4. Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. JAMA Netw Open. 2021;4(5):e2111417. https://doi.org/10.1001/jamanetworkopen.2021.11417.
5. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220–32. https://doi.org/10.1016/S0140-6736(20)32656-8.
6. Venkatesan P. NICE guideline on long COVID. Lancet Respir Med. 2021;9(2):129. https://doi.org/10.1016/S2213-2600(21)00031-X.
7. Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020;7(7):611–27. https://doi.org/10.1016/S2215-0366(20)30203-0.
8. Khraisat B, Toubasi A, AlZoubi L, Al-Sayegh T, Mansour A. Meta-analysis of prevalence: the psychological sequelae among COVID-19 survivors. Int J Psychiatry Clin Pract. 2021. https://doi.org/10.1080/13651501.2021.1993924.
9. Mazza MG, Palladini M, De Lorenzo R, Bravi B, Poletti S, Furlan R, et al. One-year mental health outcomes in a cohort of COVID-19 survivors. J Psychiatr Res. 2021;22(145):118–24. https://doi.org/10.1016/j.jpsychires.2021.11.031.
10. Mazza MG, Palladini M, De Lorenzo R, Magnaghi C, Poletti S, Furlan R, et al. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. Brain Behav Immun. 2021;94:138–47; https://doi.org/10.1016/j.bbi.2021.02.021.
11. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021;8(5):416–27. https://doi.org/10.1016/S2215-0366(21)00084-5.
12. Taquet M, Luciano S, Geddes JR, Harrison PJ. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry. 2021;8(2):130–40. https://doi.org/10.1016/S2215-0366(20)30462-4.
13. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun. 2020;89:594–600; https://doi.org/10.1016/j.bbi.2020.07.037.
14. Vai B, Mazza MG, Delli Colli C, Foiselle M, Allen B, Benedetti F, et al. Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: a systematic review and meta-analysis. Lancet Psychiatry. 2021;8(9):797–812. https://doi.org/10.1016/S2215-0366(21)00232-7.
15. Ceban F, Nogo D, Carvalho IP, Lee Y, Nasri F, Xiong J, et al. Association between mood disorders and risk of COVID-19 infection, hospitalization, and death: a systematic review and meta-analysis. JAMA Psychiat. 2021;78(10):1079–91. https://doi.org/10.1001/jamapsychiatry.2021.1818.
16. Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun. 2020;87:34–9. https://doi.org/10.1016/j.bbi.2020.04.027.
17. Passavanti M, Argentieri A, Barbieri DM, Lou B, Wijayaratna K, Foroutan Mirhosseini AS, et al. The psychological impact of COVID-19 and restrictive measures in the world. J Affect Disord. 2021;15(283):36–51. https://doi.org/10.1016/j.jad.2021.01.020.
18. Deng J, Zhou F, Hou W, Silver Z, Wong CY, Chang O, et al. The prevalence of depression, anxiety, and sleep disturbances in COVID-19 patients: a meta-analysis. Ann N Y Acad Sci. 2021;1486(1):90–111. https://doi.org/10.1111/nyas.14506.
19. Dong F, Liu HL, Dai N, Yang M, Liu JP. A living systematic review of the psychological problems in people suffering from COVID-19. J Affect Disord. 2021;1(292):172–88. https://doi.org/10.1016/j.jad.2021.05.060.
20. Liu C, Pan W, Li L, Li B, Ren Y, Ma X. Prevalence of depression, anxiety, and insomnia symptoms among patients with COVID-19: A meta-analysis of quality effects model. J Psychosom Res. 2021;147:110516; https://doi.org/10.1016/j.jpsychores.2021.110516.
21. Soltani S, Tabibzadeh A, Zakeri A, Zakeri AM, Latifi T, Shabani M, et al. COVID-19 associated central nervous system manifestations, mental and neurological symptoms: a systematic review and meta-analysis. Rev Neurosci. 2021;32(3):351–61. https://doi.org/10.1515/revneuro-2020-0108.

22. Wu T, Jia X, Shi H, Niu J, Yin X, Xie J, et al. Prevalence of mental health problems during the COVID-19 pandemic: a systematic review and meta-analysis. J Affect Disord. 2021;15(281):91–8. https://doi.org/10.1016/j.jad.2020.11.117.

23. Walker J, Burke K, Wanat M, Fisher R, Fielding J, Mulick A, et al. The prevalence of depression in general hospital inpatients: a systematic review and meta-analysis of interview-based studies. Psychol Med. 2018;48(14):2285–98. https://doi.org/10.1017/S0033291718000624.

24. Wang J, Wu X, Lai W, Long E, Zhang X, Li W, et al. Prevalence of depression and depressive symptoms among outpatients: a systematic review and meta-analysis. BMJ Open. 2017;7(8): e017173. https://doi.org/10.1136/bmjopen-2017-017173.

25. Collaborators C-MD. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021;398(10312):1700–12. https://doi.org/10.1016/S0140-6736(21)02143-7.

26. Benedetti F, Palladini M, Paolini M, Melloni E, Vai B, De Lorenzo R, et al. Brain correlates of depression, post-traumatic distress, and inflammatory biomarkers in COVID-19 survivors: A multimodal magnetic resonance imaging study. Brain Behav Immun Health. 2021;18:100387. https://doi.org/10.1016/j.bbih.2021.100387.

27. Benedetti F, Palladini M, D'Orsi G, Furlan R, Ciceri F, Rovere-Querini P, et al. Mood-congruent negative thinking styles and cognitive vulnerability in depressed COVID-19 survivors: a comparison with Major Depressive Disorder. J Affect Disord. 2022 (in press).

28. Mattioli F, Stampatori C, Righetti F, Sala E, Tomasi C, De Palma G. Neurological and cognitive sequelae of Covid-19: a four month follow-up. J Neurol. 2021;268(12):4422–8. https://doi.org/10.1007/s00415-021-10579-6.

29. Poletti S, Palladini M, Mazza MG, De Lorenzo R, group C-BOCS, Furlan R, et al. Long-term consequences of COVID-19 on cognitive functioning up to 6 months after discharge: role of depression and impact on quality of life. Eur Arch Psychiatry Clin Neurosci. 2021. https://doi.org/10.1007/s00406-021-01346-9.

30. Gouraud C, Bottemanne H, Lahlou-Laforet K, Blanchard A, Gunther S, Batti SE, et al. Association between psychological distress, cognitive complaints, and neuropsychological status after a severe COVID-19 episode: a cross-sectional study. Front Psychiatry. 2021;12:725861. https://doi.org/10.3389/fpsyt.2021.725861.

31. Alnefeesi Y, Siegel A, Lui LMW, Teopiz KM, Ho RCM, Lee Y, et al. Impact of SARS-CoV-2 infection on cognitive function: a systematic review. Front Psychiatry. 2020;11:621773. https://doi.org/10.3389/fpsyt.2020.621773.

32. Liu Y, Ho RC, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012;139(3):230–9. https://doi.org/10.1016/j.jad.2011.08.003.

33. Poletti S, Mazza MG, Calesella F, Vai B, Lorenzi C, Manfredi E, et al. Circulating inflammatory markers impact cognitive functions in bipolar depression. J Psychiatr Res. 2021;140:110–6. https://doi.org/10.1016/j.jpsychires.2021.05.071.

34. Al-Jassas HK, Al-Hakeim HK, Maes M. Intersections between pneumonia, lowered oxygen saturation percentage and immune activation mediate depression, anxiety, and chronic fatigue syndrome-like symptoms due to COVID-19: a nomothetic network approach. J Affect Disord. 2022;15(297):233–45. https://doi.org/10.1016/j.jad.2021.10.039.

35. Mazza M, Palladini M, Poletti S, Benedetti FP. 0086 Clinical and psychopathological predictors of fatigue in COVID-19 survivors: a machine learning study. Eur Neuropsychopharmacol. 2021;53:S60–1.

36. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS ONE. 2020;15(11): e0240784. https://doi.org/10.1371/journal.pone.0240784.

37. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, et al. Fatigue and cognitive impairment in Post-COVID-19 syndrome: a systematic review and meta-analysis. Brain Behav Immun. 2021;29(101):93–135. https://doi.org/10.1016/j.bbi.2021.12.020.

38. Bottemanne H, Gouraud C, Hulot JS, Blanchard A, Ranque B, Lahlou-Laforet K, et al. Do anxiety and depression predict persistent physical symptoms after a severe COVID-19 episode? A prospective study. Front Psychiatry. 2021;12:757685. https://doi.org/10.3389/fpsyt.2021.757685.

39. Babicki M, Bogudzinska B, Kowalski K, Mastalerz-Migas A. Anxiety and depressive disorders and quality of life assessment of poles—a study covering two waves of the COVID-19 pandemic. Front Psychiatry. 2021;12:704248; https://doi.org/10.3389/fpsyt.2021.704248.

40. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020;87:18–22. https://doi.org/10.1016/j.bbi.2020.03.031.

41. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses. 2020;12(4). https://doi.org/10.3390/v12040372.

42. Rodrigues Prestes TR, Rocha NP, Miranda AS, Teixeira AL, Simoes ESAC. The anti-inflammatory potential of ACE2/angiotensin-(1–7)/mas receptor axis: evidence from basic and clinical research. Curr Drug Targ. 2017;18(11):1301–13. https://doi.org/10.2174/1389450117666160727142401.

43. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607–13. https://doi.org/10.1016/j.jinf.2020.03.037.

44. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: an overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020;53:25–32. https://doi.org/10.1016/j.cytogfr.2020.05.003.

45. Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM. Glucocorticoids, cytokines and brain abnormalities in depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(3):722–9. https://doi.org/10.1016/j.pnpbp.2010.04.011.

46. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun. 2017;60:1–12. https://doi.org/10.1016/j.bbi.2016.03.010.

47. Stefano GB, Buttiker P, Weissenberger S, Martin A, Ptacek R, Kream RM. Editorial: the pathogenesis of long-term neuropsychiatric COVID-19 and the role of microglia, mitochondria, and persistent neuroinflammation: a hypothesis. Med Sci Monit. 2021;27:e933015; https://doi.org/10.12659/MSM.933015.

48. Hegazy HG, Ali EH, Elgoly AH. Interplay between pro-inflammatory cytokines and brain oxidative stress biomarkers: evidence of parallels between butyl paraben intoxication and the valproic acid brain physiopathology in autism rat model. Cytokine. 2015;71(2):173–80. https://doi.org/10.1016/j.cyto.2014.10.027.

49. Smith JA, Das A, Ray SK, Banik NL. Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. Brain Res Bull. 2012;87(1):10–20. https://doi.org/10.1016/j.brainresbull.2011.10.004.

50. Balcioglu YH, Yesilkaya UH, Gokcay H, Kirlioglu SS. May the central nervous system be fogged by the cytokine storm

in COVID-19?: an appraisal. J Neuroimmune Pharmacol. 2020;15(3):343–4. https://doi.org/10.1007/s11481-020-09932-9.

51. De Lorenzo R, Loré NI, Finardi A, Mandelli A, Cirillo DM, Tresoldi C, et al. Blood neurofilament light chain and total tau levels at admission predict death in COVID-19 patients. J Neurol. 2021;268(12):4436–42.

52. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;92(6):552–5. https://doi.org/10.1002/jmv.25728.

53. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020;92(7):699–702. https://doi.org/10.1002/jmv.25915.

54. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol. 2020;77(8):1018–27. https://doi.org/10.1001/jamaneurol.2020.2065.

55. Daly JL, Simonetti B, Klein K, Chen KE, Williamson MK, Anton-Plagaro C, et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. Science. 2020;370(6518):861–5. https://doi.org/10.1126/science.abd3072.

56. Esposito G, Pesce M, Seguella L, Sanseverino W, Lu J, Sarnelli G. Can the enteric nervous system be an alternative entrance door in SARS-CoV2 neuroinvasion? Brain Behav Immun. 2020;87:93–4; https://doi.org/10.1016/j.bbi.2020.04.060.

57. Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by human respiratory coronaviruses. J Virol. 2000;74(19):8913–21. https://doi.org/10.1128/jvi.74.19.8913-8921.2000.

58. Matschke J, Lutgehetmann M, Hagel C, Sperhake JP, Schroder AS, Edler C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol. 2020;19(11):919–29. https://doi.org/10.1016/S1474-4422(20)30308-2.

59. Spudich S, Nath A. Nervous system consequences of COVID-19. Science. 2022;375(6578):267–9. https://doi.org/10.1126/science.abm2052.

60. Dantzer R. Neuroimmune interactions: from the brain to the immune system and vice versa. Physiol Rev. 2018;98(1):477–504. https://doi.org/10.1152/physrev.00039.2016.

61. Najjar S, Pearlman DM, Alper K, Najjar A, Devinsky O. Neuroinflammation and psychiatric illness. J Neuroinflamm. 2013;10:43. https://doi.org/10.1186/1742-2094-10-43.

62. Benedetti F, Aggio V, Pratesi ML, Greco G, Furlan R. Neuroinflammation in bipolar depression. Front Psychiatry. 2020;11:71. https://doi.org/10.3389/fpsyt.2020.00071.

63. Maes M, Vandoolaeghe E, Ranjan R, Bosmans E, Bergmans R, Desnyder R. Increased serum interleukin-1-receptor-antagonist concentrations in major depression. J Affect Disord. 1995;36(1–2):29–36. https://doi.org/10.1016/0165-0327(95)00049-6.

64. Maes M, Yirmyia R, Noraberg J, Brene S, Hibbeln J, Perini G, et al. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. Metab Brain Dis. 2009;24(1):27–53. https://doi.org/10.1007/s11011-008-9118-1.

65. Blume J, Douglas SD, Evans DL. Immune suppression and immune activation in depression. Brain Behav Immun. 2011;25(2):221–9. https://doi.org/10.1016/j.bbi.2010.10.008.

66. Wohleb ES, Franklin T, Iwata M, Duman RS. Integrating neuroimmune systems in the neurobiology of depression. Nat Rev Neurosci. 2016;17(8):497–511. https://doi.org/10.1038/nrn.2016.69.

67. Simon MS, Schiweck C, Arteaga-Henríquez G, Poletti S, Haarman BC, Dik WA, et al. Monocyte mitochondrial dysfunction, inflammaging, and inflammatory pyroptosis in major depression. Prog Neuropsychopharmacol Biol Psychiatry. 2021;111: 110391.

68. Cheng Y, Desse S, Martinez A, Worthen RJ, Jope RS, Beurel E. TNFalpha disrupts blood brain barrier integrity to maintain prolonged depressive-like behavior in mice. Brain Behav Immun. 2018;69:556–67; https://doi.org/10.1016/j.bbi.2018.02.003.

69. Halaris A. Inflammation and depression but where does the inflammation come from? Curr Opin Psychiatry. 2019;32(5):422–8. https://doi.org/10.1097/YCO.0000000000000531.

70. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nat Rev Neurosci. 2016;17(8):524–32. https://doi.org/10.1038/nrn.2016.57.

71. Borroto-Escuela DO, Ambrogini P, Chruscicka B, Lindskog M, Crespo-Ramirez M, Hernandez-Mondragon JC, et al. The role of central serotonin neurons and 5-HT heteroreceptor complexes in the pathophysiology of depression: a historical perspective and future prospects. Int J Mol Sci. 2021. https://doi.org/10.3390/ijms22041927.

72. Onaolapo AY, Onaolapo OJ. Glutamate and depression: Reflecting a deepening knowledge of the gut and brain effects of a ubiquitous molecule. World J Psychiatry. 2021;11(7):297–315. https://doi.org/10.5498/wjp.v11.i7.297.

73. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9(1):46–56. https://doi.org/10.1038/nrn2297.

74. Paul ER, Schwieler L, Erhardt S, Boda S, Trepci A, Kampe R, et al. Peripheral and central kynurenine pathway abnormalities in major depression. Brain Behav Immun. 2022;6(101):136–45. https://doi.org/10.1016/j.bbi.2022.01.002.

75. Ogyu K, Kubo K, Noda Y, Iwata Y, Tsugawa S, Omura Y, et al. Kynurenine pathway in depression: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2018;90:16–25. https://doi.org/10.1016/j.neubiorev.2018.03.023.

76. Lorkiewicz P, Waszkiewicz N. Biomarkers of post-COVID depression. J Clin Med. 2021;10(18):4142.

77. Ida T, Hara M, Nakamura Y, Kozaki S, Tsunoda S, Ihara H. Cytokine-induced enhancement of calcium-dependent glutamate release from astrocytes mediated by nitric oxide. Neurosci Lett. 2008;432(3):232–6. https://doi.org/10.1016/j.neulet.2007.12.047.

78. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry. 2009;65(9):732–41. https://doi.org/10.1016/j.biopsych.2008.11.029.

79. Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. J Neurosci. 2009;29(13):3974–80. https://doi.org/10.1523/JNEUROSCI.4363-08.2009.

80. Eyo UB, Wu LJ. Bidirectional microglia-neuron communication in the healthy brain. Neural Plast. 2013;2013:456857. https://doi.org/10.1155/2013/456857.

81. Lindenau J, Noack H, Asayama K, Wolf G. Enhanced cellular glutathione peroxidase immunoreactivity in activated astrocytes and in microglia during excitotoxin induced neurodegeneration. Glia. 1998;24(2):252–6.

82. Enache D, Pariante CM, Mondelli V. Markers of central inflammation in major depressive disorder: a systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. Brain Behav Immun. 2019;81:24–40. https://doi.org/10.1016/j.bbi.2019.06.015.

83. Tremblay ME, Madore C, Bordeleau M, Tian L, Verkhratsky A. Neuropathobiology of COVID-19: the role for glia. Front Cell

Neurosci. 2020;14:592214. https://doi.org/10.3389/fncel.2020.592214.

84. Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. Lancet Microbe. 2020;1(6):e245–53. https://doi.org/10.1016/S2666-5247(20)30115-4.

85. Cobley JN, Fiorello ML, Bailey DM. 13 reasons why the brain is susceptible to oxidative stress. Redox Biol. 2018;15:490–503. https://doi.org/10.1016/j.redox.2018.01.008.

86. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35(3):676–92. https://doi.org/10.1016/j.pnpbp.2010.05.004.

87. Morris G, Berk M, Klein H, Walder K, Galecki P, Maes M. Nitrosative stress, hypernitrosylation, and autoimmune responses to nitrosylated proteins: new pathways in neuroprogressive disorders including depression and chronic fatigue syndrome. Mol Neurobiol. 2017;54(6):4271–91. https://doi.org/10.1007/s12035-016-9975-2.

88. Raony I, de Figueiredo CS, Pandolfo P, Giestal-de-Araujo E, Oliveira-Silva Bomfim P, Savino W. Psycho-neuroendocrine-immune interactions in COVID-19: potential impacts on mental health. Front Immunol. 2020;11:1170. https://doi.org/10.3389/fimmu.2020.01170.

89. Turrin NP, Rivest S. Unraveling the molecular details involved in the intimate link between the immune and neuroendocrine systems. Exp Biol Med (Maywood). 2004;229(10):996–1006. https://doi.org/10.1177/153537020422901003.

90. Pariante CM. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. Eur Neuropsychopharmacol. 2017;27(6):554–9. https://doi.org/10.1016/j.euroneuro.2017.04.001.

91. Nemeroff CB, Widerlov E, Bissette G, Walleus H, Karlsson I, Eklund K, et al. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science. 1984;226(4680):1342–4. https://doi.org/10.1126/science.6334362.

92. Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav Immun. 2011;25(2):181–213. https://doi.org/10.1016/j.bbi.2010.10.015.

93. Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. Nature. 2006;440(7087):1054–9. https://doi.org/10.1038/nature04671.

94. Bourgognon JM, Cavanagh J. The role of cytokines in modulating learning and memory and brain plasticity. Brain Neurosci Adv. 2020;4:2398212820979802. https://doi.org/10.1177/2398212820979802.

95. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience. 2013;29(246):199–229. https://doi.org/10.1016/j.neuroscience.2013.04.060.

96. Benedetti F, Poletti S, Hoogenboezem TA, Mazza E, Ambrée O, de Wit H, et al. Inflammatory cytokines influence measures of white matter integrity in bipolar disorder. J Affect Disord. 2016;202:1–9.

97. Singh S, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: a narrative review with recommendations. Psychiatry Res. 2020;293:113429. https://doi.org/10.1016/j.psychres.2020.113429.

98. Guo Q, Zheng Y, Shi J, Wang J, Li G, Li C, et al. Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: a mixed-method study. Brain Behav Immun. 2020;88:17–27. https://doi.org/10.1016/j.bbi.2020.05.038.

99. Cava MA, Fay KE, Beanlands HJ, McCay EA, Wignall R. The experience of quarantine for individuals affected by SARS in Toronto. Public Health Nurs. 2005;22(5):398–406. https://doi.org/10.1111/j.0737-1209.2005.220504.x.

100. Xin M, Luo S, She R, Yu Y, Li L, Wang S, et al. Negative cognitive and psychological correlates of mandatory quarantine during the initial COVID-19 outbreak in China. Am Psychol. 2020;75(5):607–17. https://doi.org/10.1037/amp0000692.

101. Mumtaz F, Khan MI, Zubair M, Dehpour AR. Neurobiology and consequences of social isolation stress in animal model—a comprehensive review. Biomed Pharmacother. 2018;105:1205–22; https://doi.org/10.1016/j.biopha.2018.05.086.

102. Juruena MF, Eror F, Cleare AJ, Young AH. The role of early life stress in HPA axis and anxiety. Adv Exp Med Biol. 2020;1191:141–53. https://doi.org/10.1007/978-981-32-9705-0_9.

103. Raadsheer FC, Hoogendijk WJ, Stam FC, Tilders FJ, Swaab DF. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. Neuroendocrinology. 1994;60(4):436–44. https://doi.org/10.1159/000126778.

104. Cruz-Pereira JS, Rea K, Nolan YM, O'Leary OF, Dinan TG, Cryan JF. Depression's unholy trinity: dysregulated stress, immunity, and the microbiome. Annu Rev Psychol. 2020;4(71):49–78. https://doi.org/10.1146/annurev-psych-122216-011613.

105. Walker FR, Nilsson M, Jones K. Acute and chronic stress-induced disturbances of microglial plasticity, phenotype and function. Curr Drug Targ. 2013;14(11):1262–76. https://doi.org/10.2174/13894501113149990208.

106. Mullins N, Power RA, Fisher HL, Hanscombe KB, Euesden J, Iniesta R, et al. Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. Psychol Med. 2016;46(4):759–70. https://doi.org/10.1017/S0033291715002172.

107. Poletti S, Aggio V, Brioschi S, Bollettini I, Falini A, Colombo C, et al. Impact of early and recent stress on white matter microstructure in major depressive disorder. J Affect Disord. 2018;1(225):289–97. https://doi.org/10.1016/j.jad.2017.08.017.

108. Vai B, Serretti A, Poletti S, Mascia M, Lorenzi C, Colombo C, et al. Cortico-limbic functional connectivity mediates the effect of early life stress on suicidality in bipolar depressed 5-HTTLPR*s carriers. J Affect Disord. 2020;15(263):420–7. https://doi.org/10.1016/j.jad.2019.11.142.

109. Poletti S, Aggio V, Brioschi S, Dallaspezia S, Colombo C, Benedetti F. Multidimensional cognitive impairment in unipolar and bipolar depression and the moderator effect of adverse childhood experiences. Psychiatry Clin Neurosci. 2017;71(5):309–17. https://doi.org/10.1111/pcn.12497.

110. Ahmed GK, Khedr EM, Hamad DA, Meshref TS, Hashem MM, Aly MM. Long term impact of Covid-19 infection on sleep and mental health: a cross-sectional study. Psychiatry Res. 2021;305:114243. https://doi.org/10.1016/j.psychres.2021.114243.

111. He X, Zhang D, Zhang L, Zheng X, Zhang G, Pan K, et al. Neurological and psychiatric presentations associated with COVID-19. Eur Arch Psychiatry Clin Neurosci. 2022;272(1):41–52. https://doi.org/10.1007/s00406-021-01244-0.

112. Hu Y, Chen Y, Zheng Y, You C, Tan J, Hu L, et al. Factors related to mental health of inpatients with COVID-19 in Wuhan, China. Brain Behav Immun. 2020;89:587–93. https://doi.org/10.1016/j.bbi.2020.07.016.

113. Iglesias-Gonzalez M, Boigues M, Sanagustin D, Giralt-Lopez M, Cuevas-Esteban J, Martinez-Caceres E, et al. Association of serum interleukin-6 and C-reactive protein with depressive

and adjustment disorders in COVID-19 inpatients. Brain Behav Immun Health. 2022;19:100405. https://doi.org/10.1016/j.bbih.2021.100405.

114. Kahve AC, Kaya H, Okuyucu M, Goka E, Barun S, Hacimusalar Y. Do anxiety and depression levels affect the inflammation response in patients hospitalized for COVID-19. Psychiatry Investig. 2021;18(6):505–12. https://doi.org/10.30773/pi.2021.0029.

115. Yuan B, Li W, Liu H, Cai X, Song S, Zhao J, et al. Correlation between immune response and self-reported depression during convalescence from COVID-19. Brain Behav Immun. 2020;88:39–43. https://doi.org/10.1016/j.bbi.2020.05.062.

116. Huarcaya-Victoria J, Barreto J, Aire L, Podesta A, Caqui M, Guija-Igreda R, et al. Mental health in COVID-2019 survivors from a general hospital in peru: sociodemographic, clinical, and inflammatory variable associations. Int J Ment Health Addict. 2021. https://doi.org/10.1007/s11469-021-00659-z.

117. Li X, Cai Q, Jia Z, Zhou Y, Liu L, Zhou Y, et al. The correlation between mental health status, sleep quality, and inflammatory markers, virus negative conversion time among patients confirmed with 2019-nCoV during the COVID-19 outbreak in China: an observational study. Medicine (Baltimore). 2021;100(27): e26520. https://doi.org/10.1097/MD.0000000000026520.

118. Serrano Garcia A, Montanchez Mateo J, Franch Pato CM, Gomez Martinez R, Garcia Vazquez P, Gonzalez RI. Interleukin 6 and depression in patients affected by Covid-19. Med Clin (Engl Ed). 2021;156(7):332–5. https://doi.org/10.1016/j.medcle.2020.11.013.

119. Zhou F, Wang RR, Huang HP, Du CL, Wu CM, Qian XM, et al. A randomized trial in the investigation of anxiety and depression in patients with coronavirus disease 2019 (COVID-19). Ann Palliat Med. 2021;10(2):2167–74; https://doi.org/10.21037/apm-21-212.

120. Wu C, Zhou Z, Ni L, Cao J, Tan M, Wu X, et al. Correlation between anxiety-depression symptoms and immune characteristics in inpatients with 2019 novel coronavirus in Wuhan, China. J Psychiatr Res. 2021;141:378–84; https://doi.org/10.1016/j.jpsychires.2021.07.027.

121. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat Commun. 2020;11(1):6317. https://doi.org/10.1038/s41467-020-19741-6.

122. Albert PR. Why is depression more prevalent in women? J Psychiatry Neurosci. 2015;40(4):219–21. https://doi.org/10.1503/jpn.150205.

123. Marquez EJ, Chung CH, Marches R, Rossi RJ, Nehar-Belaid D, Eroglu A, et al. Sexual-dimorphism in human immune system aging. Nat Commun. 2020;11(1):751. https://doi.org/10.1038/s41467-020-14396-9.

124. Bonafe M, Olivieri F, Cavallone L, Giovagnetti S, Mayegiani F, Cardelli M, et al. A gender–dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. Eur J Immunol. 2001;31(8):2357–61. https://doi.org/10.1002/1521-4141(200108)31:8%3c2357::aid-immu2357%3e3.0.co;2-x.

125. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84(Pt A):229–36. https://doi.org/10.1016/j.pnpbp.2018.03.012.

126. Fernandes BS, Steiner J, Molendijk ML, Dodd S, Nardin P, Goncalves CA, et al. C-reactive protein concentrations across the mood spectrum in bipolar disorder: a systematic review and meta-analysis. Lancet Psychiatry. 2016;3(12):1147–56. https://doi.org/10.1016/S2215-0366(16)30370-4.

127. Davydow DS, Hough CL, Zivin K, Langa KM, Katon WJ. Depression and risk of hospitalization for pneumonia in a cohort study of older Americans. J Psychosom Res. 2014;77(6):528–34. https://doi.org/10.1016/j.jpsychores.2014.08.002.

128. Kao LT, Liu SP, Lin HC, Lee HC, Tsai MC, Chung SD. Poor clinical outcomes among pneumonia patients with depressive disorder. PLoS ONE. 2014;9(12): e116436. https://doi.org/10.1371/journal.pone.0116436.

129. Papaioannou AI, Bartziokas K, Tsikrika S, Karakontaki F, Kastanakis E, Banya W, et al. The impact of depressive symptoms on recovery and outcome of hospitalised COPD exacerbations. Eur Respir J. 2013;41(4):815–23. https://doi.org/10.1183/09031936.00013112.

130. Facente SN, Reiersen AM, Lenze EJ, Boulware DR, Klausner JD. Fluvoxamine for the early treatment of SARS-CoV-2 infection: a review of current evidence. Drugs. 2021;81(18):2081–9. https://doi.org/10.1007/s40265-021-01636-5.

131. Hashimoto Y, Suzuki T, Hashimoto K. Mechanisms of action of fluvoxamine for COVID-19: a historical review. Mol Psychiatry. 2022. https://doi.org/10.1038/s41380-021-01432-3.

132. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs. placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA. 2020;324(22):2292–300. https://doi.org/10.1001/jama.2020.22760.

133. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Glob Health. 2022;10(1):e42–51. https://doi.org/10.1016/S2214-109X(21)00448-4.

134. Seftel D, Boulware DR. Prospective cohort of fluvoxamine for early treatment of coronavirus disease 19. Open Forum Infect Dis. 2021;8(2):ofab050. https://doi.org/10.1093/ofid/ofab050.

135. Hoertel N, Sanchez-Rico M, Cougoule C, Gulbins E, Kornhuber J, Carpinteiro A, et al. Repurposing antidepressants inhibiting the sphingomyelinase acid/ceramide system against COVID-19: current evidence and potential mechanisms. Mol Psychiatry. 2021. https://doi.org/10.1038/s41380-021-01254-3.

136. Pashaei Y. Drug repurposing of selective serotonin reuptake inhibitors: could these drugs help fight COVID-19 and save lives? J Clin Neurosci. 2021;88:163–72. https://doi.org/10.1016/j.jocn.2021.03.010.

137. Lu Y, Ho CS, Liu X, Chua AN, Wang W, McIntyre RS, et al. Chronic administration of fluoxetine and pro-inflammatory cytokine change in a rat model of depression. PLoS ONE. 2017;12(10): e0186700. https://doi.org/10.1371/journal.pone.0186700.

138. Carpinteiro A, Edwards MJ, Hoffmann M, Kochs G, Gripp B, Weigang S, et al. Pharmacological inhibition of acid sphingomyelinase prevents uptake of SARS-CoV-2 by epithelial cells. Cell Rep Med. 2020;1(8): 100142. https://doi.org/10.1016/j.xcrm.2020.100142.

139. Kornhuber J, Muehlbacher M, Trapp S, Pechmann S, Friedl A, Reichel M, et al. Identification of novel functional inhibitors of acid sphingomyelinase. PLoS ONE. 2011;6(8): e23852. https://doi.org/10.1371/journal.pone.0023852.

140. Homolak J, Kodvanj I. Widely available lysosome targeting agents should be considered as potential therapy for COVID-19. Int J Antimicrob Agents. 2020;56(2): 106044. https://doi.org/10.1016/j.ijantimicag.2020.106044.

141. Schlienger RG, Meier CR. Effect of selective serotonin reuptake inhibitors on platelet activation: can they prevent acute myocardial infarction? Am J Cardiovasc Drugs. 2003;3(3):149–62. https://doi.org/10.2165/00129784-200303030-00001.

142. Sukhatme VP, Reiersen AM, Vayttaden SJ, Sukhatme VV. Fluvoxamine: a review of its mechanism of action and its role in COVID-19. Front Pharmacol. 2021;12:652688. https://doi.org/10.3389/fphar.2021.652688.

143. Anderson G, Reiter RJ. Melatonin: Roles in influenza, Covid-19, and other viral infections. Rev Med Virol. 2020;30(3): e2109. https://doi.org/10.1002/rmv.2109.

144. Anderson GM. Fluvoxamine, melatonin and COVID-19. Psychopharmacology. 2021;238(2):611. https://doi.org/10.1007/s00213-020-05753-z.

145. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 2020;250:117583. https://doi.org/10.1016/j.lfs.2020.117583.

146. Mazza MG, Zanardi R, Palladini M, Rovere-Querini P, Benedetti F. Rapid response to selective serotonin reuptake inhibitors in post-COVID depression. Eur Neuropsychopharmacol. 2022;54:1–6. https://doi.org/10.1016/j.euroneuro.2021.09.009.

147. Kohler CA, Freitas TH, Stubbs B, Maes M, Solmi M, Veronese N, et al. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: systematic review and meta-analysis. Mol Neurobiol. 2018;55(5):4195–206. https://doi.org/10.1007/s12035-017-0632-1.

148. Liu D, Wang Z, Liu S, Wang F, Zhao S, Hao A. Anti-inflammatory effects of fluoxetine in lipopolysaccharide(LPS)-stimulated microglial cells. Neuropharmacology. 2011;61(4):592–9. https://doi.org/10.1016/j.neuropharm.2011.04.033.

149. Eskelund A, Li Y, Budac DP, Muller HK, Gulinello M, Sanchez C, et al. Drugs with antidepressant properties affect tryptophan metabolites differently in rodent models with depression-like behavior. J Neurochem. 2017;142(1):118–31. https://doi.org/10.1111/jnc.14043.

150. Fei L, Santarelli G, D'Anna G, Moretti S, Mirossi G, Patti A, et al. Can SSRI/SNRI antidepressants decrease the 'cytokine storm' in the course of COVID-19 pneumonia? Panminerva Med. 2021. https://doi.org/10.23736/S0031-0808.21.04436-0.

151. Benedetti F, Mazza M, Cavalli G, Ciceri F, Dagna L, Rovere-Querini P. Can cytokine blocking prevent depression in COVID-19 survivors? J Neuroimmune Pharmacol. 2021;16(1):1–3. https://doi.org/10.1007/s11481-020-09966-z.

152. Farnoosh G, Akbariqomi M, Badri T, Bagheri M, Izadi M, Saeedi-Boroujeni A, et al. Efficacy of a low dose of melatonin as an adjunctive therapy in hospitalized patients with COVID-19: a randomized, double-blind clinical trial. Arch Med Res. 2022;53(1):79–85. https://doi.org/10.1016/j.arcmed.2021.06.006.

153. Zhou Y, Hou Y, Shen J, Mehra R, Kallianpur A, Culver DA, et al. A network medicine approach to investigation and population-based validation of disease manifestations and drug repurposing for COVID-19. PLoS Biol. 2020;18(11): e3000970. https://doi.org/10.1371/journal.pbio.3000970.

154. Hooper PL. Heme oxygenase agonists-fluvoxamine, melatonin-are efficacious therapy for Covid-19. Cell Stress Chaperones. 2022;27(1):3–4. https://doi.org/10.1007/s12192-021-01246-w.

155. Cardinali DP, Srinivasan V, Brzezinski A, Brown GM. Melatonin and its analogs in insomnia and depression. J Pineal Res. 2012;52(4):365–75. https://doi.org/10.1111/j.1600-079X.2011.00962.x.

156. Stanford SC. Recent developments in research of melatonin and its potential therapeutic applications. Br J Pharmacol. 2018;175(16):3187–9. https://doi.org/10.1111/bph.14371.

157. Ali T, Rahman SU, Hao Q, Li W, Liu Z, Ali Shah F, et al. Melatonin prevents neuroinflammation and relieves depression by attenuating autophagy impairment through FOXO3a regulation.

J Pineal Res. 2020;69(2): e12667. https://doi.org/10.1111/jpi.12667.

158. Estrada-Reyes R, Valdes-Tovar M, Arrieta-Baez D, Dorantes-Barron AM, Quero-Chavez D, Solis-Chagoyan H, et al. The timing of melatonin administration is crucial for its antidepressant-like effect in mice. Int J Mol Sci. 2018. https://doi.org/10.3390/ijms19082278.

159. Valdes-Tovar M, Estrada-Reyes R, Solis-Chagoyan H, Argueta J, Dorantes-Barron AM, Quero-Chavez D, et al. Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression. Br J Pharmacol. 2018;175(16):3200–8. https://doi.org/10.1111/bph.14197.

160. Guaiana G, Gupta S, Chiodo D, Davies SJ, Haederle K, Koesters M. Agomelatine versus other antidepressive agents for major depression. Cochrane Database Syst Rev. 2013;17(12):CD008851. https://doi.org/10.1002/14651858.CD008851.pub2.

161. De Berardis D, Fornaro M, Orsolini L, Iasevoli F, Tomasetti C, de Bartolomeis A, et al. Effect of agomelatine treatment on C-reactive protein levels in patients with major depressive disorder: an exploratory study in "real-world," everyday clinical practice. CNS Spectr. 2017;22(4):342–7. https://doi.org/10.1017/S1092852916000572.

162. Molteni R, Macchi F, Zecchillo C, Dell'agli M, Colombo E, Calabrese F, et al. Modulation of the inflammatory response in rats chronically treated with the antidepressant agomelatine. Eur Neuropsychopharmacol. 2013;23(11):1645–55. https://doi.org/10.1016/j.euroneuro.2013.03.008.

163. Tchekalarova J, Atanasova D, Kortenska L, Atanasova M, Lazarov N. Chronic agomelatine treatment prevents comorbid depression in the post-status epilepticus model of acquired epilepsy through suppression of inflammatory signaling. Neurobiol Dis. 2018;115:127–44. https://doi.org/10.1016/j.nbd.2018.04.005.

164. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med. 2020;76:43–9. https://doi.org/10.1016/j.ejim.2020.05.021.

165. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325–31. https://doi.org/10.1016/S2665-9913(20)30127-2.

166. Arteaga-Henriquez G, Simon MS, Burger B, Weidinger E, Wijkhuijs A, Arolt V, et al. Low-grade inflammation as a predictor of antidepressant and anti-inflammatory therapy response in MDD patients: a systematic review of the literature in combination with an analysis of experimental data collected in the EU-MOODINFLAME consortium. Front Psychiatry. 2019;10:458. https://doi.org/10.3389/fpsyt.2019.00458.

167. Bschor T. Lithium in the treatment of major depressive disorder. Drugs. 2014;74(8):855–62. https://doi.org/10.1007/s40265-014-0220-x.

168. Del Matto L, Muscas M, Murru A, Verdolini N, Anmella G, Fico G, et al. Lithium and suicide prevention in mood disorders and in the general population: a systematic review. Neurosci Biobehav Rev. 2020;116:142–53; https://doi.org/10.1016/j.neubiorev.2020.06.017.

169. Malhi GS, Tanious M, Das P, Coulston CM, Berk M. Potential mechanisms of action of lithium in bipolar disorder. Current understanding. CNS Drugs. 2013;27(2):135–53. https://doi.org/10.1007/s40263-013-0039-0.

170. Pietruczuk K, Lisowska KA, Grabowski K, Landowski J, Witkowski JM. Proliferation and apoptosis of T lymphocytes in patients with bipolar disorder. Sci Rep. 2018;8(1):3327. https://doi.org/10.1038/s41598-018-21769-0.

171. Nassar A, Azab AN. Effects of lithium on inflammation. ACS Chem Neurosci. 2014;5(6):451–8. https://doi.org/10.1021/cn500038f.

172. Murru A, Manchia M, Hajek T, Nielsen RE, Rybakowski JK, Sani G, et al. Lithium's antiviral effects: a potential drug for CoViD-19 disease? Int J Bipolar Disord. 2020;8(1):21. https://doi.org/10.1186/s40345-020-00191-4.

173. Spuch C, Lopez-Garcia M, Rivera-Baltanas T, Rodrigues-Amorim D, Olivares JM. Does lithium deserve a place in the treatment against COVID-19? A preliminary observational study in six patients, case report. Front Pharmacol. 2020;11:557629. https://doi.org/10.3389/fphar.2020.557629.

174. Benedetti F, Bollettini I, Barberi I, Radaelli D, Poletti S, Locatelli C, et al. Lithium and GSK3-β promoter gene variants influence white matter microstructure in bipolar disorder. Neuropsychopharmacology. 2013;38(2):313–27.

175. Furlan R, Melloni E, Finardi A, Vai B, Di Toro S, Aggio V, et al. Natural killer cells protect white matter integrity in bipolar disorder. Brain Behav Immun. 2019;81:410–21.

176. Gomez L, Vidal B, Cabrera Y, Hernandez L, Rondon Y. Successful treatment of post-COVID symptoms with transcranial direct current stimulation. Prim Care Companion CNS Disord. 2021. https://doi.org/10.4088/PCC.21cr03059.

177. Zhang R, Lam CLM, Peng X, Zhang D, Zhang C, Huang R, et al. Efficacy and acceptability of transcranial direct current stimulation for treating depression: a meta-analysis of randomized controlled trials. Neurosci Biobehav Rev. 2021;126:481–90. https://doi.org/10.1016/j.neubiorev.2021.03.026.

178. Perrin AJ, Pariante CM. Endocrine and immune effects of non-convulsive neurostimulation in depression: a systematic review. Brain Behav Immun. 2020;87:910–20; https://doi.org/10.1016/j.bbi.2020.02.016.

179. Rajkumar RP. Ayurveda and COVID-19: where psychoneuroimmunology and the meaning response meet. Brain Behav Immun. 2020;87:8–9. https://doi.org/10.1016/j.bbi.2020.04.056.

180. Sarris J. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. Phytother Res. 2018;32(7):1147–62. https://doi.org/10.1002/ptr.6055.

181. Yadav B, Rai A, Mundada PS, Singhal R, Rao BCS, Rana R, et al. Safety and efficacy of Ayurvedic interventions and Yoga on long term effects of COVID-19: a structured summary of a study protocol for a randomized controlled trial. Trials. 2021;22(1):378. https://doi.org/10.1186/s13063-021-05326-1.

182. Thimmulappa RK, Mudnakudu-Nagaraju KK, Shivamallu C, Subramaniam KJT, Radhakrishnan A, Bhojraj S, et al. Antiviral and immunomodulatory activity of curcumin: a case for prophylactic therapy for COVID-19. Heliyon. 2021;7(2): e06350. https://doi.org/10.1016/j.heliyon.2021.e06350.

183. Soni VK, Mehta A, Shukla D, Kumar S, Vishvakarma NK. Fight COVID-19 depression with immunity booster: Curcumin for psychoneuroimmunomodulation. Asian J Psychiatr. 2020;53:102378. https://doi.org/10.1016/j.ajp.2020.102378.

184. Buemann B, Marazziti D, Uvnas-Moberg K. Can intravenous oxytocin infusion counteract hyperinflammation in COVID-19 infected patients? World J Biol Psychiatry. 2021;22(5):387–98; https://doi.org/10.1080/15622975.2020.1814408.

185. Thakur P, Shrivastava R, Shrivastava VK. Oxytocin as a potential adjuvant against COVID-19 infection. Endocr Metab Immune Disord Drug Targ. 2021;21(7):1155–62. https://doi.org/10.2174/1871530320666200910114259.

186. Benedetti F, Zanardi R, Mazza MG. Antidepressant psychopharmacology: is inflammation a future target? Int Clin Psychopharmacol. 2022;37(3):79–81. https://doi.org/10.1097/YIC.0000000000000403.

187. Cheng YC, Kuo PH, Su MI, Huang WL. The efficacy of non-invasive, non-convulsive electrical neuromodulation on depression, anxiety and sleep disturbance: a systematic review and meta-analysis. Psychol Med. 2022. https://doi.org/10.1017/S0033291721005560.

188. Dallaspezia S, Suzuki M, Benedetti F. Chronobiological therapy for mood disorders. Curr Psychiatry Rep. 2015;17(12):95. https://doi.org/10.1007/s11920-015-0633-6.

189. Sarris J, Ravindran A, Yatham LN, Marx W, Rucklidge JJ, McIntyre RS, et al. Clinician guidelines for the treatment of psychiatric disorders with nutraceuticals and phytoceuticals: The World Federation of Societies of Biological Psychiatry (WFSBP) and Canadian Network for Mood and Anxiety Treatments (CANMAT) Taskforce. World J Biol Psychiatry. 2022. https://doi.org/10.1080/15622975.2021.2013041.