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Review

The neuropsychiatric manifestations of COVID-19: Interactions with psychiatric illness and pharmacological treatment

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ABSTRACT

The recent outbreak of the corona virus disease (COVID-19) has had major global impact. The relationship between severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection and psychiatric diseases is of great concern, with an evident link between corona virus infections and various central and peripheral nervous system manifestations. Unmitigated neuro-inflammation has been noted to underlie not only the severe respiratory complications of the disease but is also present in a range of neuro-psychiatric illnesses. Several neurological and psychiatric disorders are characterized by immune-inflammatory states, while treatments for these disorders have distinct anti-inflammatory properties and effects. With inflammation being a common contributing factor in SARS-CoV-2, as well as psychiatric disorders, treatment of either condition may affect disease progression of the other or alter response to pharmacological treatment. In this review, we elucidate how viral infections could affect pre-existing psychiatric conditions and how pharmacological treatments of these conditions may affect overall progress and outcome in the treatment of SARS-CoV-2. We address whether any treatment-induced benefits and potential adverse effects may ultimately affect the overall treatment approach, considering the underlying dysregulated neuro-inflammatory processes and potential drug interactions. Finally, we suggest adjunctive treatment options for SARS-CoV-2-associated neuro-psychiatric symptoms.

1. Overview of SARS-CoV-2, with emphasis on neuropsychiatric co-morbidities

1.1. Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first identified in Wuhan, China, in December 2019 [1], has experienced progressive spread across the world in 2020. The virus, known as the novel coronavirus, causes a disease coined the 'Coronavirus Disease of 2019 (COVID-19)', that has affected human activities on an unprecedented scale. The rapid spread was fuelled by international travel and globalisation, combined with an infection that can be transmitted in the early asymptomatic phase. The illness remains an enigma, and we remain puzzled by its unknown novelty, and sometimes overwhelmed by the potential threat and observed devastation. Currently, no historical data is available to accurately predict the associated risks, death rates and other acute and long-term complications of the disease. Although promising anti-COVID-19 vaccines are being developed or are in the process of being approved, no pharmacological-effective prevention, containment strategies and/or cure is available.

While generally recognised for its often-lethal respiratory effects in especially vulnerable individuals, other potential complications, such as its effect on mental illnesses are receiving growing attention. In fact, coronavirus infections are also known as neurotropic viral infections; defined as viruses with an affinity for the nervous system [2]. In this regard, Song and colleagues [3] demonstrated SARS-CoV-2 neuro--invasion in human cell cultures and post-mortem studies. In this review, we focus on psychiatric disorders against the backdrop of this viral outbreak and discuss the potential mechanisms responsible for the interplay between these conditions. We also address the therapeutic benefits and potential adverse effects associated with treating the presenting neuropsychiatric condition and how such treatment may alter

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the course of SARS-CoV-2 infection in an afflicted individual. Such knowledge may reveal new avenues for identifying novel treatment interventions for SARS-CoV-2 associated neuropsychiatric complications.

1.2. The pathophysiology and inflammatory responses associated with SARS-CoV-2

The last decades of corona virus infections, including outbreaks of SARS (2002), Middle East Respiratory Syndrome (MERS; 2012-2017) and the most recent SARS-CoV-2 (2019), all share similar immunological features and pathological impact [4,5]. These can be classified into four main aspects namely, (*i*) viral replication in innate immune cells, (*ii*) dysregulated immune response, (*iii*) cytokine storm, and (*iv*) antibody-mediated response [4,5]. SARS-CoV-2 is part of the *Coronaviridae* family, subfamily *Coronavirinae*, which are large, enveloped, single-stranded RNA viruses [6]. Importantly, these viruses are roughly spherical and with notable 'crown-like' large spikes of glycoprotein [2,6], from whence their name is derived. Following breaching of the initial anatomical and chemical defensive barriers of the host organism, the SARS-CoV-2 mediates viral entry into cells through binding to the angiotensin-converting enzyme 2 (ACE-2) receptor of the host cell as shown in Fig. 1. The receptor binding domain is positioned within the spike of the virus in such a way, that it is hidden and evades immune surveillance [7]. Once in the cytoplasm, the virus escapes the innate immunity response by either releasing viral endoribonuclease (RNase) activity or by forming replication organelles in host cell membranes to protect the recognition of viral RNA by the innate immune sensors [8,9]. During the incubation period, viral genomes are replicated, whilst the innate immune response of the host is activated, involving cytokine synthesis and release [10] (Fig. 1). Indeed, inflammatory markers (including interleukin (IL)-2, IL-6, IL-7, IL-10 and IL-18, interferon (IFN)-γ, monocyte chemoattractant protein (MCP)-1, MCP-3 and macrophage-inflammatory protein-1α) are positively associated with symptom severity [11–13], whilst specifically IL-6 and tumour necrosis factor (TNF)-α levels can act as predictors of symptom severity and survival rates of infected patients [14].

Cytokine storm is therefore the hallmark of this disease, a viral-induced phenomenon where exaggerated cytokine production can lead to acute respiratory distress syndrome (ARDS) [15] and multiple organ dysfunction syndrome (MODS) [16], but may also drive a number of other complications, most notably of the CNS. The notable viral factors that trigger the abnormal increase in pro-inflammatory cytokines and chemokines include haemagglutinin (HA) and the polymerase gene segments. Interestingly, SARS-CoV-2-associated cytokine storm seems to be accompanied by decreased T-cell counts [13,17], and as ACE-2 receptors are not expressed on T-cells [18] the mentioned decrease in T-cell numbers are not a direct cause of the virus, but possibly the indirect result of the SARS-CoV-2-induced cytokine storm [19–21]. Taken together, COVID-19-associated alterations of the innate immune system can lead to secondary or opportunistic infections with serious consequences, involving multiple organs that includes the brain, in which case the adaptive immune response may be overwhelmed.

1.3. Psychological stress and psychiatric symptoms associated with SARS-CoV-2

What has become increasingly apparent is that patients with SARS-CoV-2 show higher manifestations of depression, anxiety and post-traumatic stress disorder (PTSD) symptoms when compared with non-COVID controls [22]. Recently, a case report showed that manic-like symptoms might be a delayed response to CNS infection by SARS-CoV-2 in patients with no history of psychiatric illness [23]. While this could be mediated by the significant psychological stress experienced by these patients [22], there may also be neuropathological underpinnings to this phenomenon.

The Inter-Agency Standing Committee that provides guidelines on mental health and psychological support during emergency settings, found that certain stressors were overly demanding, challenging or threatening to susceptible individuals during the SARS-CoV-2 pandemic [24]. These stressors include the fear of infection, symptoms being mistaken for COVID-19, concerns about the deterioration of individual's overall health as a consequence of the infection, as well as economic and family support systems and capacity for caregiving [24]. When these stressors are accompanied by fear, worry and uncertainties, it could result in long-term consequences of social stigmatisation or discrimination that in turn heighten emotional states of anger and aggression [24]. Recent reports suggest differences in psychological impact of COVID-19 on individuals residing in different regions, who also differ in terms of health statuses and occupations [25]. In China, recent surveys showed that 35 % of responders reported psychological distress [26], whilst 53.8 % rated the psychological impact of the pandemic as moderate or severe [27]. Therefore, it is crucial to determine the effect that psychological stress may have on the general population as well as on individuals with COVID-19, especially because psychological stress has a biological component which may be relevant to the pathophysiological changes associated with a SARS-CoV-2 infection [28].

The renin angiotensin system (RAS) plays an important albeit poorly researched role in neuro-immunological processes, as well as in psychiatric conditions like mood and anxiety disorders [29]. Since SARS-CoV-2 infection involves the carboxypeptidase, ACE-2, as entry receptor into the alveolar epithelial cells [30,31], a downregulation of ACE-2 expression may not only play a crucial role in the pathogenesis of SARS-CoV-2 [32] but can provide a link between SARS-CoV-2-induced vulnerability to stressful conditions. Indeed, downregulation of ACE-2 expression in mice has been shown to enhance sympathetic activity [33,34] and decrease tryptophan uptake [35] that can lead to reduced brain 5-hydroxytryptamine (5-HT; serotonin) levels [36], thereby increasing vulnerability to stressful conditions [37] (Fig. 2). Moreover, hypothalamic ACE-2 receptors supress anxiety-related behaviour and synthesis of corticotrophin-releasing hormone (CRH), a crucial hormone involved in the physiological stress response [33,38]. Critical in this context, is that ACE inhibitors, including captopril and lisinopril, may have a rapid mood-elevating effect in certain patients [39]. However, a recent animal study noted that this antidepressant effect is more associated with the bradykinin, than the renin-angiotensin system, and mediated by the mammalian target of rapamycin (mTOR) [39], making it comparable to the rapid antidepressant actions of ketamine. The mentioned decreased CRH synthesis and resultant decreased glucocorticoid production, due to SARS-CoV-2-induced ACE-2 downregulation, could also contribute to the dynamic immune response that seems to shape COVID-19 progression [40], especially by compromising the negative feedback mechanism of glucocorticoids to limit excessive inflammation (*review by* Silverman and Sternberg [41]) as shown in Fig. 2. Therefore, the expression of ACE-2 in various human tissues [42], including the brain, suggests that brain infection of SARS-CoV-2 may result in serious central nervous system (CNS) symptoms [43], predisposing these individuals to psychiatric disease development, in addition to the aggravating immune-inflammatory effects associated with a SARS-CoV-2 infection. To this extent, recent meta-analyses support the continuation of ACE modulating drugs in SARS-CoV-2 positive patients [44–46], with Song and colleagues suggesting neuronal infection to be prevented by blocking CNS located ACE-2 receptors with antibodies [47].

The psychosocial effects of COVID-19 are therefore laying the foundation for an unprecedented increase in the prevalence of especially anxiety and stress-related disorders, which in turn, can hasten the development of a number of other co-morbid psychiatric illnesses, such as mood disorders (depression and bipolar disorder), schizophrenia, substance abuse etc. Co-presenting shared pathological pathways of these psychiatric disorders and COVID-19 are therefore key to understanding the basis for these comorbidities and how to optimally treat them.

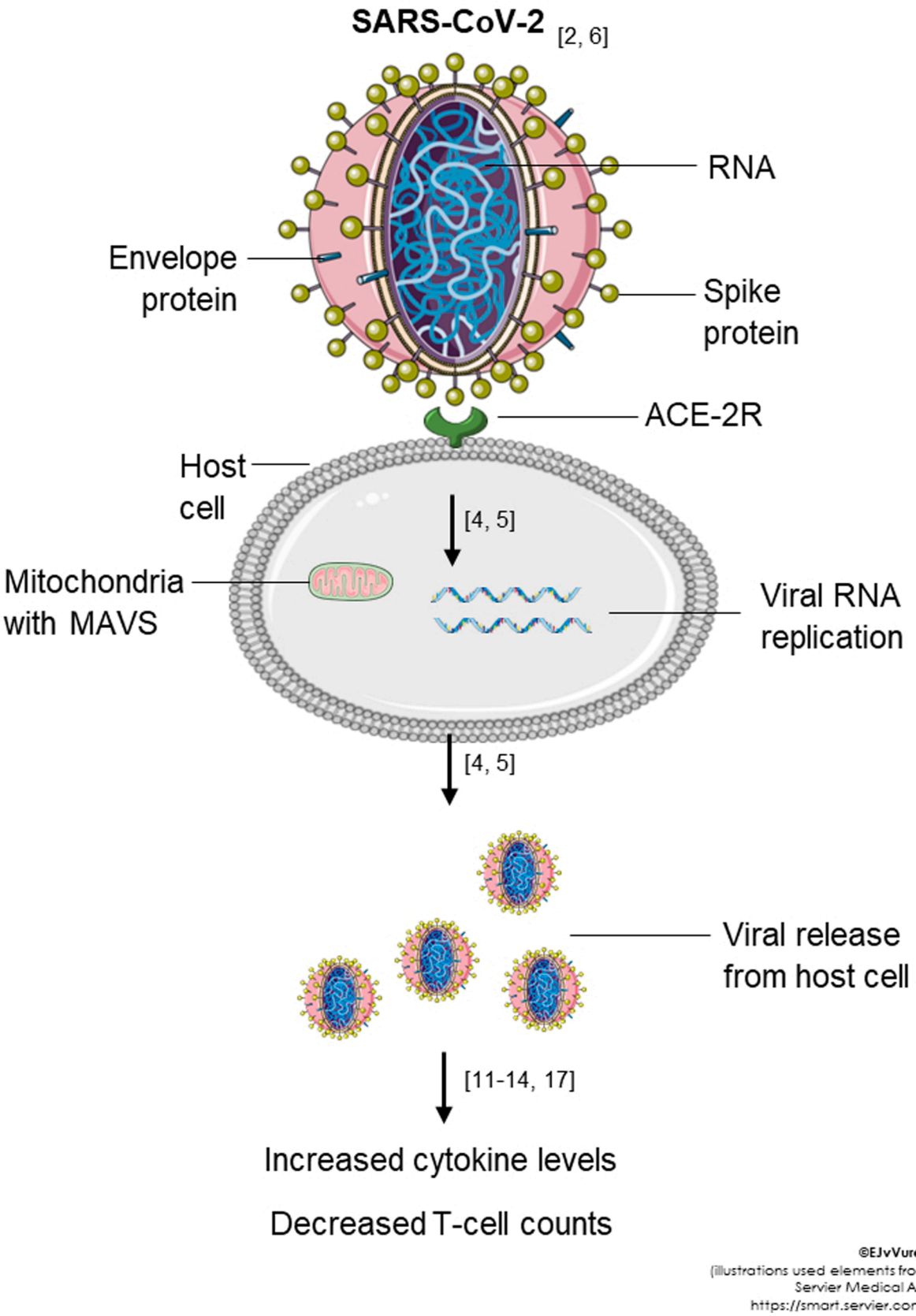

Fig. 1. The pathophysiology and inflammatory responses associated with SARS-CoV-2 infection.
The SARS-CoV-2 virus binds to the ACE-2R and enters the host cell, where after the virus utilises the host cell machinery to replicate, and where it modulates mitochondrial virus signalling. Multiple new viruses are released from the host cell and triggers the immune response and subsequent release of cytokines (*for detailed discussion please refer to the text*). *Abbreviations: ACE-2R; angiotensin converting enzyme-2-receptor; MAVS, mitochondrial antiviral signalling; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus.*

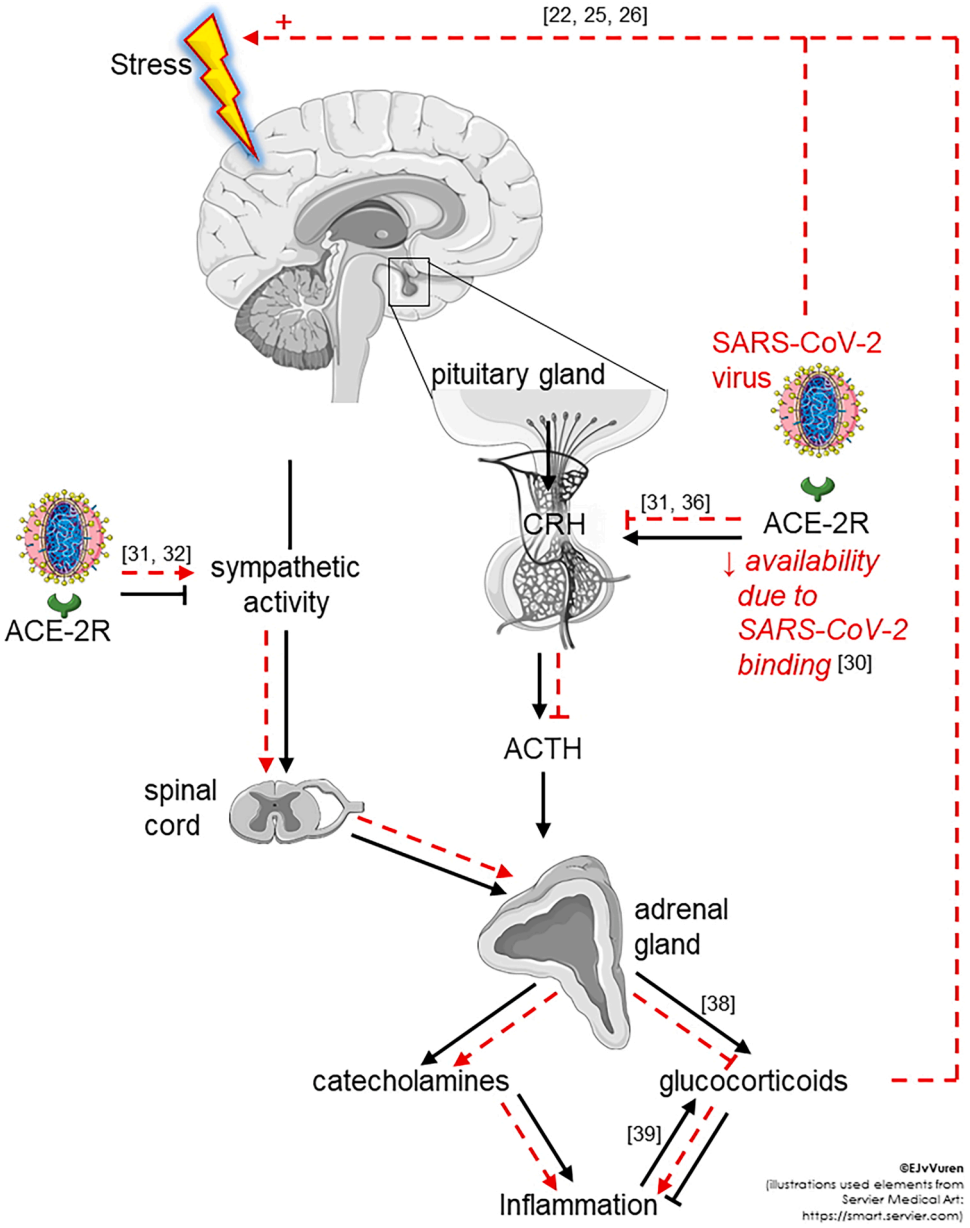

Fig. 2. The possible effects of SARS-CoV-2 infection (*indicated in red, dashed lines*) on the normal stress-inflammation cascade (*indicated in black, solid lines*).
SARS-CoV-2 binding to ACE-2Rs decreases ACE-2R availability, leading to a decrease in the downstream mechanism of CRH and decreased glucocorticoid production. Less glucocorticoids are available to limit excessive inflammation and prevent an overactive stress response, creating a perpetuating stress response. This reverberating loop is further provoked by environmental conditions and co-morbid psychiatric conditions (*for detailed discussion please refer to the text*). *Abbreviations: ACE-2R; angiotensin converting enzyme-2-receptor; ACTH, adrenocorticotropic hormone; CRH, corticotrophin releasing hormone; SARS-CoV-2, severe acute respiratory syndrome coronavirus.*

2. The association between stress, inflammation and treatment response in psychiatric illness

Inflammatory mechanisms are essential protective responses against infection or injury to maintain tissue homeostasis (*review by* Bennet and Molofsky [48]). It involves processes to mobilize defensive cells, such as macrophages that release inflammatory mediators such as cytokines, limiting the spread of pathogens and initiating tissue repair. Regarding inflammation within the CNS, a great deal of interest has focussed on the role of microglial cells, which together with astrocytes are involved in the mediation and modulation of the inflammatory processes [49]. Microglia function as the 'macrophages' of the CNS and can be activated in response to pro- or anti-inflammatory signals [50]. Upon activation, these resident innate immune cells release factors, such as pro-inflammatory cytokines, eicosanoids/prostanoids, nitric oxide (NO) and neurotrophic factors when activated by immunological stimuli, that exert a defence response and promotes tissue restoration [51]. However, when acute inflammation fails to cease after the original insult is cleared, it can lead to aggravated activation of microglia that further enhances pro-inflammatory cytokine production and oxidative stress [51], causing destruction of healthy tissue and eventual impaired brain function [52,53]. In addition, injury- or toxin-induced disruption of the blood-brain barrier can lead to the infiltration of inflammatory mediators and pathogens residing in the circulation, which can further exacerbate inflammation in the CNS (see [54] for review).

Downstream mechanisms of inflammation are multifactorial and involve various cellular signalling pathways (*review by* Bennett and Molofsky [48]) as shown in Fig. 3. Increases in peripheral and central pro-inflammatory cytokines, including TNF-α, IL-6 and IFN, lead to oxidative stress (via the production of reactive oxygen and nitrogen species (ROS; RNS)) [55,56], inducing apoptosis [57,58], and ultimately alterations in neurotransmitter signalling [59–61]. These mechanisms have all been shown to play a role in psychiatric disease development and progression [56,60,62]. Indeed, elevated pro-inflammatory cytokine levels are observed in individuals with psychotic [63–65], mood [66] and anxiety-related disorders [67,68] when compared with their respective healthy controls, while therapeutic use of pro-inflammatory cytokines, like IFN, are known to induce depressive symptoms [69].

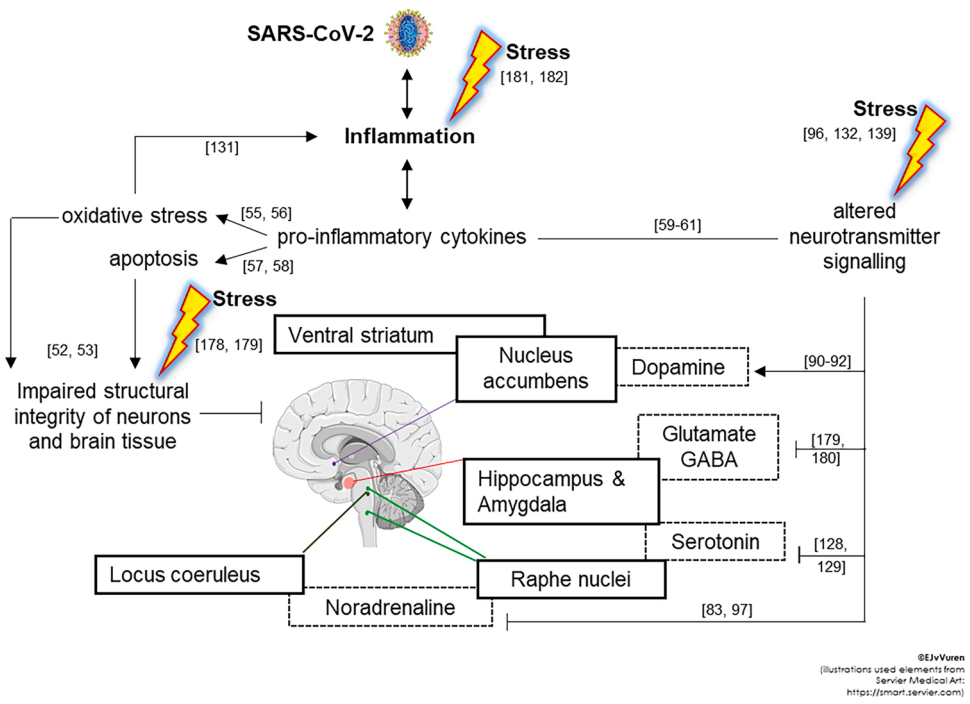

Fig. 3. Downstream effects of SARS-CoV-2 infection, stress and excessive inflammation that predisposes psychiatric disease development.
SARS-CoV-2 infection and stress contributes to excessive inflammation that can alter neurotransmitter signalling that in turn adversely affects the structural integrity of neurons via various mechanisms. These alterations can lead to abnormal dopamine, glutamate, GABA, serotonin and norepinephrine levels in various brain areas, including the ventral striatum, hippocampus, amygdala, raphe nuclei and locus coeruleus, that contributes to the development of psychotic, mood and anxiety-related disorders, or worsens pre-existing illness (*for detailed discussion please refer to the text*). *Abbreviations: GABA, gamma-amino-butyric acid.*

This is now discussed.

There is evidence to suggest that an inflammatory state in psychiatric patients plays a role in their treatment response [70]. For instance, depressive symptoms are frequent among patients diagnosed with inflammatory disorders (rheumatoid arthritis, asthma, Lupus and ulcerative colitis), while immunomodulatory drugs improve these symptoms. Moreover, ustekinumab (anti-IL-12/23 antibody) and sirukumab (anti-IL-6 antibodies) show antidepressant effects [71]. Conversely, elevated concentrations of soluble IL-2 receptor (sIL-2R) have been described in treatment resistant psychosis [72], whereas increased levels of IL-6 and IFN-γ are associated with poor treatment response in first episode psychosis patients [73]. Similarly, baseline gene expression of IL-1β, IL-6 and TNF-α increases in treatment-resistant depression [74–76]. These studies therefore highlight that add-on anti-inflammatory agents may be an important approach in the treatment of psychiatric disorders, especially in patients with an inflammatory state at baseline. Indeed, in a recent review Areaga-Henríquez et al. [77] indicated that the use of infliximab (an anti-TNFα agent), minocycline (tetracycline antibiotic) or eicosapentaenoic acid (omega-3 fatty acid) improve treatment response in depressed patients with increased baseline CRP/IL-6 levels. Similarly, Kohler et al. [78] reported that various agents with antiinflammatory actions, like celecoxib (a cyclo-oxygenase (COX)-2 inhibitor), lovastatin or simvastatin (hydroxy-methylglutaryl (HMG)-coenzyme (Co)A inhibitors), minocycline, pioglitazone (an insulin-sparing hypoglycemic agent), modafinil (a psychostimulant) and dexamethasone (corticosteroid) are similarly effective as add-on treatments to commonly used selective serotonin reuptake inhibitors (SSRIs) for depression. In fact, these augmentation strategies may be superior to SSRIs alone or placebo in reducing depressive symptoms [78]. However, in schizophrenia, these anti-inflammatory agents only have a small benefit for positive symptoms [79]. On the other hand, tocilizumab (an anti-IL-6 agent) improves cognitive symptoms, whereas minocycline and pregnenolone (an endogenous steroid) improve negative symptoms in these patients (*review by* Melbourne et al. [80]).

On the other hand, a recent study describes dose-dependent neural plasticity impairment in mice following both proinflammatory (lipopolysaccharide (LPS)) and anti-inflammatory (ibuprofen, a non-steroidal anti-inflammatory drug) states [81]. Since disordered neuroplasticity is central to a number of psychiatric illnesses [82], this highlights that a pro-inflammatory and an immunosuppressive state may influence a psychiatric illness and its response to treatment. Further on paradoxical actions associated with targeting the immune response, antioxidant compounds may act either as anti- or pro-oxidants depending on prevailing redox-inflammatory conditions in the cell. This is especially relevant when psychiatric illness severity or pathobiology changes over time. These studies clearly indicate that for psychiatric drugs to be effective, inflammation needs to be closely managed.

2.1. *Psychotic disorders*

Psychotic disorders such as schizophrenia are characterized by abnormally high mesolimbic dopamine (DA) signalling in the brain that mediates positive psychotic symptoms [83,84], while decreased mesocortical DA signalling is associated with cognitive and negative psychotic symptoms [83]. Such altered dopaminergic signalling could be mediated by inflammation due to the negative effects of cytokines on DA synthesis, packaging, release and reuptake [85] (Fig. 3). Indeed, maternal inflammation in humans is associated with later-in-life psychopathology including schizophrenia (*review by* Depino [86]). Clinical studies have shown that elevated maternal cytokine levels, such as C-reactive protein (CRP) and IL-8, increase the risk for schizophrenia spectrum disorders in the adult offspring [87,88]. Similarly, individuals that were exposed to elevated maternal levels of anti-inflammatory cytokines (i.e. IL-4, IL-5, and IL-13) were significantly less likely to develop psychosis in adulthood [89]. Indeed, TNF-α increases DA and 5-HT metabolites in the nucleus accumbens of schizophrenia patients [90]. Animal studies, in turn, have found that prenatal inflammation enhance DA levels in the nucleus accumbens and induce behavioural alterations characteristic of schizophrenia in adult rat offspring [91]. Similarly, TNF-α increases DA and 5-HT metabolites in the nucleus accumbens of mice [92]. Such on-going stressors, as well as infectious stressors, may lead to microglial activation, enhanced central inflammation and hippocampal damage [93,94] that could, at least in part, explain the dopaminergic overdrive observed in psychosis [95]. In fact, increased DA release is reported in the striatum of antipsychotic drug-naïve schizophrenia patients exposed to psychological stress [96]. Other

neurotransmitters implicated in the pathophysiology of psychosis and that are influenced by inflammation include 5-HT, norepinephrine (NE) and glutamate [83,97] as shown in Fig. 3. For example, tryptophan-kynurenine metabolism modulates 5-HT as well as glutamate signalling [98], while disordered tryptophan-kynurenine metabolism together with a pro-inflammatory state and changes in regional brain DA levels, have been described in an animal model of schizophrenia [99]. Trace amines, also relevant when discussing the stress-inflammation cascade in psychosis (*review by* Gainetdinov et al. [100]) modulate inflammatory cytokine production in macrophages via actions on trace amine associated receptor 1 (TAAR1). TAAR1 in turn modulates monoaminergic neurotransmission, preventing hyperdopaminergic and hypoglutamatergic activity [101], therefore implicating TAAR1 not only in immune-inflammatory disorders [102], but in the control of monoamine-driven psychotic behaviours [103].

Antipsychotics have distinct, albeit variable preclinical effects on immune-inflammatory cascades (as shown in Table 1), possibly due to different animal models being used. In a carrageenan-induced inflammatory rat model, haloperidol increases the inflammatory response [104] whereas trifluoperazine [105] and aripiprazole exhibit anti-inflammatory activities [106]. The activation of NF-kB, a crucial transcription factor in inflammation, depends on the phosphorylation of IκBα by IκB kinase (IKKβ), which has been shown to be blocked by thioridazine, thereby inducing anti-inflammatory effects [107]. Clozapine also exerts anti-inflammatory effects in an autoimmune encephalomyelitis mouse [108] model, and a social isolation reared (SIR) rat model [99]. Another study using the SIR model found that while olanzapine reversed the alterations in hepatic GSH-dependent defences, it induced no anti-inflammatory effect [109]. Olanzapine has also been associated with aortic inflammation in mice [110] and altered microbiota (associated with chronic inflammatory disease states as *review by* Hand et al. [111]) in rats [112], thus suggestive of pro-inflammatory actions. Other antipsychotics, such as risperidone [113] and quetiapine [114] are reported to possess anti-inflammatory activity.

Although preclinical evidence suggests a pro-inflammatory profile for haloperidol [104], clinical data do not concur [115]. Clinical studies that support the anti-inflammatory properties of antipsychotic drugs (Table 1) include olanzapine and quetiapine [116–118] and risperidone [116,119,120]. However, clozapine, which is reserved for treatment resistant schizophrenia, has been known to induce numerous serious pro-inflammatory side effects such as agranulocytosis and myocarditis in up to 50 % of patients within the first month of treatment [121]. More evidence of clozapine's pro-inflammatory effects relates to an increase in TNF-α and soluble TNF-α receptors observed in schizophrenia patients following 6 weeks of treatment [122]. However, one study observed immunosuppressive actions of clozapine after 6 months of treatment in first episode paranoid schizophrenia patients [119].

Reviewing the above-mentioned evidence, it becomes evident that antipsychotic drugs affect inflammatory mechanisms, and more specifically cytokine levels, although studies have yielded different results [80,123]. In fact, many studies have highlighted paradoxical anti- and pro-inflammatory actions. This makes it difficult to predict how each drug will perform under different pathological conditions and where neuro-progression is involved.

Table 1
The anti-and pro-inflammatory actions of psychotropic drugs.

Drug class	Anti-inflammatory	Pro-inflammatory
Antidepressants		
SNRIs		
Duloxetine	↓ IL-6, TNF-α [358,359]	–
Venlafaxine	↓ IL-1β, IL-6, IL-18, TNF-α; ↑ IL-10 [360,361,362,363]	–
SSRIs		
Citalopram	↓ CRP, IL-6, IL-7, IL-8, IFN-γ, TNF-α, TLR's [159,351,364]	–
Escitalopram	↓ TNF-α [350]	–
Fluoxetine	↓ TLR's [351]	–
Fluvoxamine	↓ COX2; iNOS, ICAM1, VCAM1 [146,364]	–
Paroxetine	–	↑ IL-6, IFN-γ, TNF-α [364]
Sertraline	↓ CRP, IL-1β mRNA, IL-6, IL-7, IL-8, IFN-γ, TNF-α [145,158,364]	–
Tricyclic and tetracyclic		
Amitriptyline	↑ IL-10; ↓ IL-1β, IL-18, ICAM-1, MIP-2, MCP-1, TNF-α [365,366,367]	–
Desipramine	↑ IL-10 [365,367]	–
Imipramine	↓ IL-1β, IL-18 [368]	↑ IL-1 [364]
Mirtazapine	↓ IL-6, IL-7, IL-8, IFN-γ, TNF-α [159]	–
Other		
Agomelatine	↓ IL-1β, IL-18, oxidative stress damage; ↑ glutathione [267,268,269,369,370]	–
Ketamine	↓ IL-1β, IL-6, TNF-α [371,372]	↑ IL-6, IL-1β, TNF-α [153]
Antipsychotics		
Atypical		
Aripiprazole	↑ IL-10; ↓ CRP, IL-1β, IL-4, IL-6, IL-7, IL-8, IL-12, IL-13,	–
Clozapine	IL-17a, IL-21, IL-23, IFN-γ, TNF-α, sTNF-R1 [106,116,118]	
Olanzapine	↓ CRP, IL-2 [117,373]	↑ TNF-α, sTNF-R's [121,122,375]
Quetiapine	↑ IL-10; ↓ CRP, IL-1β, IL-6, IFN-γ, TNFα [114,117]	↑ IL-1β, IL-6, IL-8; TNF-α [110,112,375,376,377]
Risperidone	↓ IL-1β, IL-2, IL-6, IL-7, IL-8, IL-13, IL-17α, IL-21, IL-23,	–
Ziprasidone	TNF-α [116,119,374]	
	↓ IL-2, IL-6, IFN-γ, TNF-α [374]	–
Mood stabilizers		
Carbamazepine	↓ IL-1β, TNF-α [164,165]	↑ TNF-α [378]
Lamotrigine	↓ IL-2, IL-6, TNF-α [166]	–
Lithium	–	↑ IL-4, TNF-α [167]

2.2. Mood disorders

Decreased monoaminergic neurotransmission has been established as a main cause of depressive symptoms, such as decreased mood and energy, inability to feel pleasure (anhedonia), loss of interest and motivation, and decreased alertness [83,124]. Here the tryptophan-kynurenine pathway is especially relevant. Multiple inflammatory signalling pathways seem to activate indoleamine 2,3 dioxygenase (IDO) that causes breakdown of the 5-HT precursor, tryptophan (*review by* Miller et al. [125]). Inflammation-induced reduction of 5-HT causes a depressive-like state in rodents [126], with similar findings reported in drug naïve major depressive disorder (MDD) patients [127]. Inflammation also increases expression of the 5-HT transporter (SERT), thereby increasing 5-HT reuptake, and reducing its synaptic availability [128]. This action downregulates hippocampal 5-HT receptor expression that eventually contributes to depressive symptoms [129] (Fig. 3). It is noteworthy that chronic unpredictable stress increases oxidative stress in the prefrontal cortex and striatum of rats [130], that can exacerbate central inflammation (*review by* Bakunina et al. [131]), thereby perpetuating the stress response and contributing to altered monoaminergic neurotransmission levels and the progression of MDD [132]. Altered antioxidant enzyme activity (such as superoxide dismutase) together with increased levels of lipid peroxidation [133] leads to cytokine-induced oxidative stress that is associated with MDD [132]. A resultant reduction in neurotrophin levels [134] and compromised function and adaptive plasticity of these areas [135] suggests the brain to be less likely to overcome and learn from adverse environmental conditions. NO-cyclic guanosine monophosphate (cGMP) signalling is also disturbed in patients with MDD [136], while NO signalling has been suggested to modulate inflammatory pathways that underlie the pathophysiology of MDD [137,138]. Indeed, chronic stress enhances hippocampal constitutive NOS activity in stress sensitive

rats, thereby implicating dysfunctional glutamatergic NMDA-NO activity as a vulnerability factor in MDD [139]. Importantly, both nNOS- and iNOS-derived NO levels were altered in the limbic brain regions of stressed animals [140]. These alterations may contribute to the development of behavioural and endocrine abnormalities that compromise adaptation to stress and increase vulnerability to MDD. COX-2, a rate-limiting enzyme for prostaglandin E2 (PGE2) synthesis, is also significantly elevated in chronically stressed rats, while its inhibition reverses depression-like behaviours via suppressing glial activation, oxidative stress and neuronal apoptosis [141]. These altered and sensitive redox states in turn drive many of the behavioural manifestations associated with MDD [142,143].

Approved antidepressants that primarily target the altered monoaminergic levels in MDD, also display anti-inflammatory properties [144] that contribute towards clinical improvement as shown in Table 1. In a rat model of tonic-clonic seizures, sertraline exerted anti-inflammatory properties [145]. Similarly, fluvoxamine decreased the expression of inflammatory genes in a carrageenan injection model of inflammation in rats [146]. Modulators of NO and cGMP signalling exert antidepressant effects in patients with MDD or in animal studies [147]. In fact, NO and cGMP signalling is targeted by a variety of known antidepressants in animal models of depression [148]. Not surprising too, COX-2 inhibitors may have value in bipolar disorder and as adjunctive treatments in treatment resistant depression [149,150]. Ketamine, an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, has rapid-onset antidepressant properties [151], while presenting with anti-inflammatory effects [152]. Interestingly, ketamine's activity on inflammation seems to be related to duration of treatment [153]. In this respect, *long-term* treatment is effective in bolstering a failed response to imipramine in a gene X environment model of antidepressant resistance [154]. An inflammatory component is known to contribute to clinical cases of treatment resistance [155], which may partially explain how ketamine may re-establish response [156].

In patients diagnosed with MDD, Szałach, Lisowska and Cubała [157] found that paroxetine, venlafaxine, desvenlafaxine, imipramine, amitriptyline and agomelatine significantly decrease the expression of inflammatory genes and also reduce inflammasome activity. Blood cytokine levels were found to be significantly reduced after 12-weeks of antidepressant therapy (treated with sertraline, venlafaxine, citalopram, or mirtazapine) in patients newly diagnosed with MDD [158]. Importantly, the drop in these cytokines was seen only in patients who demonstrated a clinical response to treatment. Considering NO, elevated plasma nitrate levels have been described in depressive states as well as being involved in depression symptoms during interferon-alpha therapy [69,159]. In a study with patients suffering from ischemic heart disease and depression, serum nitrite and nitrate levels were significantly decreased following paroxetine treatment but not nortriptyline, with paroxetine shown to be a more potent inhibitor of NOS than nortriptyline [160].

What is apparent from data described above is that antidepressants have variable pro- and anti-inflammatory effects, which may be a function of chemical class as well as illness progression.

2.3. Bipolar disorder

Bipolar disorder is a chronic and cyclic mental disorder, characterized by unusual mood swings between mania/hypomania and depression [161]. Due to the disease's course, often unremitting, it frequently results in cognitive deficits over time, Furthermore, the partial effectiveness of current available drugs often necessitates polypharmacy. The immune system and neuro-inflammation plays a central role in its pathophysiology, especially in disease course, while also providing targets for novel anti-inflammatory and antioxidant treatments, e.g. non-steroidal anti-inflammatory drugs, N-acetylcysteine and GSK3 inhibitors [162]. Manic-like symptoms and inflammation have been described in the ouabain model of mania, a rodent model relevant to bipolar disorder [163]. Here aspirin, a commonly used anti-inflammatory agent, partially reversed manic-like symptoms as well as decreased expression of brain-derived neurotrophic factor, IFN-Ɣ and Toll-like receptor 3, frequently found in bipolar disorder patients. Carbamazepine induces anti-inflammatory effects in a dose dependent manner in LPS-challenged rats [164], an effect not observed with valproate [165]. Lamotrigine also exhibits anti-inflammatory properties in mice after LPS exposure [166]. In a recently published study [167], it was demonstrated that T lymphocytes of patients suffering from bipolar disorder treated with lithium or valproate, are characterized by pro-inflammatory activity, including decreased proliferative activity and increased susceptibility to apoptosis. On the other hand, valproate treatment for 12 weeks had no effect on pro-inflammatory cytokines in patients diagnosed with bipolar depression [168].

2.4. Anxiety-related disorders

Anxiety or fear, as well as worry, are present in all anxiety-related disorders [169,170]. Anxiety symptoms are mainly associated with dysfunctional amygdala-centred circuits whereas worry symptoms are connected with cortico-striato-thalamocortical (CSTC) loop dysfunction, both involving disturbances of 5-HT and gamma-aminobutyric acid (GABA) [83]. Other messengers associated with anxiety include 5-HT, melatonin [171], the NO-cGMP pathway [172,173], glutamate [174] and the neuropeptides oxytocin and vasopressin [175]. Interestingly, all these pathways are inter-related with redox processes, e.g. melatonin has antioxidant properties [176], the glutamate-NOS pathway stimulates oxidative stress [173], while vasopressin and oxytocin have protective effects under conditions of oxidative stress *in vitro* [177]. Chronic stress alters the structural integrity of GABAergic neurons [178] that disinhibits the amygdala [179], most likely accounting for increased worry symptoms (Fig. 3). Chronic peripheral inflammation further increases TNF-α expression, enhances glutamatergic excitatory synaptic transmission and, by inhibiting GABA-receptor-mediated inhibitory synaptic transmission in the amygdala, contributes to the development of anxiety [180]. Inflammation-induced oxidative stress increases during stress exposure, which has been found to exacerbate anxiety states such PTSD [181,182]. Additionally, decreased endocannabinoid levels might contribute to the increased inflammatory state observed in these individuals [183], as enhanced endocannabinoid hippocampal signalling prevents PTSD-like behaviour in rodents [184]. NO has also been associated with anxiety-related central inflammation. Acute severe stress initially increases NO via activation of neuronal NOS which reverts to constitutive immunological NOS (iNOS)-mediated NO production following chronic stress [185]. These actions are accompanied by a reactive downregulation of hippocampal NMDA receptors and a decrease in inhibitory GABA, supporting a role for inflammatory NO in neuronal toxicity and hippocampal degeneration in severe anxiety disorders such as PTSD [185]. Nuclear factor-κB (NF-κB) is a crucial transcription factor in inflammation and has been shown to be mutually involved with the NMDA-NO-cyclic GMP cascade in an animal model of PTSD [186].

Arguably the most prominent example illustrating the link between inflammation and anxiety is gut dysbiosis. Here differences in bacterial taxa, characterised by a higher abundance of pro-inflammatory species (e.g., Enterobacteriaceae and Desulfovibrio), provoke anxiety and depression pathophysiology via communication of peripheral inflammation to the brain [187]. Accumulating evidence suggests that elevated inflammation contributes to the pathophysiology of anxiety disorders, such as post-traumatic stress disorder (PTSD) [173], and that anti-inflammatory drugs might be a new treatment strategy for PTSD [188]. Various clinically used anxiolytics have other actions and target redox-inflammatory processes indirectly, such as agomelatine [189] and the SSRIs [190]. These drugs are approved for the management of chronic anxiety-related disorders [190]. However, given the central role that GABA plays in anxiety-related disorders [191], it is interesting that

various peripheral benzodiazepine receptor ligands exert anti-inflammatory actions [192]. The anxiolytic, etifoxine [193,194], induces anxiolytic and anti-inflammatory effects via actions on the $GABA_A$ receptor and mitochondrial 18-kDa translocator protein (TSPO), [195], the latter responsible for its anti-inflammatory properties (*review by* [196].

Taken together, psychological stress may increase the risk of psychiatric disease and even shape the course of disease via inflammatory pathways [197] as shown in Fig. 3. This interaction is particularly relevant when considering pharmacological treatment of psychiatric disorders in the presence of infectious diseases that could exacerbate central inflammation. Infection with SARS-CoV-2 is a case in point.

3. The interaction between SARS-CoV-2-induced inflammation and the course of psychiatric illness

The psychosocial effects of SARS-CoV-2 are prompting an unprecedented increase in the prevalence of especially anxiety disorders, which in turn can hasten the development of several other co-morbid psychiatric illnesses, like mood disorders (depression and bipolar disorder), schizophrenia, substance abuse etc. To this extent, viral infections, such as influenza, varicella-zoster, herpes simplex, human immunodeficiency and hepatitis C virus infections are associated with increased risk for depression and/or anxiety [198–200]. Moreover, maternal influenza infection is a risk factor for schizophrenia, as well as bipolar disorder with psychotic features [201]. Importantly, although a recent longitudinal study did not associate common viral infections with increased risk for mental disorders [202], the prevalence of depression symptoms in the United States increased three-fold from pre-COVID to post-COVID [203], with similar observations in other countries [204–207]. Although the exact mechanism for this increase remains unknown, these patients will generally receive standard pharmacological treatments for these mental disorders, *viz*. antidepressants, antipsychotics etc. As noted earlier, a secondary effect of these aforementioned medicines will be to suppress an over-active inflammatory response and while this may be good in terms of the psychiatric illnesses being treated, this action will also lower the natural ability of these patients to ward off viral infections like SARS-CoV-2, both new and re-infection. While these drugs are not immuno-suppressants *per se*, they may exert subtle, yet significant effects in susceptible individuals. This is especially relevant in the context of COVID-19, where the SARS-CoV-2 virus is highly contagious and particularly pathogenic in individuals with a compromised immune system. With the current global SARS-CoV-2 pandemic in mind, together with the significant link between COVID-19 and mental illnesses [208,209] we will briefly review the three-way interaction between the SARS-CoV-2-induced inflammatory response, the course of viral and psychiatric conditions, and how this interaction may modulate response to psychotropic drug treatment.

A number of viruses are capable of invading and affecting the CNS [210], still the main reason for this is not yet fully understood. One working hypothesis postulates that the brain lacks immune-competent cells, making it an ideal site for viruses to reside in, forming a so called viral reservoir [210]. Alternatively, viral infections not known to infect neurons, such as the human immunodeficiency virus (HIV), can still induce CNS effects, such as HIV dementia (HIV D), also known as HIV-associated neurocognitive disorder (HAND). Although this mechanism is not yet fully understood, certain HIV proteins (gp120 and Tat) are presumed to be transported into the CNS where they trigger cellular apoptotic mechanisms that cause neuronal dysfunction and/or death (*see* [211–214] *for review*).

In general, psychiatric patients may already be at higher risk of contracting viral infections because of a myriad of contributing factors, such as a chronically dysregulated innate immune system, altered/impaired cognitive and higher motor functioning, and sometimes deficient personal hygiene [215–218]. Regardless, immune system dysregulation is central to the severity of pathogenic coronavirus infections [219–221]. Since an effective immune response depends on the activation of cytotoxic T cells to kill the virus-infected cells [20,221], SARS-CoV-2 (and other viral infected) patients would benefit from boosting the numbers and function of T cells. In support, SARS-CoV-2-positive patients present with decreased number of total T cells, CD4 and CD8 T cells, with this decline being strongly associated with infection severity and age, suggesting significant T cell loss in SARS-CoV-2 patients [17].

Still, COVID-19 is associated with an exaggerated immune response, or a SARS-CoV-2-induced cytokine storm. In these patients, this cytokine storm is negatively associated with T cell count, suggesting that high serum cytokine concentrations (that develop over the duration of the infection) negatively regulate T cell survival and proliferation over the course of the SARS-CoV-2 infection [17]. In fact, T cell exhaustion is a suggested result of SARS-CoV-2-induced cytokine storm, with markers indicative of cell exhaustion found to be higher in severely infected patients [17]. This would ultimately increase their risk for other severe secondary infections, even though they may show a general improvement at first. Interestingly, recent research highlighted the presence of neutralizing immunoglobulin G (IgG) autoantibodies in as much as 10 % of COVID patients (more men than women) who developed life-threatening pneumonia [222]. These autoantibodies disable or neutralize type I IFNs, thereby inhibiting or reducing the inflammatory response to prevent pathogen-induced inflammation. Further, at least 3.5 % of patients with life-threatening pneumonia had genetic IFN defects [223], that when interpreted together with the aforementioned results, highlight the key role that central inflammation plays in COVID-19 symptomology. A similar phenomenon is reported in HIV-positive patients and is partly responsible for the high prevalence rates of depression amongst these patients [224,225]. Downstream effects of such a cytokine storm may include increased neuro-inflammation, reduced neuroplasticity and monoaminergic neurotransmission and increased neuronal death [224], as referred to earlier.

Several psychiatric diseases have been linked to viral infections, although no particular virus has to date been unequivocally established as a causative agent [198,226–228]. Extra-pulmonary symptoms, including febrile seizures, loss of consciousness, convulsion, ataxia, status epilepticus, encephalitis, myelitis, neuritis and multiple sclerosis have been observed in patients infected with influenza, thereby highlighting the virus' capacity to cause neurological complications [229]. Indeed, obsessive compulsive disorder (OCD) is also causally linked to early life infection with influenza or other pathogens [230]. Regarding viral infections of the CNS, recent work revealed that human endogenous retrovirus W env (HERV-W env), which appears to play a role in the neurodevelopment of schizophrenia [231], may contribute to neuropathology and disease progression by regulating the expression of immunological NO synthase (NOS), thereby increasing NO production and microglial migration [232]. Overall, these neurobiological alterations are associated with increased oxidative stress that in turn drive many of the monoamine changes typical of positive and negative schizophrenia-related symptoms [233,234].

ARDS is a severe condition with high morbidity and mortality and few interventions, and the fatal pulmonary manifestations of SARS-CoV-2 are no different. Given the focus of this review, the role of sympathetic stress in the pathogenesis of ARDS is of interest from both the pulmonary and neuropsychopathological point of view. Blockade of the α_2- or α_{2A}-adrenoceptor (α_{2A}-AR) attenuates inflammation-induced lung injury in rats. Cong et al. recently noted that blockade of α_{2A}-AR inhibits TNF-α, IL-6, and IL-10 production in activated alveolar macrophages [235]. Furthermore, they demonstrate that NE down-regulates NF-κB activation, suggesting that α_{2A}-AR deficiency ameliorates lung injury by increasing NE concentrations in lung tissues and inhibiting the activation of alveolar macrophages. Given the role of the α_{2A}-AR in mood regulation and antidepressant action [236], α_2 modulating drugs such as mirtazapine may present with a bi-modal action in treating both ARDS

and psychopathology in SARS-CoV-2 infected patients. Having earlier noted the role of the NO-cGMP pathway in psychiatry and inflammation, it is noteworthy that the phosphodiesterase-5 (PDE-5) inhibitor sildenafil, which bolsters tissue brain and peripheral levels of cGMP, has been proposed as a suitable intervention in ARDS [237]. Furthermore, pre-clinical work have established its antidepressant actions [238], thus affording it as a useful adjunctive treatment option in SARS-CoV-2 associated psychopathology.

Effective antiviral drugs should not only prevent host cell infection but also inhibit or at least reduce the exaggerated viral-induced immune response. Specifically related to SARS-CoV-2, several drugs are being investigated, with remdesivir and chloroquine (and hydroxychloroquine) receiving the most attention [239]. Remdesivir selectively inhibits viral replication, whereas chloroquine seems to block viral entry and to attenuate cytokine production [239]. Because of the significant adverse effects associated with chloroquine, including neuropsychiatric [240], and a lack of evidence of its effectiveness, it has not yet been approved for the treatment of SARS-CoV-2. Interestingly, the World Health Organization recently advised against the use of remdesivir for hospitalized COVID-19 patients, due to a lack of meaningful benefits [241–243], whereas the Infectious Diseases Society of America supports its use [244,245]. These contrasting statements have attracted reactions from various scientists and restarted the search for an effective treatment strategy [246]. Nonetheless, other antivirals generally only target viral replication with no primary or direct effect on the accompanying inflammation and should therefore not have significant effects on psychiatric symptom development. In this regard, sofosbuvir-based anti--hepatitis C regimens have been associated with improved mood via its kynurenine enhancing effects [247], whereas NE-affecting antidepressants have been reported to reduce the antiviral properties of the anti-hepatitis C drug, IFN-α [248], suggesting a minor, yet sensitive interplay between antivirals and CNS-acting drugs.

We have earlier highlighted how psychotropic drugs can modify the immune response. Antipsychotics may increase an individual's risk for viral and/or bacterial infections [249]. In this regard, a higher risk for pneumonia has been observed with antipsychotic-use [250], an affect that could involve a psychotropic-caused anti-inflammatory effect. This response may also be compounded by the immune activating properties of co-administered immunomodulators (and other antivirals) [248]. Despite these concerns, the anti-SARS-CoV-2 effects of chlorpromazine (and other psychotropics) have been suggested [251]. These possible protective effects are based on the structural similarities between certain psychotropics, especially tricyclic antidepressants, phenothiazine antipsychotics and methylene blue, and investigational anti- SARS-CoV-2 drugs, such as chloroquine. These compounds are all cationic amphiphilic drugs with hydrophobic aromatic ring or ring systems, with a hydrophilic side chain containing an ionizable amine functional group, that could potentially alter host cell properties, reducing viral penetration and replication [252]. Of note, a recent clinical study associated fluvoxamine, an SSRI antidepressant, with a lower likelihood of clinical deterioration in symptomatic COVID-19 patients, over a 15-day treatment period, relative to placebo controls [253]. Future studies should investigate this promising avenue of research.

Conversely, antivirals (e.g. efavirenz, maraviroc, oseltamivir etc.) are known to cause CNS-associated adverse effects, such as mood and sleep disorders and hallucinations [254]. Within the SARS-CoV-2 context, chloroquine is also known to cause similar CNS-related adverse effects [240]. Although the exact mechanisms involved in these CNS adverse effects are unknown, it may include altered neuroplasticity [255], via direct (programmed necrosis, cell lysis and/or by inducing apoptosis and necroptosis [256–258]) or indirect mechanisms [258], such as the activation of toll-like receptor signalling receptors (TLRs) 3, 7, and 8. The latter leads to increased free radical production and inflammation and ultimately neuronal damage. A recent review has also addressed the neuropsychiatric side effects of anti-HIV drugs like efavirenz, which is purported to involve disturbances in the mitochondrial-immune-inflammatory-redox cascade [259]. In fact, mitochondrial dysfunction is considered a fundamental mechanism in the pathogenesis of many drug-induced toxicities [260,261], as well as in the pathogenesis of mood disorders [262,263], by causing increased oxidative stress and neuro-inflammation, decreased neuroplasticity and disordered monoaminergic transmission.

Pharmacokinetic interactions between anti-SARS-CoV-2 and psychotropic drugs also exist, including azithromycin-induced cytochrome inhibition [264], that could increase the risk for mentioned psychotropic-associated side effects. Finally, immune reconstitution inflammatory syndrome (IRIS), associated with initiating antiretroviral treatment (ART), is a paradoxical phenomenon that worsens or even unmasks subclinical, untreated infections, via an exaggerated inflammatory response once the immune system starts to recover [265]. Therefore, despite the mentioned CNS adverse effects of antivirals, this paradoxical reaction may itself contribute to worsening of psychiatric conditions via supplemented neuro-inflammation.

Taken together, a sensitive interplay between the viral-induced inflammation and underlying neuro-inflammation exist that may have aggravating effects in sensitive individuals. Further, a possible antagonistic net-effect of antiviral and anti-psychiatric combinations may also exist, despite certain antiviral mechanisms being beneficial in terms of neuro-inflammation and psychiatric symptomology. Therefore, adjunctive treatment strategies may be of therapeutic value to optimize clinical outcome.

4. Adjunctive psychotropic treatments during SARS-CoV-2 infection

In order to bolster both the containment of SARS-CoV-2 infection, as well as treat any presenting psychopathology that will not introduce any additional risk of worsening the outcome of either illness, the knowledge outlined in the previous sections may be called upon to devise and test novel adjunctive treatment options. Although numerous drugs are under investigation as COVID-19 treatment options (*review by* Manhas et al. [266]), adjunctive treatment options could prove useful. Despite requiring further investigation, clinically available options are briefly discussed below (see Table 2).

Agomelatine (a melatonin (MT) 1 and 2 agonist with 5-HT_{2C} antagonistic properties) reduces plasma and brain IL-1β and IL-6 levels and prevents microgliosis and astrogliosis in rat models [267,268]. Clinically, 12-week agomelatine treatment is associated with reduced CRP levels [269]. Therefore, agomelatine could prove beneficial in the treatment of COVID-19, due to its antioxidant, anti-inflammatory and antiapoptotic properties [270]. In fact, high doses MT may have a beneficial role in patients treated for SARS-CoV-2-induced pneumonia, in terms of reduced time to clinical improvement and even possible lower mortality rates [271]. Given its inherent anxiolytic and antidepressant properties [272–274], agomelatine could be a useful medicine to consider in COVID-19 related mood and anxiety disorders.

Antioxidants, which for all intents and purposes would include anti-inflammatory agents, seem to have state-dependent effects depending on the redox condition of the cell. This implies that such compounds may act differently depending on the progressive state of the illness in question [275,276], e.g. a waxing and waning of symptoms, or where the illness gets progressively worse over time. α-Lipoic acid is an antioxidant that may lower all-cause mortality in SARS-CoV-2 infected patients [277]. Indeed, lipoic acid was shown to protect against RNA virus-induced gliotoxicity [278] and inhibit viral replication of HIV [279]. Further, a recent review by Diniz et al. [280], highlights the possible adjunctive properties of natural antioxidants, especially flavonoids, for conventional antiviral therapies. In this report, the authors identify specific corona virus proteins that are targeted by these natural antioxidants to contribute towards the observed antiviral properties. This is in addition to their ROS reducing properties that inhibit viral signalling and ultimately replication abilities. Various plant species may

Table 2
Suggested clinically relevant options as adjunctive treatments during COVID-19 infection and associated psychopathology.

Drug class	Psychiatric effects	Inflammatory-related effects	Antiviral-related effects
Antioxidants			
α-lipoic acid	–	↓ ROS, apoptosis [278,279,280]	↓ gliotoxicity, viral replication and signalling [278,279]
Mangosteen pericarp	antidepressant [286]	–	↓viral proteases [288]
Sceletium tortuosum	↓ anxiety, depression [379]	anti-inflammatory [284]	↓ viral enzymes and proteases [285]
Thymoquinone	↑ spatial memory and slowdown of Alzheimer's disease complications [289,380]	↓ NO and ROS; modulating (inhibit) NF-κB and antioxidant enzyme nuclear factor 2 heme oxygenase-1 (Nrf2/HO-1) [289,290,381]	↓ viral entry into host cell [291]
Alpha-2-AR modulators			
Clonidine	↓ psychosis, anxiety [298,299]	–	↓ viral replication [297]
COX-II inhibitors			
Celecoxib	↑ mood [78]	↓ IL-6, TNF-α [302]	↓ viral transactivation of COX-2 [300,301]
Glucocorticoids			
Dexamethasone	↑ depression [78,305,306]	↑ oxidative stress, inflammation [307,308,309]	–
Lithium	antidepressant [310]	↓ NF-κB [311] ↑ pro-inflammatory activity [167] ↑ NO-cGMP pathway activity [316]	–
MT-1 and -2 agonists			
Agomelatine	anxiolytic, antidepressant [267,268]	↓ CRP, IL-1β, IL-6 [264,265,268]	
Tetracyclines			
Minocycline	↑ mood [77,78]	↓ inflammation [318]	↓ viral replication and reactivation [321]
Mitochondrial rejuvenators and modulators			
Methylene Blue	↑ mood [147]	antioxidant [325]	Inactivates RNA viruses [326] ↑ MAVS [331]
N-acetyl cysteine	↑ mood [382]	antioxidant [383]	↑ MAVS [331]
mTOR inhibitors			
Rapamycin	antidepressant [346,347]	↓ oxidative stress, hyper-inflammation [345]	↑ antiviral activity [343,344]
NF-κB inhibitors or antagonists			
Ouabain	↑ mood disorders [336]	↓ NF-κB [334]	↓ viral replication [335]
Digoxin	–	↓ NF-κB [334]	↓ viral replication [335]
PDE-4 inhibitors			
Rolipram	–	↓ cytokine storm [337]	–
Ibudilast	–	↓ cytokine storm [337]	–
PDE-5 inhibitors			
Sildenafil	anxiolytic, ↑ mood [172,238,340]	↓ pro-inflammatory cytokines [338]	–
Tadalafil	–	–	↓ cGMP [237]
PPAR-γ agonists			
Pioglitazone	↑ mood [78]	↓ cytokine storm [342]	–
Tryptophan-kynurenine modulators			
Allopurinol	↓ inflammation-induced psychopathology [98]	↓ inflammation [98]	–

hold potential as they have already been shown to alter CNS neurotransmission [281] and to display anti-COVID properties (*for detailed reviews, see* Ahmad et al. [282] and Khanna et al. [283]). For example, *Sceletium tortuosum* may be of interest as it has mild anti-inflammatory properties, without hindering an adequate immune response to acute immune challenges [284], and also exerts antiretroviral effects by inhibiting HIV enzymes and proteases [285]. *Mangosteen pericarp* extract has been demonstrated to have antidepressant and procognitive properties in rodent models [286], as well as bolster the antipsychotic effects of haloperidol [286,287]. Interestingly, gamma mangostin, a constituent of this extract, inhibits C19MP (a main protease of SARS-CoV-2), with improved binding affinity versus other known inhibitors, such as lopinavir and ritonavir [288]. Similarly, thymoquinone, a constituent of *Nigella sativa* [289] is best known for its potent antioxidant properties that contribute to the downregulation of pro-inflammatory cytokines, making it a possible candidate to avert MODS (*review by* Ahmad et al. [290]). In terms of SARS-CoV-2, thymoquinone can prevent viral binding to the ACE2 receptors via modulating the heat shock protein cell surface [291]. In critical patients with ARDS, enteral diets with ω-3 PUFAs improved oxygenation and reduced the duration of mechanical ventilation and intensive care stay [292]. However, caution must be taken as fish oil feeding in mice has shown to alter the immune response to influenza [293] and delay viral clearance [294]. Another notable antioxidant is melatonin which has been suggested to benefit patients with myocardial injury and respiratory complications in COVID-19 patients [295]. When considered with its earlier mentioned (*see Agomelatine*) role as anti-COVID-19 adjunctive therapy [271], melatonin is a strong candidate that requires further investigation. Similarly, oxytocin-vasopressin exert actions on redox systems [177] while their delicate balance is implicated in anxiety disorders [175]. In this regard, oxytocin has been noted to have potential as an adjuvant treatment in COVID-19 infection [296].

Clonidine, an α_2 AR antagonist, has been identified as a novel *in vitro* anti-influenza agent that could protect against influenza-induced pulmonary damage by inhibiting viral replication [297]. Clonidine might also be beneficial in the treatment of SARS-CoV-2-related psychiatric symptom development as it may treat psychosis and anxiety as shown in a patient with schizophrenia [298] as well as attention deficit hyperactivity disorder [299].

COX-2 inhibitors: That the nucleocapsid protein of SARS-CoV activates COX-2 expression [300], led to Tomera et al. [301] to suggest that conservation of SARS-CoV-2 nucleocapsid N protein N2 sequences with celecoxib, a COX-2 inhibitor, treatment may mitigate the effects of direct viral transactivation of COX-2 expression in infected cells. Moreover, it has been shown that celecoxib significantly reduced TNF-α and IL-6 cytokine levels in mice infected with influenza-A when compared to controls [302], further emphasizing the anti-inflammatory role of COX-2 inhibitors in viral infections. Celecoxib also has potential beneficial mood elevating effects, as an adjunctive treatment [78], that could contribute towards clinical improvement of neuropsychiatric

manifestations in SARS-CoV-2-infected patients.

Dexamethasone is a high potency glucocorticoid. A preliminary report by the RECOVERY Collaborative Group [303] showed that the use of dexamethasone resulted in lower 28-day mortality among hospitalized SARS-CoV-2 patients who received either invasive mechanical ventilation or oxygen alone, but not among those receiving no respiratory support. Similarly, the use of intravenous dexamethasone, in addition to standard care resulted in a statistically significant increase in the number of ventilator-free days in SARS-CoV-2 patients [304]. However, treatment with dexamethasone aggravated depressive behaviour in rats [305] and mice [306], which could prove problematic in these patients, considering the prevalence of psychiatric conditions associated with COVID-19. Based on the mentioned preclinical studies, dexamethasone could worsen underlying psychiatric conditions by increasing oxidative stress, inflammation and inducing dysregulated glutamatergic neurotransmission [307–309].

Lithium salts have antidepressant/antimanic/mood stabilizing properties as well as having pro-inflammatory effects [310]. The latter appears beneficial in some disorders associated with immunological deficits, such as HIV and systemic lupus erythematosus (SLE) [311,312]. In this regard, lithium has diverse effects on inflammatory mediators, such as modulating the expression of several inflammatory genes including IκB-α, TRAF3, Tollip, and NF-κB1/p50, while it inhibits NF-κB activity by lowering nuclear translocation of NF-κB in LPS-activated macrophages [313]. Animal studies have also shown lithium to either decrease [314] or increase activity of the NO-cGMP pathway [315,316]. Recently, Pietruczuk et al. [167] demonstrated that T lymphocytes of patients suffering from bipolar disorder that were treated with lithium or valproate, are characterized by pro-inflammatory activity, decreased proliferative activity and increased susceptibility to apoptosis. Finally, a case report by Spuch et al. [317] showed that lithium carbonate improved inflammatory activity and immune response in patients with severe SARS-CoV-2 infection.

Minocycline, a tetracycline, is a protein synthesis inhibiting antibacterial with anti-inflammatory, immunomodulatory and neuroprotective properties [318]. Minocycline may be a preferred alternative to azithromycin as it may mitigate the risk of azithromycin-associated QT prolongation and cardiac arrythmias [319]. Indeed, minocycline was shown to prevent respiratory syncytial virus infection [320] and to reduce HIV replication and reactivation by altering the cellular environment [321]. It may also be an alternative to azithromycin due to a penchant of the latter for drug-drug interactions [319].

Mitochondrial rejuvenators and modulators. Cationic amphiphilic drugs with hydrophobic aromatic ring or ring systems, especially with a hydrophilic side chain containing an ionizable amine functional group, like methylene blue, have mitochondrial rejuvenating actions [147], including enhancing mitophagy [322], increasing cellular oxygen consumption and delaying mitochondrial dysfunction [323]. N-acetyl cysteine (NAC) too has beneficial effects on mitochondrial function, as well as potent antioxidant properties [324]. A case report by Alamdari et al. [325] showed that treatment of SARS-CoV-2 patients with a combination of methylene blue, vitamin C and NAC could increase the survival rate of these patients, possibly due to anti-inflammatory and anti-oxidative effects. Indeed, methylene blue is effective in inactivating various RNA viruses, including influenza [326]. Methylene blue [147] and NAC [327] have also been proposed to have beneficial mood elevating effects. Mitochondrial modulators could potentially be anti-SARS-CoV-2 augmentation strategies because of the role optimal mitochondrial function (and consequent reduced oxidative stress) play in the immune response. Mitochondria contain mitochondrial antiviral signalling (MAVS) proteins in their membrane that can contribute towards antiviral defence mechanisms by regulating anti-inflammatory responses [328,329]. Melatonin has recently been proposed as adjuvant anti-SARS-CoV-2 option due to its mitochondrial enhancing properties [330]. Therefore, mitochondrial modulators may present a novel drug target to induce antiviral effects [331].

NF-κB inhibitors or antagonists. Activation of NF-κB may contribute to apoptosis and enhanced inflammation (*review by* Ludwig & Olivier [332]). Inactivation of the NF-κB pathway was shown to inhibit influenza-A viral replication [333]. The digitalis alkaloids, digoxin and ouabain, are recognised as NF-κB antagonists [334]. Cho and colleagues [335] reported that both compounds inhibited over 99 % of SARS-CoV-2 replication, leading to viral inhibition at the post entry stage of the viral life cycle. However, pathological increases in the production of endogenous ouabain-like compounds was shown to play a role in the pathophysiology of mood disorders (*review by* Christo & El-Mallakh [336]). Therefore, these patients need to be monitored for possible psychiatric side-effects induced by these compounds.

Phosphodiesterase inhibitors: Selective PDE-4 inhibitors (*e.g.* ibudilast and rolipram) may attenuate the cytokine storm in SARS-CoV-2, through their action on glia, especially upstream inhibition of pro-inflammatory molecules and the regulation of pro-inflammatory/anti-inflammatory balance [337]. PDE-5 inhibitors (*e.g.* sildenafil and tadalafil) could be useful as adjunctive SARS-CoV-2 treatment by counteracting the Ang-II-mediated downregulation of AT-1 receptor and reducing pro-inflammatory cytokines [338]. Indeed, sildenafil seems promising for the treatment of otherwise fatal HIV-related pulmonary hypertension in patients infected with HIV [339]. Moreover, these agents display preclinical anxiolytic and mood elevating properties [172,238,340].

Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)-γ agonist that has been shown to provide protection in mice infected with highly pathogenic and pandemic strains of influenza virus [341]. Consequently, Carboni et al. [342] hypothesized that pioglitazone could potentially be used to reduce the cytokine storm, associated with SARS-CoV-2, at least in those patients that have a manifest condition of metabolic syndrome. PPAR-γ signalling also represents a susceptibility factor in developing depression [82].

Rapamycin, an mTOR inhibitor, may enhance the antiviral actions of aplaviroc and vicriviroc, used specifically in maraviroc-resistant strains of HIV [343,344]. The mTOR pathways may offer valuable targets to control cell injury, oxidative stress, mitochondrial dysfunction, and the onset of hyper-inflammation, a significant disability associated with COVID-19 [345]. The mTOR pathway is also a critical messenger in antidepressant action, being recognized as the target for the rapid antidepressant actions of ketamine and rapastinal [346,347], and hence may have relevance in COVID-19 associated mood disorders.

Selective serotonin-targeting antidepressants: SSRIs have recently been investigated for their adjunctive benefit in the treatment of COVID-19. In this regards, fluoxetine was effective in decreasing SARS-CoV-2 viral expression [348], while others associated SSRI-treatment with lower risk of death or intubation in hospitalized patients with SARS-CoV-2 infection [253,349]. The beneficial effects could in part be ascribed to the anti-inflammatory effects of SSRIs [145,146,350]. In fact, fluoxetine and citalopram have been shown to display anti-inflammatory properties by inhibiting endosomal TLRs, a class of pattern recognition receptors that recognize bacterial or viral pathogen-associated molecular patterns and play a key role in innate immune responses to suppress pro-inflammatory cytokines [351].

Tryptophan-kynurenine modulators, such as allopurinol, inhibit xanthine oxidase as well as tryptophan 2,3-dioxygenase (TDO), thereby modulating the formation of kynurenine and the depletion of tryptophan for 5-HT synthesis. The tryptophan-kynurenine pathway plays an important mediating role in inflammation-induced psychopathology [98]. An early report suggested that treatment with allopurinol, in combination with a chemically modified superoxide dismutase (a scavenger of O_2), improved the survival rate of influenza virus-infected mice [352].

5. Implications for the SARS-CoV-2 pandemic, and risk assessment

In brief, one needs to identify the risks, identify the patients at risk

and indicate a risk management strategy (see Fig. 4).

From the review it follows that SARS-CoV-2 poses risk of psychological trauma, neuro-inflammation and the induction of a dysfunctional immune system that may ultimately impact on the nervous system. Psychiatric disease increases vulnerability of the individual to disease modulating factors. Given the redox-inflammatory actions of psychotropic medicines, comorbid SARS-CoV-2 infection and its treatments may alter how patients respond to these drugs, so that a triple factor interaction between SARS-CoV-2 as disease, psychiatric disease and psychotropic drug response may ensue. The picture gets more complex when dealing with patients with multiple comorbidities and/or when multi-drug treatment is prescribed. It therefore becomes important to be able to predict and evaluate the likelihood and potential magnitude of the involved risk.

Lastly, the risk may be managed by monitoring SARS-CoV-2 patients with psychiatric co-morbidity closely in terms of clinical response and, when applicable and possible, by also measuring appropriate biomarkers of inflammation and immune response. Broad, non-specific markers of immune inflammation include CRP, erythrocyte sedimentation rate (ESR) and plasma viscosity, as well as procalcitonin as marker of immune response [353]. These are probably the most practical to implement as indicators of enhanced inflammation and increased risk. In addition, biomarkers of haemodynamics may also be useful, such as fibrinogen, P-selectin, D-dimer and Von Willebrand Factor that seems to be associated with progression of SARS-CoV-2 and inflammation, as precursors to a cytokine storm [354,355]. Elevated cortisol and adrenocorticotropic hormone (ACTH) are not only markers of biological stress but have also been associated with stress and psychiatric disease [82]. Other experimental and more specific biomarkers, which may not always be practical to measure in clinical and limited resource settings, include CD4 + T cells, CD14+, CD16+, inflammatory monocytes, IL-2, IL-7, IL-10, granulocyte colony- stimulating factor (G-CSF), IP-10, MCP-1, macrophage inflammatory protein 1α (MIP-1α), TNF and S protein: V483A, L455I, F456 V and G476S [356]. Lately the ACE-2 receptor has been implicated as potential binding domain for SAB-CoV-2 [357]. In this regard a link has also been proposed between ACE-2 and dopa decarboxylase expression, with the latter involved in the synthesis of DA and 5-HT. The levels of both DA and 5-HT are closely associated with several psychiatric disorders and may in future turn out to be important biomarkers for psychiatric complications of SARS-CoV-2.

Monitoring and clinical response should prompt the clinician to record response, adjust treatment and continue monitoring. In the end, findings should be reported so that the broader health community can benefit from this knowledge, enhance treatment and optimise therapeutic outcome.

6. Concluding statement

The current SARS-CoV-2 pandemic is the third serious Coronavirus outbreak within the last 20 years, following SARS-CoV in 2002–2003 and MERS in 2012. Both SARS-CoV-2 and the previous SARS-CoV infections are associated with the elevation of the pro-inflammatory cytokines and chemokines (cytokine storm) while the pathogenicity of MERS-CoV is based on its IFN antagonist proteins. Ongoing research shows that many psychiatric disorders are characterized by inflammation, with their treatments having variable anti-inflammatory properties. The profound psychosocial effects of SARS-CoV-2 mean that patients will be receiving standard antidepressants and antipsychotics for these disorders. These medicines, together with a compromised immune status brought on by the psychiatric illness, may lower the natural ability of these patients to fight off ongoing SARS-CoV-2 infection or reinfection. This review has brought together the above elements, considering both theoretical *and* evident risks that clinicians may encounter as this new pandemic unfolds, while at the same time putting forward possible preventative treatment strategies. This paper has also attempted to open new opportunities for research by considering existing and novel treatments as adjunctive treatments in SARS-CoV-2 associated neuropsychiatric complications.

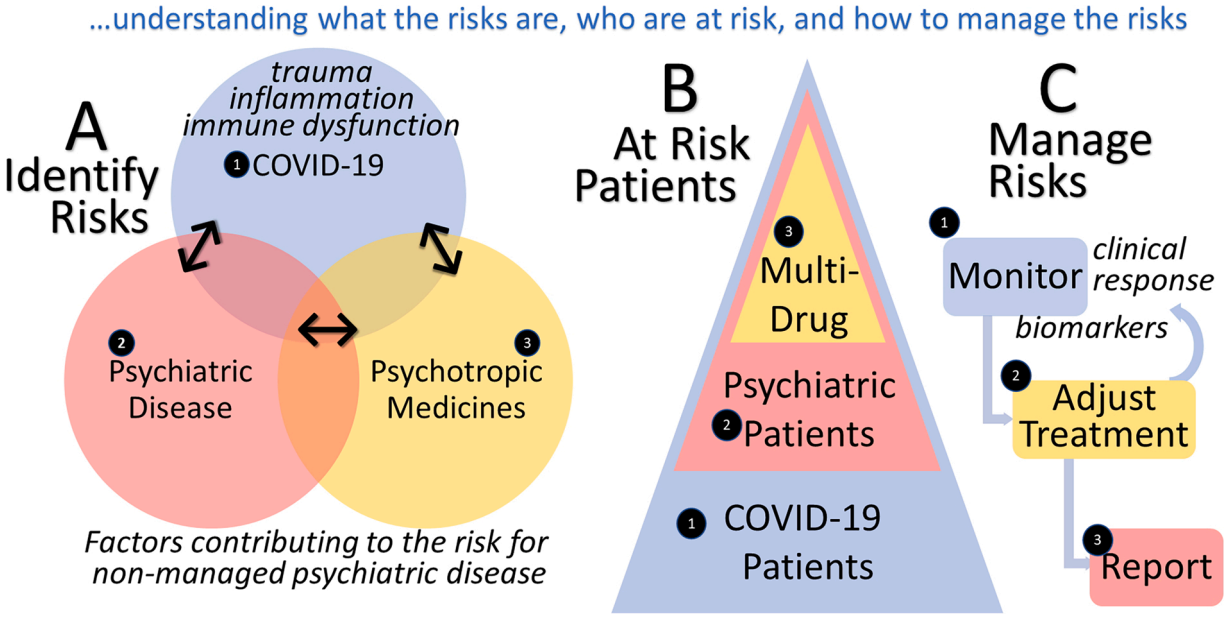

Fig. 4. Schematic representation of a basic risk assessment and management of psychiatric disease within the COVID-19 paradigm.
Fundamental steps of a risk assessment include (A) to identify the risks, (B) to identify the patients most at risk and (C) to describe how to properly manage these risks. In the schema the risks include the SARS-CoV-2 virus itself, causing inflammation and immune dysfunction. In addition, any pre-existing psychiatric disease and the use of psychotropic (or any other psycho-active) medicines add to the risk of a COVID-19 associated psychiatric condition. Patients at risk include those with SARS-CoV-2 infection, pre-existing psychiatric disease and multi-drug use. Important components of risk management include active monitoring of clinical response, identifying and monitoring biomarkers of inflammation, adjustment of treatment according to response, and continued monitoring. Lastly to report such findings for record keeping and to optimise future treatment strategies, e.g. adjunctive treatments *(further discussion is provided in the text). Abbreviations: COVID-19, corona virus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus.*

Author contributions

BHH conceptualized and designed the layout of the paper, and contributed to preparation of the manuscript; EJVV and SS jointly first-authored the paper, researched, collated and prepared the first draft; EJVV prepared the tables and figures (assisted by CBB); all other authors contributed various sections of the manuscript.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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