SARS-CoV-2 infection in patients with serious mental illness and possible benefits of prophylaxis with Memantine and Amantadine

ILEANA MARINESCU1, DRAGOȘ MARINESCU2, LAURENTIU MOGOANTĂ3, ION CRISTIAN EFFREM4, PUȘIU OLIVIAN STOVICEK5

1Discipline of Psychiatry, 5th Department, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania
2Doctoral School, University of Medicine and Pharmacy of Craiova, Romania
3Department of Histology, University of Medicine and Pharmacy of Craiova, Romania
4Department of Internal Medicine, University of Medicine and Pharmacy of Craiova, Romania
5Department of Pharmacology, Faculty of Nursing, Târgu Jiu Subsidiary, Titu Maiorescu University, Bucharest, Romania

Abstract
Patients with serious mental illness are a high-risk category of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Patients with schizophrenia are not participatory and have increased mortality and morbidity, patients with dementia cannot be cared for while depression, anxiety, bipolar tubing are associated with low immune status. Social stress is amplified by social isolation, amplifying depression and the mechanisms of decreased immunity. Hygiene measures and prophylactic behavior are impossible to put into practice in conditions of chronic mental illness. In coronavirus disease 2019 (COVID-19), the risk for severe development is associated with the presence of comorbidities and immune system deficiency. Prothrombotic status, cytokine storm and alveolar destruction are mechanisms that aggravate the evolution of patients, especially in the context in which they have dysfunction of the autonomic system. The activity of proinflammatory cytokines is accentuated by hyperglutamatergia, which potentiates oxidative stress and triggers the mechanisms of neural apoptosis by stimulating microglial activation. Activation of M1-type microglia has an important role in pathogenesis of major psychiatric disorders, such as major depression, schizophrenia or bipolar disorder, and may associate hippocampal atrophy and disconnection of cognitive structures. Memantine and Amantadine, N-methyl-D-aspartate (NMDA) glutamate receptor inhibitors, have demonstrated, through their pharmacological profile, psychotropic effects but also antiviral properties. In the conditions of the COVID-19 pandemic, based on these arguments, we suggest that they can be associated with the therapy with the basic psychotropics, Memantine or Amantadine, for the control of neuropsychiatric symptoms but also as adjuvants with antiviral action.

Keywords: SARS-CoV-2, dysautonomia, cytokine storm, inflammation, Memantine, Amantadine.

Introduction
The infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a large epidemic invasion power, with lethal risk for some categories of patients. Since there is no well-defined therapeutic strategy at the moment, the main measures that can influence the evolution and limit the unfavorable effects are those of social distancing and observance of hygiene rules and prophylactic behavior recommended by World Health Organization (WHO). The risk groups for SARS-CoV-2 infections identified in the existing studies until now were represented by patients with deficient immune system, old age, and multiple comorbidities (cardiovascular illness, high blood pressure, chronic lung disease, obesity, hyperglycemia).

Starting from these circumstances, we consider that patients with serious mental illness (SMI) and chronic evolution [psychotic disorders, schizophrenia, severe depression, bipolar disorder, Alzheimer’s disease (AD), dementia and non-motor disorders in Parkinson’s disease (PD), Lewy body dementia (LBD), other forms of dementia], represent a group of population with high risk to contract the coronavirus disease 2019 (COVID-19).

This risk is due to decreased judgement, consequent from the chronic psychiatric suffering, to decreased cognitive capacity, as well as incapacity to observe the hygiene rules, social distancing and ability to the special conditions imposed by the pandemic. Another factor aggravating the spread of the infection among this population is the hospitalization for chronic care, for long term, in psychiatric units, psychosocial or nursing homes.

The analysis of the data in literature shows that this population presents early death rate at a young age and multiple somatic comorbidities. In 2017, the USA statistical data estimated that 14.5% of adults suffer from SMI, age group prevalence being 7.5% for 18–25 years, 5.6% for 26–49 years, and 2.7% for patients over 50 years. Out of this population group only 66.7% of cases benefited from specific psychiatric treatment in the last year [1].

The epidemiological studies performed in UK showed that the mortality rate in SMI patients is 3.7 times higher than in the general population and the deaths appear 15 years earlier. Approximately 66% of death cases could have been prevented, their major cause being the associated chronic somatic diseases, the most serious being cardiovascular and lung disease, high blood pressure, diabetes. Other major risk factors for the early deaths are the
associated infections and acute respiratory illnesses, especially pneumonia. Among other early death causes are suicide, PD, AD, and other forms of dementia. The ratio between the prevalence for comorbidities in these SMI patients and the prevalence for comorbidities in the total number of patients is significantly higher for SMI in the case of obesity (1.8), asthma (1.2), diabetes (1.9), chronic obstructive pulmonary disease (COPD) (2.1), coronary heart disease (1.2), stroke (1.6), heart failure (1.5) [2]. These comorbidities are recorded as risk factors for severe evolution or death in the case of SARS-CoV-2 infection.

Besides the multiple somatic comorbidities, the schizophrenic patients smoke excessively, have respiratory dysfunctions, important cognitive deficits, a reduced social compliance, and great difficulty in observing hygiene and dietary recommendations. These particularities are associated to a distressed immunity, with major potential to trigger proinflammatory factors both at cerebral level and in the vital internal organs: heart (dilated cardiomyopathy, heartbeat attack, chronic or acute coronary disease) and lung (COPD, multiple pulmonary infectious episodes). Due to disorganized behavior, the patients with severe mental disorders have a major risk for pulmonary diseases and infection with human immunodeficiency virus (HIV), Herpes simplex virus (HSV) type 1 and 2, hepatitis viruses, with negative impact on morbidity and early mortality [3, 4].

Clinical pharmacology aspects for Memantine and Amantadine

Memantine (derivate of Amantadine) and Amantadine are part of the adamantine class and are recognized for their psychotropic qualities, with therapeutic indications in AD (Memantine) and PD (Amantadine). From the point of view of the main pharmacological action, Memantine (3,5-Dimethyladamantan-1-amine) is a non-competitive antagonist for N-methyl-D-aspartate (NMDA) glutamate receptor, voltage-dependent, with moderate affinity [5]. The blockage of NMDA receptors determines the decrease of the glutamate level, mechanism that improves the neuronal excitotoxicity, induced by hyperactivity of glutamate. Other demonstrated effects of Memantine are the antagonizing of 5-hydroxytryptamine (5-HT₃) receptor and nicotinic acetylcholine receptors (nAChRs) [6]. Also, the antagonist action on the D2 dopamine receptors is similar in intensity with the one on NMDA receptors [7]. This pharmacological profile gives Memantine multiple pharmacodynamic effects, demonstrated in clinical or animal studies: the symptomatology improvement in AD, neuroprotection, stimulation of neurogenesis, improvement of inflammatory, neuropathic or visceral pain, antiparkinsonian effect [6]. Memantine acts through multiple cellular and immunological mechanisms, slowing the neurodegenerative progress triggered by the amyloid β (Aβ) and tau proteins and have neuroprotective effects. The important therapeutic benefits from major psychiatric disorders were demonstrated by the cognitive improvement and in the aggressive, psychotic, and depressive-anxious behavioral disorders.

Amantadine (1-Adamantylamine) has antiparkinsonian effect (increase dopamine levels by encouraging release and blocking reception), antiviral (especially on influenza viruses by blocking the function of M2 viral protein and impacting viral replication) and antihyperalgesic (through the anticholinergic action consecutive to inhibition of NMDA receptors) [8].

Memantine and Amantadine, psychotropic medication with antiviral action

The surprising fact is that both substances have known antiviral effect, Memantine showing efficacy for viral infections with neurotropism, such as human coronavirus (HCoV), HIV, HSV, while Amantadine is even indication approved by Food and Drug Administration (FDA) for the prophylaxis and treatment of the infection with influenza A virus (IAV) [9, 10]. On the other hand, the infections with HIV, HSV and IAV were correlate with PD pathogenesis or parkinsonism [11], while HIV and HSV were involved in AD pathogenesis [12].

Coronavirus infections

HCoV, including Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) strains, can severely affect the respiratory function, especially in the older population, with low immune system or with comorbidities and can migrate from the pulmonary level to the central nervous system. The viral neurotropism in these vulnerable groups can trigger or exacerbate encephalopathies, neurodegenerative processes, neurological illnesses, and sequelae [13]. The neurotoxic mechanisms of HCoV were correlated with glutamate excitotoxicity, increase in cytokine release and immune cells infiltrates [14].

Animal studies showed that the cerebral invasion of SARS-CoV virus takes place mainly through the olfactory bulb and dissemination is rapidly carried out by neuronal ways. Even though pulmonary symptomatology is not severe, a reduced viral infection can lead to death through neuronal apoptosis in cardio-respiratory centers [15]. The animal model also showed that the coronavirus infection triggers a demyelination process consecutive to inflammatory processes, aspects characteristic to multiple sclerosis. The OC43 strain of HCoV was identified during autopsy in 35.9% of patients with multiple sclerosis, while the seasonal model of the coronavirus infections was correlated with acute episodes in the multiple sclerosis symptomatology. The viral induced acute demyelination process comes together with the increase of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and inducible nitric oxide synthase (iNOS), released especially by macrophage cells. These proinflammatory factors show high values both in chronic demyelination but through astrocytary release [16].

The HCoV-OC43 strain infection at cerebral level determined imbalances of the glutamate homeostasis through motor deficits or paralysis. Memantine administration improved the motor symptomatology, by partial recuperation of the phosphorylation function of neurofilaments and decreased the viral replication in the brain. Due to this antiviral action, Memantine can become a medication with possible indications in several neurological diseases with viral etiology [17].
HSV infection

The HSV infection, getting to cerebral level by retrograde axonal transport, is involved in triggering neurodegenerative processes Aβ aggregation and forming amyloid plaques. The HSV positive patients have a more pronounced cognitive deficit. It was demonstrated, in cell culture model and on mouse brains, that the administration of anti-HSV drugs has led to a decrease in Aβ and tau proteins, with a significant effect on attenuating cognitive decline. The clinical studies demonstrated the efficiency of the Valacyclovir antiviral medication in improving the memory in the schizophrenic patients and for AD the research is in progress [18, 19].

The HSV-1 infections are considered risk factors for AD development. The concept underlining the role played by viral infections in AD, especially HSV-1 infection, has gained ground in the last decades. The viral determinism of AD through HSV-1 infection was confirmed in pharmacological studies that showed the antiviral efficacy of Memantine, Amantadine and Tromantadine. This antiviral action can be explained by their capacity to stop viral replication, but also by diminishing glutamatergic neurotoxicity [20]. Memantine might bring moderate benefits also in the antalgic treatment of post herpes zoster neuropathy [21], but the existing data is not conclusive due to reduced scientific information [22].

HIV infection with cognitive disorders

Approximately 50% of the HIV-infected patients will have cognitive deficit, considered in the dementia from acquired immunodeficiency syndrome (AIDS). Associating antiviral therapy with neuroprotective medication can improve the innate neuronal repair, by neuroplasticity improvement and neurological functional recovery. Memantine reduces the level of intracellular calcium and glutamate neurotoxicity, induced by the transactivator of transcription (Tat) and glycoprotein 120 (gp120) viral proteins [23].

The in vivo and in vitro studies highlighted that gp120, present on HIV-1 envelope, determines destrucions and apoptosis in the neuronal cells by glutamate hyperactivation, even if the viral replication does not take place in neurons. The viral infection of microglia and astrocytes triggers proinflammatory, neurotoxic mechanisms and disturbance of the glutamate metabolism. An important proinflammatory marker in the HIV-1 infection, correlated with neuronal lesions and cognitive deficit, is osteopontin, having high levels in the cerebral tissue, plasma, and cerebrospinal fluid [24].

The neurotoxic effects of the HIV infection associated with dementia and encephalitis are due to the Tat and gp120 proteins in the viral structure, maintaining a high level of intracellular calcium and increasing the cytokine release with cytopathic effect. This cytopathic effect, determining the apoptosis of virus infected cells, was demonstrated also in SARS-CoV-2 [25].

Memantine succeed to block the neurotoxic effects of these viral proteins [26], leading to neuronal apoptosis also through hyperactivation mechanism of NMDA receptors [27, 28]. Alcohol consumption represents a risk factor for patients with cognitive deficit in AIDS because it exacerbates the gp120-induced neuronal destructions, through glutamatergic activation [29]. Memantine had effects in diminishing neuronal apoptosis induced by Tat proteins in cellular cultures for rat hippocampal neurons and stimulated neuroplasticity [30]. Also, Memantine demonstrated neuroprotective effects by diminishing the cognitive deficit in AIDS-associated dementia [31].

Zika virus infection

Memantine is in pre-approval stage with FDA for the use in the infection with Zika virus due to the capacity to reduce neuronal apoptosis, demonstrated in vitro and in mouse model [32]. This mechanism can improve the viral induced neurological symptomatology through neurotoxicity and microgliosis mechanisms [33, 34]. In studies on mice, Memantine reduced the intraocular pressure induced by Zika virus and significantly prevented the neurodegeneration and microgliosis processes [35].

Influenza A infection

Amantadine showed antiviral effects at micromolar concentration, inhibiting the IAV replication, in one of the final stages of viral ageing. In high doses, the inhibition takes place in an early replication stage, showing therapeutic effects in infections with influenza B, HSV and other enveloped viruses [36]. The efficiency rate in preventing influenza A infection was estimated between 70–90% [37]. In influenza A, Amantadine may shorten the duration of the illness by 1.5–2.5 days and reduce the severity of the illness [38]. These indicators recommend the administration of Amantadine, especially for the patients in the listed risk categories, the institutionalized patients and those who do not have a high protection rate following vaccination.

Association between SARS-CoV-2 and influenza infection represents a risk factor with severe evolution, reason why the prophylaxis in elderly persons with Parkinson phenomena in premotor or manifest phase, not vaccinated, can be done in the current pandemic conditions with Amantadine. Amantadine [39] and Memantine [39, 40] correct the manifestations specific to dysfunction of the autonomic nervous system (dyssyautonomia), as well as depression and cognitive impairment in PD. It is interesting that the HCV-OC43 infections affect the dopamine synthesis in the black substance determining PD symptomatology. The PD patients had increased level of anti-coronavirus antibodies in cerebrospinal fluid [41].

Pathological aspects in SARS-CoV-2 infection

In SARS-CoV-2 infection have been reported acute respiratory distress syndrome (ARDS) (29%), renal insufficiency (7%), heart failure (12%), in these cases the cytokine storm being an unfavorable, severe prognostic factor [42]. Cases of infection with coagulation disorders and high risk of thromboembolic events have been reported [43, 44]. Acute lung damage from alveolar destruction, following high levels of proinflammatory cytokines, has been observed in infections caused by influenza viruses [45], and SARS-CoV [46]. Some patients, who have lung damage through the destruction of alveolar lung cells, also have acute heart damage (myocardial infarction, cardiac arrest). Among deceased patients who did not have pre-existing cardiac pathology, 11.8% developed...
major heart damage after infection. The onset of heart failure following acute lung injury has been explained by several mechanisms: involvement of angiotensin-converting enzyme 2 (ACE2) receptors, cytokine storm, respiratory failure, and hypoxia [47].

Since the asymptomatic phase of SARS-CoV-2 infection, neurological signs have been identified, such as loss of smell and taste, neuralgia, myalgia [48]. Also, in some cases, epileptiform seizures have been described, which could be caused by neuronal invasion, hypoxia, organ failure or drug induction [49]. There may be other mechanisms caused by increased excitability of cortical and subcortical neurons, correlated with microglial activation, glutamatergic hyperactivity, blood–brain barrier (BBB) disruption and high levels of cytokines that may anticipate the risk of epileptic seizures. The seizures are associated with an increase in IL-1β and TNF-α [50]. Therapies with NMDA receptor blockers reduce levels of these cytokines, with a strong antiepileptic effect [51].

There have been reports of severe forms of COVID-19, seizures, confusion and even strokes that may be correlated with cerebral oxygenation deficiency but also with increased neural excitability following cytokine aggression. Neurological symptoms were present in 36.4% of patients with COVID-19 and in 45.5% of patients with severe infection [52]. These data show the importance of decreased olfactory acuity and polynuropathic pain as the disease progresses. The generalized hyperalgesia condition in COVID-19 may be correlated with the hyperexcitability of the glutamatergic system and may be a valuable clinical sign of predicting severe evolution. Blockade of NMDA receptors can improve pain relief by increasing the neuroprotective effect in the brain and significantly decreasing the state of central and peripheral neuronal excitability following cytokine hyperactivity.

Neuronal invasion is a severe prognostic factor in respiratory progression, which can go as far as death by spreading the virus to the cardiorespiratory centers [53]. This clinical picture of the neurological type that appeared in viral infections signals the neuronal viral invasion and the transition to central nervous system symptoms. Due to the viral neurotoxicity, dysautonomia is accentuated, probably by involving the regulation mechanisms at the bulbar and pontine level. In our opinion, the neurological manifestations are favored by the existence of dysautonomia, similar to the non-motor symptoms in the prodromal phase of PD.

Olfactory disorders may be quantitative, characterized by global hyposmia induced glutamatergic aggression on the olfactory bulb and olfactory circuits, and a qualitative decrease in olfactory discrimination capacity determined by olfactometry, correlated with decreased dopamine levels. Olfactory dysfunctions are also reported in the prodromal phases of PD, associated with a series of non-motor phenomena that precede motor phenomena by several years: odor loss and signs of autonomic system dysfunction [54]. Some clinical features, such as constipation, erectile dysfunction and orthostatic hypotension, may occur 10–16 years before PD, in the preclinical phase and delay the diagnosis. In the symptomatic prodromal phase may occur: pupillary hypersensitivity, sialorrhea, thermoregulatory disorders (hyperhidrosis or on the contrary dry skin, hyperthermia or chills hypothermia with changes in heart rate), gastrointestinal, urinary or cardiovascular disorders (supine hypertension, postprandial hypotension) [55]. The atypical forms of COVID-19 onset may be correlated with dysautonomia that disrupts the functionality of the gastrointestinal system or through gastroparesis, neuropathies of the intestinal vegetative plexuses, and altered gut–brain barrier [56, 57].

In this context, a pathogenic mechanism of the “vicious circle” type can be supported, the dysautonomia favoring the appearance of neurological clinical manifestations and the cerebral pathogenic support, and this accentuates the dysautonomia. The importance of this syndrome in the PD model becomes important in clinical psychiatry due to the similarity of this model with the manifestations of drug or vascular parkinsonism that can be found in most chronic SMI. For schizophrenia, the theoretical perspective of the neurobiological model highlights the presence of “soft” extrapyramidal signs, a phenomenon that suggests in this category of patients the vulnerability to dysautonomia [58, 59].

Clinical manifestations associated with dysautonomia

Orthostatic intolerance syndrome

Dysautonomia, since the asymptomatic phase of SARS-CoV-2 infection, is associated with orthostatic intolerance syndrome characterized by decreased orthostatic blood pressure associated with chronic fatigue syndrome, dizziness and balance disorders, tachycardia, and vasovagal syncope [60]. Orthostatic intolerance syndrome causes orthostatic stress that increases prothrombotic state [61]. In orthostatic intolerance syndrome associated with repeated syncope, a significant increase in von Willebrand factor has been reported [62].

On the other hand, prothrombotic status is associated with increased endothelial activation factors and plasma protein and hematocrit concentration, as well as decreased C-reactive protein. Increased activity was observed for several factors involved in coagulation: fibrinogen, von Willebrand factors, V and VIII, prothrombin fragments 1 and 2 [63]. These biological markers can identify the risk of hypercoagulability syndrome caused by orthostatic stress under dysautonomia since the asymptomatic stage of COVID-19. Dysautonomia with noradrenergic hyperactivity and sympathetic dominance is associated with arteriole and venous vasoconstriction in the cerebral, coronary territory but also at the level of the pulmonary or renal systems, this mechanism being able to favor multisystemic thrombosis.

Glaucoma

The prevalence of glaucoma in PD is estimated at 16–24% [64, 65]. In conditions of glaucoma, especially in the form of a closed angle, a headache may occur accompanied by eye pain and redness, nausea, and vomiting, and may mimic a SARS-CoV-2 onset. Glaucoma can also trigger progressive optic neuritis. Dysautonomia is associated with glaucoma, the intensity of dysautonomia involved in the pathogenesis of glaucoma can be correlated with the intensity of changes in pupillary contractility
objectified by dynamic pupillometry tests. This marker indicates the risk of developing antineutrophil cytoplasmic antibodies (ANCA) syndrome associated with the high potential for ANCA-associated vasculitis (AAV) [66, 67]. AAV is an evolutionary risk indicator in patients with renal failure and dialysis, a risk that can be correlated with the intensity of dysautonomia clinical-biological indicators. In elderly patients and dialysis, the increase in ANCA may be an indicator of evolutionary risk to end-stage renal disease [68]. In the conditions of the SARS-CoV-2 pandemic, we consider that special protocols are required for the safety of these patients, with a high risk of unfavorable evolution.

The neuroprotective action in conditions of autoimmune mechanisms that can trigger optic neuritis has been reported using experimental translational blockers for NMDA receptors. The administration of Memantine stops the demyelination process of the optic nerves, reduces the apoptosis of the cells in the retinal ganglion and improves the clinical symptoms by reducing the inflammatory infiltrates that will cross the BBB. The increased inflammatory status located in the optic nerves has been correlated with high levels of glutamate in the retina [69, 70].

In the conditions of an asymptomatic infection with SARV-CoV-2, the identification of the triad composed of dysautonomia, a symptom of orthostatic intolerance with hypotension and changes in dynamic pupillometry, indicates the state of evolutionary risk. The appearance of plasma indicators that anticipate hypercoagulability requires urgent prophylactic intervention, with anticoagulant pharmacological treatment. This possible mechanism (multisystemic thrombosis) may be involved in explaining sudden deaths in quarantined patients (home deaths) and the risk of death in relatively young patients with no clear evidence of other comorbidities.

Progressive optic nerve neuropathy associated with glaucoma may have an autoimmune component that explains the favorable response in translational studies to intravitalreral administration of Memantine [71–73]. The identification of glaucoma in patients with mental illness becomes important because it signals a negative evolution of SARS-CoV-2 infection, and on the other hand glaucoma can be induced or exacerbated by psychotropic medication [74, 75].

**Myalgia**

Viral aggression can be announced in a first phase of the toxic state, with general condition deeply altered, with myalgia type of autonomic neuropathy with viral toxic component. Another theoretical pharmacological argument that supports our hypothesis is that these myalgias are little influenced by the usual analgesic medication indicated in therapeutic protocols, instead Memantine and Amanadine have positive studies to control myalgia from HSV infection and fibromyalgia.

Myalgia associated with viral infection may be present in the asymptomatic phase of the disease and requires, especially in patients with pre-existing psychiatric disorders, the differentiation of fibromyalgia from depressive syndromes that can be amplified by stress caused by conditions of social isolation. Persistence of pain may promote the development of depression in patients without a psychiatric history, or autolytic behavior in patients with depressive disorders. Thus, the depressive syndrome after HSV infection in the elderly is triggered by neuralgia, which is why the pain syndrome is sometimes included in fibromyalgia. The viral origin of the pain is also confirmed by the very good therapeutic response to the association between Pregabalin and Memantine [76].

In SARS-CoV-2 infection appears the pain syndrome, predominantly muscular, which can be caused by the phenomenon of autonomic peripheral neuropathy and glutamatergic hyperactivity. Also, in the pathogenesis of persistent pain, the hyperglutamatergic mechanisms are involved. NMDA receptor blockade, on the model of Ketamine and Memantine, has shown positive results in the control of neuropathic pain [77–80]. Based on this hypothesis, the use of an NMDA blocker that also has antiviral action, could bring therapeutic benefits in the management of COVID-19.

**Cardiovascular clinical manifestations**

Hypertrophic cardiomyopathy syndrome associates dysautonomia with an imbalance alternating between the parasympathetic and sympathetic systems. The predominance of parasympathetic activity associated with ventricular hypertrophy in essential familial or primary hypertrophic cardiomyopathy expresses a high risk for severe ventricular arrhythmias. The predominance of the sympathetic system is associated with hypertension and ventricular hypertrophy due to the tendency of arterial spasm can frequently cause acute coronary syndromes. It is important to identify hypertrophic cardiomyopathy in the elderly with cognitive impairment and predominantly parasympathetic activity, because the use of acetylcholinesterase inhibitors can cause arrhythmia and sudden death [81].

Takotsubo syndrome (TTS) is characterized by an acute dysfunction of the left ventricle triggered by conditions of emotional or physical stress. This syndrome supports the presence of autonomic dysfunction and altered connections with the limbic system by altering the brain–heart axis [82].

Dysautonomia preceding PD also affects the cardiovascular system. Myocardial scintigraphy correlated with postural hypotension in the premotor phase of PD can announce with a probability of up to 90% the onset of PD. $^{125}$I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy showed a decrease in sympathetic innervation of the heart associated with the tendency for dilated cardiomyopathy [83–85].

PD and parkinsonism are frequently associated with pulmonary complications: airway obstruction, hypophonia, sleep apnea, pleuro-pulmonary fibrosis, decreased ventilation, aspiration pneumonia, and other complications associated with decreased regulation of central respiratory muscle strength. Because of this, in the early stages of PD and parkinsonism, there is a ventilatory dysfunction with increased CO$_2$ and a decrease in red blood cell load with O$_2$. The reduction of the functional respiration capacity is also associated with cognitive deficit, conditions in which the vulnerability for viral or microbial pneumonias appears [86, 87].
Respiratory disorganization is significantly altered in patients with PD, especially by affecting the cardiac sympathetic system, with a predisposition to atrial fibrillation that is responsible for pulmonary, cerebral or small vessel thromboembolic events. Both in Parkinsonism and in the early non-motor phases of PD, there are multiple conditions that favor premature death, such as pneumonia, brain or cardiovascular disease, cardiac arrhythmias, cardiac conduction disease, which can cause sudden unexpected death in Parkinson’s disease (SUDPAR) [88].

Cardiovascular protection of Memantine can be argued based on the evidence of cardiac and vascular NMDA receptors [89, 90]. Animal studies have shown that Memantine has a myocardial protective effect by stopping proinflammatory events following lipid peroxidation, with decreased malondialdehyde (MDA) and reducing neutrophil invasion in the heart [91].

Neurological clinical manifestations

The most common neurological manifestations in COVID-19 are decreased or lost sense of smell, accompanied by loss of taste, neuronal hyperexcitability syndromes due to increased glutamate activity, such as rapid eye movement (REM) sleep behavior disorder or epileptic seizures.

Olfactory dysfunction

Olfactory dysfunction can be triggered by HSV-1 and HSV-2 infections, Chlamydia pneumoniae, spirochetes and other bacterial infections, raising the issue of pathogenic associations between two or more concomitant viral diseases. Unfavorable evolution may be a consequence of these infectious conditions.

In elderly patients, dopamine deficiency may be associated with the onset of motor symptoms in PD and cognitive impairment but also with decreased ability to discriminate olfactory sense. The decrease in the number of dopamine receptors in the olfactory bulb demonstrates the involvement of dopamine in olfactory acuity. Because the olfactory bulb is a dopamine-controlled structure, decreased olfactory performance, especially odor discrimination, may be a first sign of non-motor onset of PD [92].

The decrease in olfactory dysfunction may anticipate a rapid evolution from the mild cognitive impairment (MCI) stage to AD, but it can also be a marker for a negative evolution in schizophrenia, through the involvement of dopamine [93]. Decreased olfactory acuity on translational research is considered a valid pathogenic model for both AD and PD. The olfactory bulbectomy performed in rats showed, in addition to a decrease in cognitive abilities, a 300% increase in homocysteine. Also, at the plasma level, the proinflammatory cytokine factors were much increased, especially IL-1α and IL-1β, IL-6 and TNF-α. Given the occurrence of olfactory deficit in the asymptomatic phase of SARS-CoV-2 infection, these markers may suggest the installation of acute respiratory syndrome, which is why early prophylactic intervention measures are required [94].

The neuroprotective and cognitive-enhancing effect of Memantine in rats with olfactory bulbectomy has been demonstrated [95]. On the other hand, the beneficial role of Memantine may be correlated with NMDA receptor blockade and the possible relationship between NMDA receptors and the brain renin-angiotensin system (RAS) in AD and PD [96]. Angiotensin II enhances NMDA activity and increases the production of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2)-dependent superoxides in paraventricular neurons located in hypothalamus [97].

Gustatory dysfunction

Decreased taste to total loss is a neurological syndrome that suggests the aggressiveness of viral infection with SARV-CoV-2, because from the points of emergence and cannontment of the virus in the nasal mucosa, tongue, and oropharynx, through the ascending pathways, reaches the nucleus of the solitary tract located in the medulla oblongata. From here, the neural connections are ascending and connect the ventral postremedial nucleus located in the thalamus and gustatory cortex of the frontal lobe, consisting of the anterior insula and the frontal operculum. Bulbar projection may be associated with a major risk of respiratory arrest, a consequence of inflammatory processes secondary to viral neurotoxicity (proinflammatory edema) [98]. This mechanism may explain rapid and severe respiratory failure in some COVID-19 patients, especially those who have had the onset of hyposmia disease [99].

REM sleep behavior disorders

REM sleep behavior disorders can have a psychiatric appearance due to aggressive manifestations during REM sleep. This disorder may have idiopathic determinism occurring in the context of neurodegenerative neurological disorders: PD, multiple system atrophy, LBD. The pathogenesis of the disease has been correlated with dopamine deficiency and favorable results have been reported with Amantadine treatment [100]. In PD, during the prodromal period, a specific syndrome occurs with sleep disorders and eye movements, with a high risk of mortality due to coronary vascular mechanisms [101]. The particular character of this syndrome in the conditions of COVID-19 infection can lead to an atypical onset of psychiatric or neurological aspect.

Epileptic symptoms

Epileptic manifestations may be associated in psychiatric clinical practice with glutamate system hyperactivity and increased excitability of neural systems, amid decreased efficiency of gamma-aminobutyric acid (GABA) inhibitory transmission. This symptomatology can be identified in the history of patients with schizophrenia, following hypoxic-ischemic encephalopathy (HIE). In these patients, there is a primary hyperglutamatergic activity and the presence of febrile convulsions or epileptic manifestations in the first year of life may be a risk factor for schizophrenia. Vulnerability for epileptic manifestations and primary hyperglutamatergia is associated with symptoms of dysautonomia [102]. This link may justify the administration of selective NMDA receptor blockers, as Memantine, to control dysautonomia and epileptic symptoms. In the conditions of SARS-CoV-2 infection, proinflammatory mechanisms triggered by M1-type microglial activation are associated, the presence of which can anticipate an unfavorable prognosis.
Pathogenic mechanisms with evolutionary risk, specific to SARS-CoV-2 infection

Prothrombotic state

The prothrombotic state, favored by dysautonomia and other comorbidities, can generate alteration of self-regulation mechanisms and maintenance of immune homeostasis with the onset of cytokine storm. Increased serum levels of fibrinogen, von Willebrand factors, V and VIII, announce a severe evolution and a high risk of mortality [103]. Atherothrombotic events can be induced by increased cytokine activity, especially IL-1, IL-6, and TNF-α, by exacerbating endothelial dysfunction, decreased collagen synthesis, and activating the blood clotting processes. This mechanism may explain the lack of therapeutic response to anti-inflammatory medication and the atheroprotective effects of targeted anti-cytokine therapy [104]. Atherothrombosis is associated with hypertension, dysautonomia and increased activity of hemostatic factors that promote thrombogenesis, causing a lethal risk in patients infected with SARS-CoV-2. On the other hand, thrombotic events, vascular inflammatory phenomena, and endothelial dysfunction are accentuated by the RAS [105, 106].

Cytokine storm

The second pathogenic mechanism involved in the severe evolution of acute respiratory syndrome in SARS-CoV-2 is cytokine aggression. The rapid increase in proinflammatory cytokines, especially IL-6, IL-1, TNF-α, and interferon (IFN), triggers cytokine storms, which cause endothelial dysfunction, vascular barrier damage, alveolar damage, and multiple organ failure [107]. Controlling the immune response and inflammatory processes is extremely important in reducing the severity of the disease and the risk of death [108].

Memantine has evidence for its important role in balancing cytokine mechanisms, confirmed by studies on animal models, but also in clinical trials for depressive disorder in type 2 bipolar disorder. A randomized, double-blind clinical study of the efficacy of Memantine in combination with Valproic Acid (VPA) in patients with type II bipolar disorder revealed a significant decrease in the TNF-α cytokine marker in the group with VPA + Memantine vs. VPA + placebo [109]. This effect can be explained by the fact that cytokine aggression is mainly triggered by the imbalance in the excitatory glutamatergic system, which is hyperactive, and the inhibitory GABA system, which is deficient. Glutamatergic hyperactivity favors the onset of inflammatory mechanisms and implicitly an exaggerated increase in the level of cytokines in the peripheral blood but also through the M1 microglial activation of cytokines with destructive action [51, 110, 111].

In the animal model, cognitive impairment induced by okadaic acid was associated with increased aggressiveness of the TNF-α and IL-1/β proinflammatory cytokines and increased total nitrates in the cortex and hippocampus. The levels of NO synthesis proteins were altered, the neuronal NOS (nNOS) isoform being low, and the iNOS isoform being increased. Oxidative stress has been demonstrated by elevated levels of reactive oxygen species (ROS) and mitochondrial calcium in the brain [112].

Prophylactic administration 13 days before of Memantine associated with Donepezil, had a protective effect, thus demonstrating the involvement of neuro-inflammatory processes in the onset or worsening of cognitive deficit [113, 114]. On the other hand, the important effect of Memantine in reducing cerebral vasospasm and in ameliorating endothelial dysfunction by restoring endothelial NOS (eNOS) functionality has been demonstrated [115]. nNOS is found predominantly in central and peripheral neurons, having a role in synaptic plasticity, central blood pressure regulation and smooth muscle relaxation. iNOS is a pathogenic factor for several inflammatory conditions, being expressed in cells involved in the cytokine response and associated with septic shock. eNOS, through its presence in endothelial cells, has effects in regulating blood pressure, vascular protection, in reducing atherosclerotic processes and in avoiding apoptosis induced by proinflammatory cytokines. Balancing eNOS and relieving oxidative stress can be done with the help of angiotensin and renin conversion enzyme inhibitors as well as angiotensin receptor blockers [116].

Alveolar dysfunction

Aggression in the alveolar tissue causes severe damage to the alveolar epithelium. Through single-cell ribonucleic acid (RNA)-seq analysis, the role of the development of lung alveolar type I (AT1) cells. AT1 was demonstrated both during the postnatal evolution of the lungs and in alveolar regeneration. This type of alveolar cells is present in 95% of the alveolar surface, ensures the integrity and proper functioning of the air–blood barrier but contributes to maintaining the plasticity of cell development in the process of alveolar regeneration. The presence of insulin-like growth factor-binding protein 2 (IGFBP2) in AT1 cells is a valuable marker, which increases during alveologenesis and in the post-pneumonectomy repair process [117, 118].

Cytokine storm triggers dysfunctional but hyper-aggressive immune mechanisms, with direct destructive action on the alveolar cell. Translational research on animal models has objectified the protective role in the pulmonary alveoli of Memantine against substances with destructive aggression in the alveolar level. Lung damage characterized by pulmonary edema and leukocyte infiltrates was caused by increased cytokines and oxidative stress. By blocking NMDA receptors in the lungs, Memantine has led to a decrease in the inflammatory response and oxidative stress, with a decrease in lung damage. In the animal model, Memantine can stop the inflammatory process in the lungs in mice by inhibiting the release of proinflammatory factors such as TNF-α, IL-6 and IFN-γ [119]. In addition, Memantine can increase the resistance of the alveolar barrier to the destruction of destructive factors (Bleomycin) and prevent the increase of oxidative stress, an important pathogenic factor of the destruction of the alveolar barrier, by reducing the oxidative marker MDA [120].

SARS-CoV-2 aggression on the central nervous system may be associated with increased cytokine storm intensity as the mechanism of activation of microglial structures...
occurs. The cytokine mechanisms are triggered by the activation of M1-type microglia, which trigger the production and high release of proinflammatory cytokines IL-1, IL-6, TNF-α, NO and ROS, to the detriment of neuroprotective M2 microglia, whose activity is related to anti-inflammatory cytokines IL-4, IL-10, IL-13 and transforming growth factor-beta (TGF-β) [93, 104, 121]. The imbalance ratio M1/M2 microglia have an important role in pathogenesis of major psychiatric disorders, such as major depression, schizophrenia or bipolar disorder [122]. At the same time, long-term M1-type microglial activation may associate hippocampal atrophy and disconnection of cognitive structures [123]. For this reason, in the long term, SARS-CoV-2 infection may cause cognitive deficits, which may be a pathogenic mechanism of triggering AD or PD by neurotoxic viral action.

Effectiveness of Memantine and Amantadine in SMI treatment

The positive therapeutic effects of Memantine and Amantadine obtained in the treatment of patients with SMI, are pharmacological arguments to support the possible efficacy of these two psychotropic drugs in the prophylactic use for SARS-CoV-2 infection in this category of patients. Control of psychiatric symptoms may reduce the risk of infection and disease transmission, and on the other hand, reducing the effects of the pathogenic mechanisms of SARS-CoV-2 may decrease cases with a risk of severe evolution or death.

Schizophrenia

The efficacy of Memantine in schizophrenia has been demonstrated in clinical trials in which Memantine has been associated with antipsychotic treatment in patients with chronic disease [124], cognitive deficits [125], predominance of negative symptoms [126, 127], or in patients with positive and negative symptoms [128]. Patient aggression is associated with glutamate hyperactivity, and the use of Memantine in combination therapies has been based on the glutamatergic hypothesis of schizophrenia and the major role played by NMDA receptors [129]. Glutamatergic hyperactivity potentiates oxidative stress, activates ion channels for calcium, sodium, and potassium, triggering excitotoxicity mechanisms that stimulate microglia activation in the brain and peripheral causing a true destructive cytokine storm. Oxidative stress accentuates the mechanisms of neural apoptosis, and in association with cerebral circulatory disorders, promotes the development of atrophy of the hippocampus, cerebral amygdala, and frontal cortex, with the occurrence of residual symptoms of schizophrenia [130].

Under COVID-19 conditions, the severe course of the disease can be explained by the mechanism of cytokine storm that produces neuronal apoptosis followed by cortical atrophies, destruction of the neurovascular and astroglia unit and significant endothelial dysfunction with decreased cerebral vascular perfusion (stroke risk), as well as at the level of the coronary territory (risk of infarction), renal (renal insufficiency) or of the alveolar capillary (alveolar destruction). Treatment with Memantine in combination with antipsychotics, in patients with schizophrenia significantly decreased TNF-α proinflammatory factor and the negative symptoms [131].

In addition to immune mechanisms, the risk of severe evolution can also be correlated with dysautonomia, following drug-induced parkinsonism. If schizophrenia is frequently correlated with a neurodevelopmental etiopathogenesis, dysautonomia may be primary [59]. In addition, it is hypothesized that in patients with schizophrenia who have a history of neurodevelopmental abnormalities or parkinsonism disorders within the neurological soft sign class, prior to any psychotropic therapy, greatly increases the risk of central nervous system symptoms in conditions with SARS-CoV-2.

Dysautonomia in schizophrenia is associated with multiple comorbidities, such as diabetes, cardiometabolic syndrome and obesity, which leads to a significant cardiovascular risk [132]. On the other hand, antipsychotic therapies can induce cardiometabolic syndrome, diabetes, QT changes, but also agranulocytosis and leukopenia [133, 134]. The high level of homocysteine can be considered a marker of negative evolution of neurodegenerative type. In patients with schizophrenia and COVID-19, homocysteine increases coagulability with a risk of thrombosis and leukopenia and agranulocytosis favor secondary bacterial or viral infections, which is why the combination of these two conditions causes a high risk of early mortality.

Depression

Depression has a biological mechanism dominated by hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, with increased cortisol, patients being prone to decreased immunity and multiple somatic complications on an inflammatory background. Cytokine mechanisms are more strongly expressed in bipolar depression. Due to a high rate of incomplete remissions, patients with unipolar or bipolar depression may be considered at risk for SARS-CoV-2. Memantine infection and Ketamine has demonstrated antidepressant effects, by extrasynaptic inhibition of NMDA receptors (Memantine) or by synaptic inhibition of these receptors (Ketamine) [79]. Memantine therapy combined with other antidepressant or anxiolytic medications could have a prophylactic effect in SARS-CoV-2 pandemics. Depression can be a consequence of the social stress associated with the COVID-19 pandemic and especially of the economic losses following the pandemic.

In addition, Memantine has efficacy studies for bipolar disorder [135], depression in bipolar disorder [136], depression in schizophrenia [137] and treatment-resistant depression [138]. This efficacy is correlated with the specific modulatory effect of NMDA receptors and hyper-glutamatergia is involved in the biochemical pathogenesis of these diseases [139].

Ketamine has a strong and rapid antidepressant effect, managing to rebalance the cellular mechanisms of proinflammatory cytokine and endothelial dysfunction, in resistant depression or in depressions with incomplete response [140]. Ketamine also reduced the rate of suicide in cases of treatment-resistant depression [141]. The S(+)-enantiomer of Ketamine (Esketamine) received in 2019 FDA approval for the treatment of resistant depression associated with an oral antidepressant medication [142].
Depressive disorder is an evolutionary risk factor in SARS-CoV-2 infection, due to the presence of dysautonomia that can be triggered by hypercortisolemia induced by HPA axis hyperactivity, which causes overstimulation of the coeruleus locus and massive release of norepinephrine with sympathetic hyperactivity. Dysautonomia may also be due to extrapyramidal phenomena of parkinsonian type induced by mood stabilizers medication, selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) antidepressant, or anti-psychotics with antidepressant effect.

Depression from bipolar type 2 disease causes significant changes in cytokines, while high levels of cytokines especially brain-derived neurotrophic factor (BDNF), IL-2, IL-6, and TNF-α cytokines especially brain-derived neurotrophic factor (BDNF), IL-2, IL-6, and TNF-α induce or amplify depression [143, 144]. The mechanism by which depression promotes the inflammatory process and triggers the cytokine storm is directly related to excess glutamate, which may be corrected by Memantine. Another argument that correlates the cytokine storm with the onset or exacerbation of depression is the significant antidepressant effect of anti-cytokine medication in patients with chronic inflammatory process, an effect demonstrated in a meta-analysis [145].

Depressive disorder may be present in the prodromal stages of AD. Treatment of AD prodromal depression with Memantine and Escitalopram had positive results [146, 147]. In major depressive disorder, treatment with Memantine in combination with Sertraline improved depressive symptoms and had a good safety profile [148]. Depression in the non-motor prodromal stage of PD is dopamine-dependent and does not respond to antidepressant medication, but NMDA antagonists may have benefits in reducing psychiatric symptoms [39]. Therapeutic responses may be obtained with Amanadine [149, 150].

In patients with depression and COVID-19, cytokine storms can be triggered rapidly, which is why proper and early antidepressant treatment is extremely important. At the same time, depression favors prothrombotic status, inflammation and oxidative stress, mechanisms that in the context of SARS-CoV-2 infection induce a severe evolution, with a high risk of death [151]. The connection between the RAS and depression and the presence of ACE2 receptors in the brain should also be considered. Inhibition of RAS activity had positive effects in neurogenesis, with decreased oxidative stress and inflammatory processes [152].

**Alzheimer’s disease**

There are arguments that may support the role of infections in accentuating the neurodegenerative mechanisms of AD since there is an association between HSV infection and apolipoprotein E4 (APOE4) spectrum, especially in patients with cytomegalovirus, but also in patients whose other respiratory infections: influenza A and B, *Chlamydia*, group B streptococcus, *Mycoplasma pneumoniae* [153, 154]. The involvement of multiple infectious factors in the elderly’s cognitive deficit can also be explained by impaired immunity. Respiratory infections can be considered a risk factor for the progression of dementia, and dementia can be a risk factor for the severe course of a lung infection. These aspects are not fully confirmed, being supported by some authors, and denied by others, but certainly, in nursing home care conditions, the mortality of patients with AD and lung infections is high [155, 156].

Astrocytes have a major role in triggering the neurodegenerative mechanisms in AD and PD [157]. Astrocytes influence the modeling of brain damage, by increasing the release of glutamate, GABA, and inflammatory factors, as well as by astrogliosis with the formation of glial scars. Elevated levels of cytokines responsible for the neuroinflammatory response have been identified in the brain affected by AD, for IFN-γ, IL-1β, TNF-α, IL-6 and TGF-β. Cellular stressors increase the number of reactive astrocytes that amplify Aβ synthesis. This mechanism is correlated with the innate immune response, and it has been shown that Aβ has an anti-inflammatory cytokine role in the brain [158]. 

The action of Aβ as AMP has been explained by the ability to form extracellular neurofibrils that can encompass viral pathogens. Aβ overproduction has been associated with high resistance to viral or bacterial infections, while blocking Aβ synthesis in Alzheimer’s patients has been correlated with high infection rates [160]. Two of the Aβ isoforms, the 42-residue Aβ42 and the 40-residue Aβ40, have an antiviral effect for enveloped viruses with cerebral affinity such as HSV-1, which may explain the infectious cause of amyloid plaque formation, with a risk of AD progression [161].

It has been shown in vitro that Aβ42 and Aβ40 inhibited IAV replication types H3N2 and H1N1, by blocking the entry of viruses into epithelial cells, favoring entry into neutrophils, inhibiting the replication of viral proteins in monocytes, and decreased virus-induced IL-6 synthesis [162]. Overproduction of Aβ has also been shown in HIV infection by the accumulation of Aβ plaques in plaques or intraneuronal in the frontal cortex [163].

Oxidative stress and neuroinflammatory processes triggered by cytokine activation may have an excitotoxic effect through the action of quinolinic acid from tryptophan metabolism. The protective effect of Memantine has been demonstrated in hippocampal cell cultures from Wistar rats by reducing the apoptosis of neurons and astrocytes due to the antagonistic effect of NMDA receptors [164]. Memantine may have antiparkinsonian effects because it prevents the in vivo and in vitro death of brain neurons damaged by excitatory amino acids. These acids are involved in triggering neurodegenerative processes in parkinsonism and dementia in AIDS. Memantine in rats prevented the destruction of retinal ganglion cells triggered by NMDA receptor activation [165].

A major role in the rapid evolution of cognitive impairment in AD and PD is played by cerebral vascular dysfunction. The presence of symptoms of dysautonomia and especially orthostatic hypotension by decreasing cerebral perfusion, accentuates cognitive impairment. The use of hypotensive medication in the elderly with dementia must be personalized and correlated with some pharmacological mechanisms, because the ROS system is an important pathogenic mechanism in dementia in AD and PD [166, 167].
Vulnerability of patients with SMI to SARS-CoV-2 infection

Considering the high incidence of major mental disorders and their association with multiple comorbidities, correlated with the inability of patients to self-care, the risk of SARS-CoV-2 infection is amplified, as well as severe evolution. Schizophrenia correlates with cognitive deficit, major impairment of self-care and non-compliance with hygiene measures, social distancing, and isolation. Depressive disorders worsen under conditions of social stress and social isolation and are associated with a low immune status and a high potential for increased mechanisms of cytokine activation. Anxiety is amplified by the implementation of restrictive measures related to the pandemic and causes biochemical changes related to hyperactivation of the HPA axis, with increasing levels of endogenous cortisol and proinflammatory cytokines. Patients diagnosed with AD, vascular dementia or other forms of dementia are a major risk category for SARS-CoV-2 infection due to age, cognitive deficit, comorbidities, and dependence on specialized care.

Due to these reasons, Memantine or Amantadine therapy, possibly combined with melatonin for sleep disorders or Valacyclovir for viral infection, can decrease the incidence of contamination by improving mental status, increasing self-care but also by prophylaxis of comorbid events with unfavorable evolution in case of infection with SARS-CoV-2. The use of Memantine could be a means of preventing the negative evolution in patients positive for SARS-CoV-2, asymptomatic or with minimal symptoms, who have a history of depressive episodes or who have depressive anxiety in conditions of pandemic reactive stress. The use of Memantine could also be facilitated by the low rate of side effects and very good tolerance. Short-term administration (14–21 days) in these categories of patients, especially those in isolation or quarantine, could be beneficial.

Amantadine could be used in combination with influenza A infections with SARS-CoV-2. Recognition of the patient population with SMI and chronic evolution as a risk group for SARS-CoV-2 infection and the major potential for adverse outcome should become a priority of mental health strategies in the COVID-19 pandemic. At the same time, patients with SMI can also be vectors of transmission and maintenance of the pandemic condition. Their inclusion in a program for the prevention of SARS-CoV-2 infection, as well as the prevention of the major risk of unfavorable evolution, may be a second major priority of public health strategies. The use of Memantine and Amantadine in these prophylaxis programs can be confirmed in further studies or by repeated testing of the patient population with hospitalized mental illness and at risk of SARS-CoV-2 infection.

Prophylactic or therapeutic recommendations can be made based on the effectiveness of Memantine in schizophrenia, elderly depression and bipolar depression, anxiety and treatment-resistant depression, and cognitive impairment in AD and other forms of dementia. The administration of Memantine can be done during the quarantine or isolation period and continued during the persistence of the risk of contamination. The effectiveness of these recommendations can be confirmed or refuted by further studies or by repeated testing of the patient population with SMI and the risk of SARS-CoV-2. The possible specific antiviral efficacy in COVID-19 of early Memantine therapy in the asymptomatic phase may be questioned, especially in patients with decreased olfactory acuity and generalized hyperalgesia syndrome. Olfactory decrease (dependent on increased glutamate activity) and odor discrimination (related to dopamine deficiency) are non-motor signs that may precede the onset of PD. The presence since the asymptomatic stage of SARS-CoV-2 infection of multiple pain manifestations (myalgia, fibromyalgia) and loss of smell and taste, suggests the neuroinvasive potential of the virus, a tendency that can be prevented or controlled by Memantine.

Conclusions

Memantine and Amantadine represent, from the point of view of the clinical psychopharmacologists, a therapeutic alternative in COVID-19 associated with major psychiatric pathology. Due to comorbidities, patients with chronic SMI have an increased and early mortality. Many cases of sudden death can be explained by dysfunction of the autonomic system, which causes cardiovascular and cerebrovascular changes and a complex symptomatology that includes constipation, visual deficit, visual hallucinations, sleep disorders. For all the evolutionary risk mechanisms of SARS-CoV-2 infection detailed in this material, there are arguments that make the prophylactic administration of Memantine and Amantadine appropriate. Memantine can provide protection for olfactory neuronal circuits, decrease the aggressiveness of NMDA receptor hyperactivity, alveolar protection, and regulate cytokine mechanisms. Amantadine can alleviate viral myalgias and may be indicated in those who do not differentiate odor by dopamine deficiency. Future studies are needed to confirm or infirm the antiviral properties of the two psychotropic drugs in the SARS-CoV-2 virus. In terms of patient safety, Memantine is considered the NMDA inhibitor with the best clinical tolerance. The recognized action of Amantadine in influenza infection correlated with the antiviral effects of Memantine could be an argument for the association of Amantadine with Memantine, which may have a reciprocal potentiation for antiviral prophylaxis simultaneously with the control of neurological and psychiatric symptoms in patients with SMI.

Conflict of interests

The authors declare that they have no conflict of interests.

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This paper was written in memory of Academician Nicolae Cajal (1919–2004), an outstanding personality of world virology.

References


[56] Ileana Marinescu et al.


Bár KJ. Cardiac autonomic dysfunction in patients with schizophrenia and their healthy relatives – a small review. Front Neurol, 2015, 6:139. https://doi.org/10.3389/fneur.2015.00139 PMID: 26157417 PMCID: PMC4478389


Bahr R, Lopez A, Rey JA. Intranasal Esketamine (Spravato™) for use in treatment-resistant depression in conjunction with an oral antidepressant. P T, 2019, 44(6):340–375. PMID: 31168888 PMCID: PMC6534172


Bourdage K, Garneau H, Giroux G, Le Page AY, Bocti C, Dupuis G, Frost EH, Fülöp T Jr. β-Amyloid peptides display...


Corresponding authors
Dragoș Marinescu, Professor, MD, PhD, Doctoral School, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Dolj County, Romania; Phone +40251–522 458, e-mail: marinescu_psy@yahoo.com

Ion Cristian Efrem, Assistant Professor, MD, PhD, Department of Internal Medicine, Faculty of Dental Medicine, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Dolj County, Romania; Phone +40785–216 697, e-mail: ic_efrem@yahoo.com

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