Review Article

Depressive Disorders and Incidence of COVID-19: Is There a Correlation and Management Interference?

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**ABSTRACT**

Corona virus Disease-2019 is a new strain of Coronaviruses (COVID-19) causing an infection which has rapidly spread all over the Globe, where the primary pathways of infection spreading reported to be through large respiratory droplets and the disease severity has varied from mild self-limiting flu like illness to acute pneumonia, respiratory collapse and death. On the other hand, depression is a disease that could be progress to a life-threatening condition that affects globally hundreds of millions of people. The aim of this review is desired to investigate and find a correlation between depressive disorders and the incidence of COVID-19, where, pathogeneses of depressive disorder and its effect on the immunity system was addressed, besides the impact of depression on individual food intake and its complications regarding weight gain, insulin resistance, and immune system disruption was also discussed which by turn might increase the risk for infection with COVID-19. Finally, the possible drug-drug interactions between drugs included in management protocols of both depressive disorder including antidepressants and anxiolytics and COVID-19 with possible proposed alternatives.

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**Introduction**

Corona virus Disease-2019 is a new strain of Coronaviruses caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) [1]. Nowadays, COVID-19 infection has rapidly spread all over the Globe, where the primary pathways of infection were reported to be through large respiratory droplets. Also, SARS-CoV-2 has been found in feces and urine of affected individuals [2]. Besides, the disease severity has varied from mild self-limiting flu-like illness to acute pneumonia, respiratory collapse and death [3]. There are geographical variations in death rate estimates which are subject to change as more data are becoming available.

There were 19,462,112 confirmed cases of COVID-19 worldwide with a death rate of 3.7% according to the situation report of World Health Organization on August 9, 2020 [4]. Africa showed 884,990 confirmed cases with a mortality rate of 1.85%, Europe showed a 3,562,774 confirmed cases with a mortality rate of 6.07%, USA showed a 10,447,261 confirmed cases with a mortality rate of 3.68% till 9th August 2020 [4]. The understanding of epidemiological characteristics of this infection is evolving on a daily basis as the disease is spreading to different parts of the globe. Development of a critical disease with septic shock, respiratory or multi-organ failure may occur in a minor number of patients, 80% of the cases show minor symptoms, 14% have severe symptoms, and 5% develop serious or critical illness [5, 6].

Depression is a disease that could be progress to a life-threatening condition that affects globally hundreds of millions of people. The age group incidence is wide which means that it can occur at any age ranged from early childhood to geriatrics. Its society cost is tremendous, as depressive disorder causes severe life distress and life disruption and, can lead to death if left without treatment. Depression prevalence globally is about 20% in the entire population women to men ratio of about 5:2. The assumption that about 1/3 of depressed patients are not well due to incomprehension, but it could be attributed to the fact that depression symptoms may be not well differentiated from those of daily routine experience [7]. Even so, a considerable percentage of the patients become chronic patients, 12%

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and 7% of patients are still suffer from depression after 5 and 10 years of follow-up respectively [8].

In this review, an investigation of a correlation between depressive disorders and the incidence of COVID-19, the effect of depressive disorders on immune system disruption, food intake and its complications regarding weight gain, and insulin resistance. The presence of other comorbid conditions in mentally ill patients that exacerbate COVID-19 infection and worsen clinical outcomes. Moreover, detection of the possible drug-drug interactions between the repurposed drugs used for treatment of COVID-19 and drugs used for management of mental illness disorders. Also, we will highlight the proposed drug alternatives and therapeutic regimens modifications for management of COVID-19 in order to avoid potential drug-drug interaction and obtain a better therapeutic outcome.

Discussion

I How Do Depressive Disorders Progress and Its Effect on Body Systems?

The main depression symptoms are attributed to brain functional deficiency of monoamine neurotransmitters like norepinephrine (NE), 5-HT, and/or dopamine (DA), in contrast with the fact that mania is caused by functional excess of monoamines at critical synapses in the brain [9]. It is fully understood that monoaminergic systems are the main controller for many behaviours, such as mood, vigilance, motivation, fatigue, and psychomotor agitation or retardation. Variations in synthesis, retention, or discharge of neurotransmitters, and disrupted sensitivity of their receptors can result in an abnormal functional and behavioural changes of either depression or mania [10]. Chronic stress acts as a triggering factor for anxiety and depressive disorders, which in turn lead to an elevated concentration of pro-inflammatory cytokines and glucocorticoids, that contribute to the behavioural changes associated with depression [11]. The function of immune-modulators and immune-transmitters was carefully investigated, especially pro-inflammatory and anti-inflammatory cytokines and it was reported that interleukin-6 (IL-6) which is a pro-inflammatory cytokine was elevated in the blood of individuals suffering from depressive disorders [11]. As per recent studies in major depression, it was concluded that only the basal blood levels of IL-6 and TNF were remarkably elevated [11].

Number of studies have showed the existence of a correlation between depression and food intake, and intense food cravings that occurs in women with premenstrual syndrome. As individuals become depressed a remarkable increase in the percent of individuals that have a preference for eating sweet, carbohydrate and fat-rich diets. This led to high energy intake from sweets, and carbohydrates in depressed individuals compared to non-depressed ones. The increased intake sweets, and carbohydrates are aimed to improve mood and seek relief from depression symptoms [12]. The final result of such food craving behaviour is an overweight individual that may progress to obesity. One of main complications of obesity is altered immune responses, and progression of insulin resistance and Type 2 Diabetes mellitus.

Besides, high fat diet leads to obesity-induced insulin resistance, weight gain, visceral adipose tissue mass, high glucose, it also leads to elevated TNFα and IL-6 [13]. Fat cells are capable of producing IL-6 and macrophages within fatty tissues and induce inflammation, and so, care should be taken upon interpretation of elevated levels of C-reactive protein (CRP) and IL-6 in obese patients [14]. Regulatory T cells (Treg cells) have a main functional contribution in managing the immunity system and thus help in prevention of autoimmune disease. Treg cell number in visceral adipose tissue exhibits a substantial decrease upon development of obesity [13]. Postulations mentioned that antidepressants act on neurotransmitter receptors in order to effectively treat depressive disorders. There is an evidence proposing that different therapeutic classes of antidepressant drugs act by immune-modulation and cause reduction of pro-inflammatory cytokines like interferon-gamma and tumor necrosis factor-alpha (TNF α) and increase of anti-inflammatory cytokines like (interleukin-10) [15].

It is worthy to mention that diabetes and uncontrolled blood glucose levels were reported as a significant predictive factor of severity and mortality of infected patients with different viral infections, including the 2009 influenza A virus (H1N1), SARS-CoV and MERS-CoV [16]. Reports from China and Italy showed that older patients suffering from comorbidities like diabetes were at higher risk for severe SARS-CoV-2 and mortality [16].

Moreover, an increased synthesis of glycosylation end products (AGEs) and pro-inflammatory cytokines, oxidative stress, in addition to stimulating the production of adhesion molecules that mediate tissue inflammation are promoted by insulin resistance and hyperglycaemia [17, 18]. This inflammatory process may compose the underlying mechanism that leads to a higher propensity to infections, with worse outcomes thereof in patients with diabetes [17]. Also, Neutrophil dysfunction, reduced T cell response and disordered humoral immunity are contributory [19].

II Relation between Mental Illness and COVID-19

Severe mental illness is often used to describe schizophrenia and bipolar disorder, but it can be more broadly applied to any mental illness that causes severe functional impairment. People living with mental illness are more vulnerable to SARS-CoV-2 infection. The consequences of the severe and chronic nature of mental illness and its associated social drawbacks lead many people with severe mental illness live in a private, and crowded facilities such as psychiatry inpatient units, supported housing, homeless shelters, hostels, and prisons. Shared spaces and, over-crowding in such environments are main factors for increased risk of outbreaks of infectious diseases, including COVID-19 [20].

Some people suffering from psychiatric disorders do not follow infection control measures, as they are suffering of cognitive impairment and poor risk awareness which will lead to further increase in SARS-CoV-2 infection risk [21]. Also, people living with severe mental illness may be highly susceptible for bad outcomes from SARS-CoV-2 compared to healthy individuals, where high mortality rates are associated with those severely infected cases with accompanied by complications such as acute respiratory distress syndrome [22]. Severe mental illness population are highly susceptible for severe infections, as a result of increased rates of comorbid conditions like obesity, cardiovascular disease and chronic obstructive pulmonary disease which are found in people with severe mental illness [23].
Above 70% of all schizophrenic patients might have one or more comorbidities as type 2 diabetes mellitus, chronic pulmonary disease, elevated blood pressure and coronary heart disease. About 50-90% of schizophrenic patients are estimated to be heavy smokers which is another potential risk factor for bad respiratory prognosis. Upon hospitalization for pulmonary conditions, schizophrenic patients have higher rates of ICU admissions, acute respiratory collapse, IMV, and in-hospital death than other patients. Overall, schizophrenia would be considered as one known risk factor for COVID-19. Upon hospitalization, the probability of worse clinical outcomes is high and should be considered [24].

Life-style related risk factors like smoking, obesity and inactivity provoke medical conditions leading to an increased mortality and morbidity amongst patients with mental disorders and it was estimated that a 13-30 year shortening in life span of people with severe mental illness [25]. Hospitalized patients with schizophrenia, bipolar disorders, depression, anxiety disorders or autism are highly vulnerable for pneumococcal infection. These patients often have a poorer ability to defend themselves against infections. This was shown by the epidemiological associations between psychiatric disorders and a very large number of infections as toxoplasmosis and herpes in the course of psychiatric pathologies. Comorbidities which are often insufficiently screened and treated, are a main responsible factor for the decrease in life expectancy of 10 to 15 years of patients with chronic psychiatric disorders compared to the general population [26].

III Treatment Options for COVID-19 and Depression

Nowadays, there is no vaccine or specific therapeutic drugs that target SARS-CoV-2. Healthcare professionals are facing a major challenge to decide what potential therapeutic choices are suitable for preventing and treating severe cases of COVID-19 patients, until we have a specific drug or vaccine for SARS-CoV-2, repurposed drugs have been used in the treatment of COVID-19 patients. These repurposed drugs have been previously approved by the US FDA for treatment of other indications [27]. Thus, special care should be taken in consideration upon managing SARS-CoV-2 infected patients specially in those who are suffering from depressive, mental disorders and other comorbidities that in need for chronic therapeutic drug treatment in order to avoid probable drug interactions and fatal adverse events.

IV Incidence of Drug Interactions in Management Protocols for Both Mental and Depressive Disorders and COVID-19

The interactions between psychotropic and COVID-19 drugs have two pathways: The first one is a pharmacokinetic drug-drug interaction, where drug change the disposition rate of a co-administered agent and the second one is intensifying of drugs side effects [28]. Cytochrome P450 plays a principle role in the metabolic fate of medications and their interactions, like hepatic CYP 2D6, 1A2, 3A4, 2C19 which are responsible for tricyclic antidepressants metabolism [29]. Most first and second-generation neuroleptics metabolized by the cytochrome P450 system mainly include 2D6, 1A2, and 3A4 [30]. On the other hand, some Selective Serotonin Reuptake Inhibitors (SSRIs) are cytochrome P450 inhibitors and can result in drug-drug interactions by changing the blood concentration of the drugs activated or metabolized by these enzymes [31]. Consequently, psychotropic drug hepatic metabolism extent and their ability to make a significant change in cytochrome P450 activity are the main factors in determining pharmacokinetic interactions when they are used with other medications in COVID-19 treatment.

i Antidepressants

a Selective Serotonin Reuptake Inhibitors

Fluoxetine and Nor-fluoxetine (its active metabolite) inhibit CYP2D6 (strong), CYP2C9 (moderate), CYP2C19 (weak to moderate), CYP3A4 (weak to moderate), and CYP1A2 (weak). Thus, Fluoxetine and its metabolites increase the area under the curve (AUC) of ritonavir by up to 19% through inhibiting CYP2D6 and CYP3A4 (especially CYP2D6) without significant change in other kinetic parameters of ritonavir [32]. Fluoxetine as a CYP2D6 inhibitor (strong) may decrease the metabolism of CYP2D6 substrates like chloroquine and Hydroxychloroquine [32].

Paroxetine is metabolized mainly by CYP2D6 (high affinity) and CYP3A4 (low affinity) and partially by CYP1A2, CYP2C19, and CYP3A5. Its protein binding is 95% and can inhibit the CYP2D6 enzyme. Manon et al., reported that co-administration of paroxetine (20 mg/d) with fosamprenavir and ritonavir (700 mg/100 mg twice per day) for 10 days causes a decrease of paroxetine levels by 55% compared to its administration alone because of protein binding displacement [32].

Medications like Citalopram / Escitalopram and Chloroquine / Hydroxychloroquine are known for causing cardiac complications (such as QTc prolongation), where the possibility of this complication seemed additive and can be aggravated by old age, cardiac disease, electrolyte disturbances (hypokalemia, hypomagnesemia), and bradycardia [32]. Sertraline may enhance the risk of hypoglycemia when co-administered with agents that have blood glucose effects like chloroquine/Hydroxychloroquine [32].

b Serotonin-Norepinephrine Reuptake Inhibitors

Venlafaxine is metabolized mainly by CYP2D6 and CYP3A4 and partially by CYP2C19. It does not affect (inhibit or induce) CYP450 microsomal. Venlafaxine may cause arrhythmia associated with QTc prolongation in high-risk people [33]. A clinical study was conducted to investigate 21 healthy individuals on venlafaxine in the presence of ketoconazole, which is a potent CYP3A4 inhibitor, where the results showed that levels of venlafaxine increased upon co-administration of ketoconazole. Also, ritonavir has a strong inhibitory effect on CYP3A4 which may elevate venlafaxine level [33].

Besides, chloroquine may affect the concentration of duloxetine by inhibiting CYP2D6 [34]. Despite the inhibitory effect on CYP2D6 and induced CYP1A2 by ritonavir, concomitant use of duloxetine with ritonavir is allowed [35].

c Serotonin Modulators

The metabolism of trazodone in humans is mediated through CYP3A4 and CYP2D6. Trazodone peak plasma concentration and the AUC significantly increase 34% and 137%, respectively in concomitant use with ritonavir (a CYP3A4 inhibitor). Trazodone elimination half-life was prolonged 122% and oral clearance decreased 52% by ritonavir.
Additive effects for example; some potent CYP450 3A4 inhibitors like ritonavir, chloroquine Hydroxychloroquine may result in QTc prolongation when used with trazodone [36].

d Norepinephrine-Serotonin Modulator

Mirtazapine is metabolized by CYP1A2, CYP3A4, and CYP2D6 [29]. Clinically significant interactions between mirtazapine and ritonavir boosted lopinavir have not been reported. No interaction has been found between mirtazapine and Hydroxychloroquine, chloroquine, ribavirin and interferons [32].

e Norepinephrine-Dopamine Reuptake Inhibitor

Bupropion is metabolized by CYP2B6 isoenzyme, and thus, CYP2B6 inducers as ritonavir may decrease its serum concentration. In a clinical trial phase 1 performed on 12 subjects administration of ritonavir and ropinavir (400 mg/100 mg two times daily) resulted in 57% reduction in bupropion AUC. In another study, the results showed that high dose (600 mg two times daily) and low dose (100 mg twice daily) of ritonavir resulted in 67% and 22% lowering in bupropion serum concentrations, respectively [32].

f Tricyclic Antidepressants

These drugs are metabolized through the hepatic CYP Iso-enzymes, mainly CYP2D6, CYP1A2, CYP3A4, and CYP1C19. Since protease inhibitors such as ritonavir can inhibit CYP2D6 and CYP3A4; thus, serum concentration of TCAs may increase. A clinical study showed the effect of low-dose ritonavir on the activity of CYP450, where the administration of 100 mg twice per day of ritonavir resulted in a 26% increase in the AUC of desipramine [32]. Dose reduction is not necessary and only the patient should be monitored for toxic effects of TCAs [37].

g Monoamine Oxidase Inhibitors (MAOIs)

Interaction has been reported between MAOIs and Hydroxychloroquine causing hypoglycemic effect; thus, concomitant use of chloroquine with MAOIs may cause hypoglycemia [38, 39].

h Newer Antidepressants

Lopinavir and ritonavir can potentially increase the level of both vortioxetine and vilazodone by affecting CYP2D6 and CYP3A4 respectively, and proposed suggestion is to make a 50% reduction in vilazodone dose or to use an alternative drug [40, 41].

i Olanzapine

Ritonavir may lead to a reduction in olanzapine concentration as it induces CYP1A2 and or glucuronosyltransferase-mediated metabolic pathways which are responsible for olanzapine metabolism. A clinical study conducted on 14 healthy subjects showed that upon tapering up ritonavir dose gradually olanzapine Cmax, AUC, and half-life reduced by 40%, 53% and 50%, respectively [42].

j Quetiapine

Ritonavir is a CYP3A4 inhibitor causing delay in quetiapine metabolism with a resulting outcome of an increase in quetiapine serum concentration and high incidence of adverse reactions, therefore, reduction of the dose of quetiapine with close monitoring is highly recommended [42].

k Risperidone

Ritonavir is a strong inhibitor for both CYP2D6 and CYP3A4 which are the main sites for risperidone metabolism, and studies have shown that co-administration of these drugs increases the side effects of risperidone [43].

ii Anxiolytics

a Benzodiazepines

A psychotropic medications with sedative, hypnotic, and anxiolytic effects that are metabolized via CYP450 enzymes particularly subtype CYP3A4 in the liver [44]. Therefore, medications with CYP3A4 inhibitory effect like (ritonavir/lopinavir) is a strong CYP3A4 inhibitor which may decrease the metabolism of a CYP3A4 substrate as chlor Diazepoxide, diazepam, clonazepam, flurazepam, triazolam, midazolam, and alprazolam. Patient monitoring should be tightly close, using an alternative agent with lower interaction as lorazepam, oxazepam, and temazepam or dose adjustment should be considered [45].

b Non-Benzodiazepine

Non-benzodiazepines are another sedative, hypnotic, and anxiolytics drugs, including zolpidem, eszopiclone, zaleplon, and ramelteon that is extensively metabolized via the CYP450 system, where there is a potential drug-drug interaction [46]. Despite of which, no interaction has been reported between anxiolytics and ribavirin, hydroxychloroquine, and chloroquine [32].

V Prophylaxis and treatment of COVID-19

Zinc nanoparticles were shown to have inhibitory effects on H1N1 viral load, though their effect in COVID-19 is unknown and untested [47]. Synergistic effect can be attained by co-administering of Zn with the standard antiviral therapeutic regimes. This was revealed in patients with Hepatitis C virus, Human Immunodeficiency Virus, and SARS-CoV-1. Zn may also aid in protection or stabilization of cellular membrane which prevent viral cell entry. Viral replication may be inhibited by Zn in rhinoviruses, Hepatitis C virus, and influenza virus, and reduce the activity of RNA- synthesis of nidoviruses, for which SARS-CoV-2 belongs [48].

Vitamin C supplement has some role in prevention of pneumonia and its effect on COVID-19 needs evaluation [49]. As per mentioned in literature review that an intravenous Vitamin C decreases the cytokine storm in the end stage of Covid-19 infection and, as other antioxidants, is extremely good agent for acute respiratory distress syndrome, besides, the known safety and effectiveness of high doses of IV Vitamin C [50].
Probiotics means a living micro-organisms that allow a health benefit to the host, including the gastrointestinal tract, when administered in a suitable amount which stimulate immune response by increasing the antibody production [51, 52].

Sofosbuvir is an approved direct antiviral therapy for HCV and is effective against other types of positive-strand RNA viruses. Coronavirus viruses are a family of positive-strand RNA viruses with conserved polymerase, so SARS-CoV-2 RdRP is most probably to be effectively inhibited by Sofosbuvir. It is safe and well tolerated at 400 mg daily in a 24-week therapeutic regimen. Besides, Sofosbuvir active metabolite shows a high degree of intracellular stability which leads to a proposal that SARS-CoV-2 infection could also likely to be cured by Sofosbuvir. Moreover, it was reported that Sofosbuvir does not affect the main cytochrome metabolizing enzymes as cytochrome P450 system [53].

Regarding Chloroquine/Hydroxychloroquine, hypoglycemia is an important specific safety concern that should be taken in consideration which is a known adverse effect of chloroquine/Hydroxychloroquine treatment, where, the suggested interaction mechanisms for CQ/HQC are reduced intra-cellular insulin degradation, an increase in glucose transport, an increase in release of insulin and enhanced insulin sensitivity [36, 54]. CQ/HQC might cause prolonged QTc and thus electrocardiography should be done regularly before starting administration of these drugs [55].

Ribavirin is a guanosine analog which act by interfering with the replication of RNA and DNA viruses [56]. The usage of ribavirin in management of COVID-19 is beneficial for several reasons as having a broad activity toward conventional and novel virus of DNA and RNA types, multiple mechanisms of direct anti-viral action, well-known safety and tolerability, accessible, and affordable [57]. In vitro studies showed that ribavirin is not a substrate of CYP450 enzymes which means that occurrence of drug-drug interaction is minimum [58].

Conclusion

From the previously mentioned facts concerning pathogenesis, management and prevalence of both depressive disorders and COVID-19 it can be concluded that;

i. Patients with serious mental illness and depressive disorders are more vulnerable to COVID-19 infection with worsening of disease condition which can be contributed to several factors as impaired cognitive functions followed by poor awareness and non-compliance with infection control measures. Moreover, food craving is also one of the contributing factors leading to an obese depressed patient with insulin resistance and type 2 diabetes mellitus contributing to an increase in risk of incidence and severity of COVID-19 infection.

ii. Immunity system is altered by depression leading to an increase in blood pro-inflammatory cytokine levels like interleukin-6 and TNF which consequently favors cytokine storm in case of acute respiratory distress syndrome causing failure in management of critical cases with higher mortality rates, thus depression might be on the top of serious risk factors of COVID-19.

iii. The incidence and probabilities of drug-drug interactions between antidepressant and COVID-19 medications is highly significant and thus affecting negatively the management and therapeutic outcome of both diseases. Interactions include pharmacokinetic interactions are based on the induction or inhibition of hepatic CYP450 enzymes, while other interactions are related to pharmacodynamic interactions.

iv. The aforementioned antidepressants and anxiolytic drug classes in the review seem to be an ideal choice for administration with COVID-19 therapeutic agents used in management of COVID-19 depressed patients with some precautions and dose adjustment to be considered in some cases. Most interactions are related to SSRIs, SNRIs, and Serotonin modulators, Norepinephrine-serotonin modulator, Norepinephrine-dopamine reuptake inhibitor, Tricyclic antidepressants, Monoamine Oxidase Inhibitors (MAOIs) which can be resolved by dose modification of an alternative drug choice.

v. Different antiviral drugs are CYP450 inhibitors / inducers or substrates, like atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, lopinavir/ritonavir which may show a potential drug interaction with SSRS, SNRIs, and Serotonin modulators, Norepinephrine-serotonin modulator, Norepinephrine-dopamine reuptake inhibitor, Tricyclic antidepressants, Monoamine Oxidase Inhibitors (MAOIs) upon administration in COVID-19 management. Thus, Sofosbuvir, Favipiravir, Oseltamivir, Remdesivir, and Ribavirin are considered a clinically accepted alternative for the previous antiviral agents with almost no or minimal drug interaction.

vi. Chloroquine and Hydroxychloroquine for management of COVID-19 are to be avoided in depressed patients on Citalopram or Escitalopram to avoid anticipated QTc prolongation and possible cardiac complications.

vii. Moreover, hypoglycemia is a known adverse effect for Chloroquine/Hydroxychloroquine and should be careful upon concomitantly administered with MAOIs, or Sertraline in depressed patients with comorbid diabetic conditions.

viii. Finally, Intravenous Vitamin-C and/or Tocilizumab can be applied for reduction of Cytokine storm in case of ARDS instead of using CQ/HQC.

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