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DRUG INTERACTIONS BETWEEN COVID-19 AND PSYCHIATRIC MEDICATIONS: A MINI REVIEW

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Abstract

Coronavirus disease 2019 (COVID-19) has become a pandemic with 8.708.000 confirmed cases and, 461.715 death in the world until 21 June 2020. The SARS-CoV-2 virus which is an enveloped and single-stranded RNA virus belonging to Coronaviridea family causes multiple organ systems diseases such as respiratory, gastrointestinal, hepatic and neurological tracts in humans and, animals. With the rapid and global spread of COVID-19, the scientific authorities have developed treatment algorithms for COVID-19. Besides the supportive care, chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir, tocilizumab, azithromycin, vitamin C, Convalescent plasma therapy are frequently used off-label to treat COVID-19. For severe COVID-19 cases, US Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) Remdesivir, which is the first drug to earn the title. COVID-19 treatment may cause many side effects and drug interactions. Psychiatric diseases are also chronic diseases and psychiatric drugs may have severe interactions with COVID-19 medications. Drug interactions with psychiatric medication and neuropsychiatric side effects should be considered within the action mechanism of COVID-19 treatments. Thus, In this review, we aimed to elucidate the interactions of COVID-19 medications with the antidepressants, antipsychotics and, the other psychotropic drugs that have been frequently used in psychiatric diseases. Chloroquine, hydroxychloroquine, azithromycin, ribavirin, lopinavir/ritonavir have interactions with psychiatric medications such as antidepressants, antipsychotics, anticonvulsants and, anxiolytics in terms of QTc interval prolongation, hepatotoxicity, myelosuppression, increased or decreased concentration of medications. Remdesivir has lower interactions with most of the psychiatric drugs except St John's Wort and some anticonvulsants. However, favipiravir is considered as the COVID-19 medication which has lower interaction and side effects in combination with psychiatric medication. The use of tocilizumab is also safe with most of the psychiatric drugs and has a positive effect on depressive symptoms, although there is a risk of hepatotoxicity.

Keywords: COVID-19, treatment, pschotropic drugs, drug interactions, psychiatric diseasest

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1. Introduction

In December 2019, Coronavirus Disease-2019 (COVID-19) was first identified in Wuhan city, China. This disease was caused by a novel coronavirus was named with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This virus had not been previously identified in humans before. Since December 2019, COVID-19 has become a severe risk factor for global health. In March 2020, due to a rapid increase in the number of cases outside China WHO declared COVID-19 a pandemic (Li et al., 2020).

The SARS-CoV-2 virus which is an enveloped and single-stranded RNA virus belonging to Coronaviridea family causes multiple organ systems diseases such as respiratory, gastrointestinal, hepatic and neurological tracts in humans and, animals. The symptoms of COVID-19 can range from asymptomatic clinical features to severe symptoms (Agrawal et al., 2020).

With the rapid and global spread of COVID-19, the scientific authorities have developed treatment algorithms for COVID-19. The treatment algorithms of COVID-19 are composed of the medications that have been used in previous pandemics and the medications that have been thought potentially effective for COVID-19. For severe COVID-19 cases, US Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) Remdesivir, which is the first drug to earn the title. However, numerous medication like chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir, tocilizumab, azithromycin, vitamin C, Convalescent plasma therapy are frequently used off-label to treat COVID-19 (Kalil, 2020).

Multiple organ systems can be affected by COVID-19 and, it also causes psychiatric conditions. It has been reported that COVID-19 causes psychiatric disorders such as panic attacks, anxiety, depression, insomnia in especially patients and health care profesionals (Agrawal et al., 2020); Nguyen et al., 2020); Li et al., 2020). Since COVID-19 medications have possible side effects and affects multiple organs, psychiatrists should be aware of the mechanism of action of COVID-19 treatments, neuropsychiatric side effects and potential drug interactions with psychiatric drugs. In this review, we aimed to elucidate the interactions of COVID-19 medications with the antidepressants, antipsychotics and the other psychotropic drugs that have been frequently used in psychiatric diseases.

2. Chloroquine and Hydroxychloroquine

Chloroquine and Hydroxychloroquine are antimalarial drugs and have also been used for various rheumatic diseases such as systemic lupus erythematosus and, rheumatoid arthritis. Besides the antimalarial effects, these two drugs have immune-modulating effects as well (Schrezenmeier & Dörner, 2020).

A synthetic form of quinine, Chloroquine is used for the treatment and prophylaxis of malaria, inhibits glutamate-induced death of a neuronal cell by reducing reactive oxygen species through the sigma-1 receptor. Thus, using chloroquine as a neuroprotector against oxidative stress has been suggested (Hirata et al., 2011). The hydroxychloroquine is frequently used in inflammatory disorders. Both chloroquine and hydroxychloroquine have been suggested as a possible treatment for COVID-19 due to their immune-modulating and anti-inflammatory effects, antiviral effects by interference with virus-receptor binding (Colson et al., 2020).

Antidepressants, antihistamines, antipsychotics and, verapamil were used to investigate the increasing in vitro susceptibility of chloroquine in several studies (Gerena et al., 1992);(Safa, 1988);(Basco & Le Bras, 1992). In a study that investigated the role of antidepressants in reversing chloroquine resistance, Citalopram which is a selective serotonin reuptake blocker, was found the most effective to reversing the chloroquine resistance among amitriptyline, oxaprotiline and, nomifensine (Taylor et al., 2000). However, in another study that the pharmacokinetic interaction between chloroquine and imipramine was investigated, no significant change was found in plasma concentrations of chloroquine and its pharmacokinetic parameters when imipramine was coadministered with chloroquine (Onyeji et al., 1993).

Similarly, in another study chloroquine and chlorpromazine were found to inhibit Crimean-Congo Hemorrhagic Fever virus (CCHFV) replication in vitro. Moreover, it was reported that a synergistic effect was observed when ribavirin was added to those two molecules combination (Ferraris et al., 2015). In sum, the synergistic effect of psychiatric drugs such as citalopram, chlorpromazine may cause increasing in levels of chloroquine should be taken into account during the combination usage of these drugs.

Hydroxychloroquine which is a less toxic derivate of chloroquine, is also effective in inhibiting SARS-CoV-2 infection in vitro (Liu et al., 2020). In a recent observational study, 80 relatively mildly infected inpatients treated with a combination of hydroxychloroquine and azithromycin and a rapid fall of nasopharyngeal viral load was reported at the end of the day 7 (Gautret et al., 2020). However, it has been shown that the body temperature recovery time, the cough remission time was shortened and pneumonia was improved in patients with hydroxychloroquine treatment (Chen et al., 2020). Both hydroxychloroquine and chloroquine have neuropsychiatric side effects from mild to (mood swings, agitation, nervousness, sleep disturbances) to severe (psychosis, delirium, suicidality). Risk factors for induced neuropsychiatric effects caused by hydroxychloroquine and chloroquine include family history of psychiatric disease, alcohol usage, using of CYP3A4 inhibitors, glucocorticoids, and female gender (Good & Shader, 1977);(Mascolo et al., 2018).

3. Psychiatric drug interaction with Hydroxychloroquine and Chloroquine:

CYP3A4 enzyme metabolizes both hydroxychloroquine and chloroquine. Therefore, CYP3A4 inhibitors may cause an increase in the plasma levels and increase the possible effects of hydroxychloroquine and chloroquine whereas CYP3A4 inducers could decrease the plasma levels so that hydroxychloroquine and chloroquine could be less effective with the combination of CYP3A4 inducers (Browning, 2014). The cardiogenic side effects of hydroxychloroquine and chloroquine are; QT interval prolongation, AV block (McGhie et al., 2018). Usage outside of the hospital setting is not recommended, and the cardiogenic side effects

should be taken into account when used in combination with QT-prolonging antipsychotics.

Combination with Anticonvulsants:

The anticonvulsants that have the effects of mood-stabilizing, anxiolytic and sedation are using in psychiatric treatments.

- Because hydroxychloroquine and chloroquine are metabolized by CYP3A4, CYP3A4 inducers such as carbamazepine, oxcarbazepine may cause lower levels of hydroxychloroquine or chloroquine. Thus, a combination of these drugs is not suggested (Mascolo et al., 2018).

- No interaction has been reported with lamotrigine, valproic acid, clonazepam.

- Lithium, as a mood stabilizer, should be used cautiously, with chloroquine or hydroxychloroquine due to the QT interval prolongation effect of these drugs.

Combination with antidepressants:

-Antidepressants that have fewer interactions with hydroxychloroquine and chloroquine are sertraline, reboxetine, milnacipran, agomelatine and, bupropion.

-Amitriptyline, clomipramine, citalopram, escitalopram, trazodone should be used carefully due to the QT interval prolongation effect.

- Paroxetine, fluoxetine, amitriptyline, fluvoxamine, venlafaxine, mirtazapine may increase the plasma levels of chloroquine and hydroxychloroquine

-A combination with St John's Wort Oil is not recommended due to decreasing plasma levels of chloroquine and hydroxychloroquine.

Combination with Antipsychotics:

-Aripiprazole, amisulpride, asenapine, olanzapine, paliperidone, perphenazine are the antipsychotics that have lower side effects with the combination of chloroquine and hydroxychloroquine.

-Chlorpromazine, clozapine, haloperidol, pimozide, quetiapine, zuclopenthixol should be used carefully due to their potential QT interval prolongation effect.

-A combination with ziprasidone is contradicted due to higher risk for QTc interval prolongation.

- Due to clozapine is associated with myelosuppression risk, monitoring hematological parameters is essential during the combination with clozapine.

Combination with anxiolytics:

- Although the combination with anxiolytics is safe, hydroxyzine combination should be taken into account for prolonged QTc (http://Www.Covid19-Druginteractions.Org, n.d.).

Azithromycin:

Azithromycin is an antibacterial agent and used in the treatments of respiratory tracts, skin and soft tissues infections and urethritis/cervicitis (Peters et al., 1992). Besides the antibacterial activity, azithromycin has also antiviral and anti-inflammatory activities that may help the treatment of COVID-19 if used in combination with chloroquine and hydroxychloroquine. In a recent study, azithromycin and hydroxychloroquine combination was found higly more effective against the virus, when compared to hydroxychloroquine treatment alone (Gautret et al., 2020). Controversially, in another study, no clear benefit was found with the combination of hydroxychloroquine and azithromycin in patients with serious COVID-19 infection (Molina et al., 2020). However, the risk of QTc prolongation, cardiogenic comorbidities should be considered when using a combination of both hydoxychloroquine and azithromycin.

Psychiatric side effects of azithromycin are listed as; catatonia, delirium, agitation, anxiety, psychotic depression, and somnolence (Bilbul et al., 2020).

Psychiatric drug interaction with Azithromycin:

Combination with Anticonvulsants:

-Lithium has a moderate risk due to the risk of QTc prolongation.

Combination with antidepressants:

- Citalopram, escitalopram have a severe risk for QTc prolongation.

- Amitriptyline, clomipramine, trazodone, imipramine have a moderate risk for QTc prolongation

Combination with Antipsychotics:

-Amisulpride, ziprasidone, clozapine, pimozide, haloperidol, thioridazine have a severe risk for QTc prolongation.

-Aripiprazole, chlorpromazine, olanzapine, paliperidone, perphenazine, quetiapine, risperidone have a moderate risk for cardiac side effects.

Combination with anxiolytics:

-Due to the risk of QTc prolongation, combination with Hydroxyzine is not suggested (Https://Www.Drugs.Com/Drug-Interactions/Azithromycin-Index.Html, n.d.).

Remdesivir:

Remdesivir is an antiviral whcih acts by inhibiting RNA polymerase, hence lowering viral RNA levels. It has been shown that remdesivir has activity against SARS-CoV-2. Apparently, it has a clinical safety profile. The most common side effects are hypotension, sweating and, shivering. No neuropsychiatric side effect has been reported so far. However, on May 1, 2020, US Food and Drug Administration (FDA approved to use Remdesivir for treatment of suspected or confirmed severe COVID-19 (Https://Www.Fda.Gov/Media/137566/Download, n.d.).

Psychiatric drug interaction with Remdesivir:

Combination with Anticonvulsants:

- Due to carbamazepine is decreasing the plasma levels of remdesivir, combination with carbamazepine is not recommended

-No interaction has been reported with lamotrigine, valproic acid, topiramate and, lithium.

Combination with Antidepressants:

-No interaction has been reported between most of the antidepressants. But, as St John's Wort may decrease the plasma levels of Remdesivir, a combination of those two drugs is not recommended.

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Combination with Antipsychotics:

- No interaction has been reported with antipsychotics

Combination with Anxiolytics:

- No interaction has been reported with anxiolytics.

Lopinavir/Ritonavir

Lopinavir/ritonavir combination is an antiviral medication. Lopinavir is a protease inhibitor and ritonavir inhibits the metabolism of lopinavir and leads to increasing the plasma levels of lopinavir. This combination is used in treatment of HIV-1 infection and it was used to treat MERS as well. Recently, this combination is used to treat COVID-19 infection. But, according to a recent randomized, controlled, open-label trial involving hospitalized adult patients with COVID-19 in Wuhan China, no significant benefit was observed with Lopinavir/ritonavir combination. The most common neuropsychiatric effects of Lopinavir/Ritonavir are reported as agitation, anxiety, confusions, emotional instability (Cao et al., 2020).

Psychiatric drug interaction with Lopinavir/Ritonavir:

Combination with Anticonvulsants:

-A combination with carbamazepine may decrease the plasma levels of Lopinavir/Ritonavir so that the single dose of carbamazepine per day is recommended.

-Lopinavir/ritonavir lowers the concentration of lamotrigine. The increased dose is required.

-Lopinavir/ritonavir increases the plasma levels of Valproic acid. Thus, the dose requirement is needed.

- No change in plasma levels of lithium when it is combined with Lopinavir/ritonavir. It should be taken into account for QTc interval prolongation

Combination with Antidepressants

-Lowering the doses of trazodone is recommended due to side effects such as dizziness, nausea.

-The risk of QTc prolongation increases due to the plasma levels of clomipramine, citalopram, escitalopram, desipramine, imipramine, amitriptyline increase.

-The concentration of Bupropion decreases. Thus, the dose requirement is needed.

-A combination with St John's Wort is not recommended due to it decreases the concentration of antiviral medication.

Combination with Antipsychotics

-A combination with lurasidone ve pimozide is contraindicated due to lopinavir/ritonavir increases drug levels and side effects.

-A combination with quetiapine is contraindicated due to the side effect of a coma.

-No interaction has been shown with amisulpride.

-It is not recommended to use with clozapine due to myelosuppression side effect.

Combination with Anxiolytics:

- A combination with midazolam and triazolam is contraindicated due to increased drug levels.

- Combination with anxiolytics which do not depend on CYP metabolism is suggested, such as lorazepam. (Http://Www.Covid19-Druginteractions.Org, n.d.).

Favipiravir:

On 15 February 2020, China has approved Favipiravir for treatment of influenza, which is an antiviral that act as a RNA dependant RNA polymerase inhibitor. It is also used in clinical trials for COVID-19 treatment (Baranovich et al., 2013). In a recent review that 29 studies were identified, it has been reported that favipiravir was tolerable and showed a safety but more evidence was needed to assess the long-term side effects such as hyperuricemia, teratogenicity and QTc prolongation (Pilkington et al., 2020). However, no neuropsychiatric side effect has been reported so far.

Psychiatric drug interaction with Favipiravir:

-No interaction with anticonvulsants, antidepressants, antipsychotics, anxiolytics has been reported with the combined use of Favipiravir so far (Http://Www.Covid19-Druginteractions.Org, n.d.).

Tocilizumab:

Cytokine storm has been observed in patients with SARS-CoV-2 and it is caused by elevated Interleukin-6 (IL-6) (Luo et al., 2020). Tocilizumab is a monoclonal antibody and acts as an IL-6 receptor antagonist. Recently, it has been used as an alternative treatment for COVID-19 for lessening cytokine storm (Zhang et al., 2020). In a recent study that investigates the efficacy and safety of tocilizumab in patients with COVID-19, no obvious side effect was reported and the rate of secondary infection was not so high. It was reported as an effective treatment to reduce mortality (Xu et al., 2020).

According to the literature, the medications that have immune-modulating effects such as adalimumab, etanercept, infliximab, tocilizumab, have positive effects on depressive symptoms (Kappelmann et al., 2018). Similarly, it has been also indicated that inflammation and IL-6 activity may be related with clinical features and pathophysiology of schizophrenia (Girgis et al., 2018).

Psychiatric drug interaction with Tocilizumab

Combination with Anticonvulsants:

-No major interactions reported with anticonvulsants

Combination with Antidepressants:

- No major interactions reported with antidepressants.

Combination with Antipsychotics:

- No major interactions reported with antipsychotics. But risky used with clozapine is reported for potentially hepatotoxic side effects

Combination with Anxiolytics:

-No major interactions reported with anxiolytic (Http://Www.Covid19-Druginteractions.Org, n.d.).

4. Conclusion

Since COVID-19 impacts multi organs systems, the infection and its treatment may cause many side effects and drug interactions as well. Psychiatric diseases are also chronic diseases and psychiatric drugs may have severe interactions with COVID-19 medications. Thus, drug interactions should be known for providing the best treatment with lower side effects for psychiatric patients with COVID-19.

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It has been reported that chloroquine, hydroxychloroquine, azithromycin, ribavirin, lopinavir/ritonavir have interactions with psychiatric medications such as antidepressants, antipsychotics, anticonvulsants and, anxiolytics in terms of QTc interval prolongation, hepatotoxicity, myelosuppression, increased or decreased concentration of medications. Remdesivir has lower interactions with most of the psychiatric drugs except St John's Wort and some anticonvulsants. However, favipiravir is considered as the COVID-19 medication which has lower interaction and side effects in combination with psychiatric medication. The use of tocilizumab is also safe with most of the psychiatric drugs and has a positive effect on depressive symptoms, although there is a risk of hepatotoxicity.

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