AN OVERVIEW OF THE EFFECTS OF THE COVID-19 OUTBREAK ON MENTAL HEALTH

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INTRODUCTION

COVID-19 infection which is first seen in Wuhan, China in December 2019, being caused by the zoonotic RNA virus spread rapidly throughout the world and it was declared as a pandemic by the World Health Organization in March 2020. Most common symptoms are fever, malaise and dry cough. Apart from fever and respiratory system symptoms, there are many findings relating with the disease causing organ failure and even multi-systemic involvement which may lead to death. Most common form of transmission is by means of the respiratory system through droplets. Virus enters host cells via surface proteins. Angiotensin converting enzyme 2 (ACE2) has been determined as the entry receptor. Main entry point of the virus is the respiratory system, but the virus may also infect the digestive, urinary, neurological and hematological systems. Infection can be transmitted from animals to humans and from person to person. Other possible routes of transmission are fecal-oral and mother-to-child. It is known that the incubation period changes between 5 and 14 days, rarely being longer. Severity of the disease varies depending on the age and presence of other accompanying chronic diseases. Heart diseases,
asthma, obesity, HIV, liver and kidney diseases are defined as comorbid conditions which may affect the course of the disease negatively. The disease is more common in men than in women.

Against the COVID-19 pandemic, scientists and managers focus on pathogen and biological risk in order to understand the pathophysiological mechanisms involved, and to prevent, control and treat disease. At the same time, psychological and psychiatric comorbid conditions that occur due to the disease at both individual and collective levels are being neglected. This situation creates gaps in people’s coping strategies and increases the burden of relevant diseases.

Entire world has been fighting against COVID-19 pandemic for more than a year. And this process affects people’s mental health negatively in many ways. When impact of COVID-19 on mental health is evaluated systematically, primarily, the impact of pandemic process on mental health regardless of whether there is disease transmission or not, secondly comorbid spiritual disorders developing in patients catching COVID-19 disease and finally, mental disorders experienced by patients who had psychiatric disorder and got treatment during pandemic period and during when they had COVID-19 disease are being evaluated.

IMPACT OF PANDEMIC ON MENTAL HEALTH

Early in the epidemic process, managers provided suspicious and false information about the transmission route, incubation period, geographic spread, number of infected people, and actual mortality rates. This situation has caused insecurity and fear in societies. Inadequate control measures and lack of effective treatment made the situation worsen. Many physiological, cognitive, emotional and behavioral reactions have been observed with the triggering of the stress situation in the society due to reasons such as this uncertainty, limitation of information, and the contagious nature of the disease, and these had direct effects on mental health. In a study conducted in China, where the pandemic first came out, it was shown that depression, anxiety and perceived stress levels were higher than they were another times.

Effects of pandemic on human psychology include many individual differences. In Turkey and other countries in the world, mask use to control the epidemic, social distancing, hygiene, prevention of collective bargaining, closing schools and workplaces, travel ban and curfew restrictions are being implemented. These affect societies both socially and economically. Disaster
that has occurred disrupts the daily routines of people and requires them to adapt to new conditions. Adaptation to new situations is not the same for every individual. Social and cultural characteristics of a person may vary according to socioeconomic conditions, psychological well-being and individual characteristics. Variables such as the insufficiency of the basic needs of individuals such as security, accommodation, nutrition, incomplete or misinformation about what happened, prolonged quarantine period, lack of social support, financial losses in the epidemic, developing COVID-19 symptoms or contacting with COVID-19 positive individuals in this process make people psychologically more risky during the epidemic process.

Furthermore, in a study conducted in China, it was reported that individuals under the age of 18 and over 50, individuals with low education levels, divorced or widowed individuals, agricultural workers, and minority persons had more obsessive-compulsive symptoms, interpersonal sensitivity, phobic anxiety and psychotic symptoms in this process. In other similar studies, people who may experience more negative consequences in the COVID-19 outbreak were determined to be the elderly, young people, women, students, immigrants, prisoners and homeless people. In this process, it has been reported that living with the family, having a fixed / regular income of the family, and living in urban areas rather than rural areas are protective against the development of psychological disorders in individuals.

Diseases are seen as traumatic negative events that can cause post-traumatic stress disorder (PTSD) in people. The experiences and reactions of the people during the pandemic process can be evidence of this. A study conducted asserted that the COVID-19 epidemic had a negative impact on mental health, stating that one fourth of the subjects experienced acute stress and more than a quarter experienced depression, anxiety and sleep problems. Another study reports higher rates. More than three quarters of the subjects had moderate to severe anxiety, two thirds had moderate to severe depression, and one third had post-traumatic stress disorder symptoms. In this process, the prevention of socialization, which is associated with the mental well-being of the person, and the disruption of daily routines have been associated with the development of acute stress disorder symptoms. Especially, it has been observed that quarantine has negative effects on mental health, and approximately 35% of people under quarantine experience psychological distress. This situation was found to be associated with stigma, sleep problems, fear, low self-esteem, depression and PTSD in individuals. It has also been shown that female gender, young age, low education level, low income level and prolonged
social isolation areas sociated with higher levels of anxiety, depression and PTSD.

Additionally, it is predicted that mental problems experienced during the process may lead to suicidal behavior. Nowadays, there are no systematic studies on the COVID-19 pandemic and suicides, but experiences in pastepidemics such as Plague, Spanish Flu, SARS, Ebola have shown an increase in suicide attempts and suicide rates as well as psychiatric comorbidities. With the COVID-19 epidemic, an increase in panic, fear, depression, anxiety disorder, PTSD and sleep disorders has been observed in societies. Quarantine measureslled to social isolation and economic difficulties in closed workplaces. The anxiety that patients with the disease will have the disease again and the limitations of the treatment possibilities have increased the fear. These are all characteristics that may pose a risk for suicidal behavior.

When effects of the pandemic process on mental health are examined, healthcare workers should be evaluated as a separate group. Because they are at the forefront of this process and face higher levels of psychological problems compared to other people due to high risk of infection, inadequate working conditions, long working hours, physical fatigue, loneliness and separation from their families. In a study, it has been shown that the levels of depression and anxiety observed in health care workers are high, mainly due to stress, insomnia, and anxiety about contamination. It has been reported that health care workers dealing with the diagnosis, treatment and care of patients diag-nosed with COVID-19 more frequently show symptoms of depression, insomnia and stress.

Increase in mental disorders occurring due to the process causes people to receive professional support in this sense. But since frequent visits of patients to the hospital during the pandemic process will increase the risk of contami-nation, patients’ access to healthcare practices has been restricted with the measures taken. In this case, telepsychiatry applications were recommended for patients to receive psychiatric support by evaluating the current pandemic conditions. Telepsychiatry enables remote psychiatric examination by using electronic communication and information technologies. Although face-to-face interviews have the advantages of detecting body language and gestures, examination without physical contact reduces the possibility of transmission to healthcare workers and the risk of spreading asymptomatic viruses during the epidemic process. And besides physical isolation, it offers people living in social isolation the opportunity togetherr support they need.
Role of the psychiatrist in supporting people spiritually during the pandemic process was determined as educating individuals about common negative psychological symptoms and encouraging mental health-enhancing behaviors; to integrate the applied treatments into existing health services and to facilitate problem solving. In this context, telepsychiatry applications with accurate and reliable information to reduce the fear and panic of COVID-19; plays an important role in raising awareness for psychiatric comorbidities and in the treatment of these comorbidities. It also offers mental health professionals the opportunity to undertake psychological interventions, including cognitive behavioral therapy and other forms of psychotherapy.

MENTAL HEALTH IN COVID-19 PATIENTS

One of the difficulties that is experienced during the pandemic process is the psychiatric disorders accompanying the COVID-19 disease. Being infected with the virus adversely affects the mental health of the individual by causing the fear of death, health anxiety, anxiety that it will transmit to relatives, and a feeling of stigma in addition to physical complaints.

Anxiety and depression symptoms were found to be significantly higher in hospitalized patients. Female gender, advanced age, being alone in the hospital increase this risk. For these patients it has been found that staying in the same room with family members who test positive for COVID-19 can reduce the levels of anxiety and depression observed in people, indicating that social support has significant contributions to the mental health of people in the process. It has been shown that neuropsychiatric effects such as fatigue, widespread muscle pain, headache, shortness of breath and concentration difficulties may continue in patients who have survived the COVID-19 disease and recovered from the infection. Another study showed that patients continue to have psychological distress approximately 50 days after being diagnosed with COVID-19. While PTSD symptoms are reported in approximately one quarter of these patients, it is emphasized that 40% of the more accompanied by depression. The anxiety levels of the patients were also found to be high, and it was shown that they had shortened sleep times and difficulty falling a sleep.

COVID-19 process has brought up various difficulties for both physicians and patients in terms of measures that can be taken and practices to protect the mental health of these patients. It is predicted that anxiety disorders, depression, PTSD, sleep disorders, psychotrophic drug use and drug abuse increase with the pandemic. While the pandemic has increased the need for
safe prescribing of psychotropic drugs, it has made it difficult to prescribe safe
drugs due to both the limitation of face-to-face outpatient services and drug
side effects and interactions. The systemic effects of the COVID-19 infection
itself and the drugs used in its treatment should be taken into account when
choosing drugs in these patients. Knowing about possible side effects is of
great importance in the management of the disease.

**EFFECTS OF SYSTEM INVOLVEMENT OBSERVED IN COVID-19
DISEASE ON PSYCHOTROPES**

It is known that COVID-19 infection does not only affect the respiratory
system but also many organs including the heart, liver, kidney, immune and
hematological system. This situation is in the use of psychotropic drugs can
cause drug interactions by affecting the absorption, distribution, metabolism
and excretion of drugs.

It has been reported that lymphopenia and leukopenia developed in 63%
of patients in COVID-19 infection. Lymphopenia, which is among the poor
prognostic factors, has been observed in severe cases of COVID-19. In the
course of the disease, it may be necessary to avoid drugs that can increase
lymphopenia and leukopenia. Among the psychotropic drugs, especially car-
bamazepine, clozapine and olanzapine, although there is a high risk, first and
second generation antipsychotics, tricyclic antidepressants (TCA) and benzo-
diazepines can adversely affect white blood cell production.

Coagulopathy and diffuse intravascular coagulation are commonly seen
in COVID-19 patients. In addition, anticoagulants are used in treatment due
to the increased thrombotic risk. In this case, it is necessary to be careful in
the use of drugs that disrupt the blood platelet function and may increase the
risk of bleeding (such as valproic acid, selective serotonin reuptake inhibitors,
serotonin-norepinephrine reuptake inhibitors).

Impact of COVID-19 infection on the cardiac system can be in the form
of arrhythmias, myopericarditis, acute cardiac syndrome and heart failure.
And the drugs used in treatment may have cardiac side effects. It is known
that chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir
increase the risk of torsades de pointes (TdP) by prolonging QT. Antipsychotics
(eg. thioridazine, intravenous haloperidol, ziprasidone, iloperidone, aripipra-
zole and lurasidone), citalopram, tricyclic antidepressants are drugs that can
increase the risk of QT prolongation and TdP. These drugs are known to
increase the risk of QT prolongation. In particular, patients with a history of
cardiac disease, female gender, family history of heart disease, electrolyte imbalance and substance abuse are in the risk group for this side effect.

The risk of liver damage is particularly increased in severe cases. In acute liver failure, an increase in alanine aminotransferase, aspartate aminotransferase and bilirubin is observed in the laboratory findings. In this case, chlorpromazine, carbamazepine, valproate, duloxetine and nefazodone should be avoided in preferred drugs to protect the patient from drug-induced liver damage. Dose adjustment is required when its use is necessary.

Acute kidney injury has been observed in patients with chronic kidney disease and acute respiratory distress syndrome (ARDS) in COVID-19 infection. Renal functions of these patients should be closely monitored and dose adjustment of drugs eliminated from the kidneys, especially lithium, gabapentin, topiramate, pregabalin, paliperidone, and duloxetine, should be made. Potential nephrotoxic drugs should be avoided.

COVID-19 infection is primarily a respiratory disease. Cough and shortness of breath are the first clinical symptoms observed. Pneumonia and acute respiratory distress syndrome may be observed in severe cases. In these patients, the side effect of benzodiazepines, which can cause respiratory depression, especially at high doses, should be considered. While prescribing benzodiazepines (especially preferred in anxiety and panic disorder patients), it is recommended to make a choice of drugs by evaluating the benefit and loss situation.

Corona viruses are viruses with neurotropic properties. ACE2 receptor functional for COVID-19 is also found in neurons, microglia cells, astrocytes and oligodendrocytes. Anosmia, mouth and neuropathic pain due to peripheral nerve involvement of the virus; Headache, dizziness, ataxia, confusion, delirium, epileptic seizures and acute cerebrovascular diseases can be observed due to central nervous system involvement. It is thought that direct invasion of the virus may play a role in the formation of these clinical symptoms, as well as inflammatory cytokines. Among the neurological symptoms, delirium is the clinical picture that concerns us the most in terms of psychiatry and creates difficulties in treatment. The prevalence of neuropsychiatric symptoms in COVID-19 patients was found to be 22.5%. This rate increases in those who are taken to intensive care due to ARDS and it has been shown that 84.3% have delirium and neurological symptoms. Many etiological factors play a role in causing delirium. In addition to organic reasons such as organ failure, hypoxia, sepsis, drug effect, metabolic disorders, long-term adherence to the ventilator; Prolonged immobility and social isolation
contribute to delirium etiology. In the management of delirium, firstly conservative approaches and then drug therapies are recommended. In conservative approaches; It is necessary to provide ambient lighting compatible with the circadian rhythm, to regulate night sleep, to establish communication that will ensure the orientation of the patient to time, person and place, and to ensure physical activity as quickly as possible. In the medical treatment of delirium; melatonin can be used to regulate the sleep-wake cycle. Trazodone alone or in combination with ramelteon is one of the other alternative drugs that can be recommended for sleep. Benzodiazepines are not recommended as they can deepen delirium (except delirium tremens). It was found that haloperidol, olanzapine, quetiapine and aripiprazole were effective in delirium pictures accompanied by behavioral disorders.

**MEDICINES USED IN TREATMENT OF COVID-19 AND THEIR INTERACTION WITH PSYCHOTROPES**

**Chloroquine and hydroxychloroquine (HCQ)**

HCQ, a synthetic form of quinine used in the treatment and prophylaxis of malaria, is considered a possible treatment for COVID-19 infection. Neuropsychiatric side effects such as psychosis, delirium, agitation, depression, sleep disorders, suicidal tendency and personality changes can be observed due to the use of the drug. Having a family history of psychiatric disease, female gender, low body weight and high doses increase this risk. HCQ is metabolized in the liver by cytochrome 2C8, 3A4, 3A5 and 2D6 enzymes. Use of these enzymes together with inhibitors or inducers can change the plasma concentration. In addition, since chloroquine and HCQ are moderate inhibitors of cytochrome 2D6 and P-gp, caution should be exercised in their use with drugs that are metabolized by these enzymes and have a narrow therapeutic index. Chloroquine and HCQ can increase the risk of TdP by prolonging the QT interval. This situation increases the risk of TdP by making an additive effect when used together with the antidepressants citalopram and escitalopram. Therefore, although their use is not recommended, ECG monitoring is recommended in mandatory situations.

It is known that among antipsychotic drugs, haloperidol, iloperidone, pimozide, sulpiride, ziprasidone cause QT prolongation and increase the risk of TdP. Thoridazined and zuclopenthixol are metabolized by cytochrome 2D6. When used with HCQ, plasma concentrations of drugs increase, increasing
the risk of QT prolongation and TdP. Combination of these drugs is not recommended.

In addition, chlorpromazine, risperidone, aripiprazole, clozapine, paliperidone, zotepine, amisulpride, quetiapine also increase the risk of QT prolongation and TdP. It is suggested that these drugs can be used together with chloroquine and HCQ by ECG monitoring.

**Tocilizumab**

It is a recombinant humanized monoclonal antibody that is an interleukin-6 receptor antagonist used in the treatment of autoimmune arthritis. No drug-related neuropsychiatric side effects have been reported. No significant interaction has been reported when used with psychotropes.

**Favipiravir**

It is an antiviral that is an RNA-dependent RNA polymerase inhibitor. It is used in influenza and other RNA virus infections. No neuropsychiatric side effects have been reported due to favipiravir use. No significant interaction has been reported when used with psychotropes.

**Remdesevir**

It has been identified as a potential treatment for Ebola. It is a nucleoside analog used to inhibit the RNA polymerase effect. No drug-related neuropsychiatric side effects have been reported. No significant interaction has been reported when used with psychotropes.

**Oseltamivir**

It is an antiviral used in the treatment of influenza. It is a sialic acid analog that inhibits neuraminidase activity. Neuropsychiatric side effects such as sleep disturbance, headache and dizziness related to drug use have been reported. No significant interaction has been reported when used with psychotropes.

**Azithromycin**

It is a broad-spectrum macrolide antibiotic used in the treatment of respiratory, enteric and genitourinary infections. It has been reported that it may
prolong the QT interval and increase the risk of cardiac arrhythmia in patients using the drug. It has been associated with toxic effects on the liver. ECG monitoring is recommended when used with psychotropes that cause QT prolongation.

**Plasmatherapy**

Plasma from patients who have recovered from COVID-19 infection is used especially in patients with severe respiratory failure. No specific neuropsychiatric side effects related to plasma transfusion have been reported. No significant interaction has been reported when used with psychotropes.

**C Vitamin**

Vitamin C, an antioxidant, is used in the treatment of Covid-19 to increase the immune response at high doses intravenously. No neuropsychiatric side effects have been reported with the use of high doses of vitamin C. However, although vitamin C deficiency is seen as a risk factor for delirium, it can lead to depression, confusion and danger. Combined use with barbiturates may reduce the effectiveness of vitamin C.

**Corticosteroids**

It was not recommended in the treatment of viral infections, considering that it would increase the severity of the disease. However, clinical experience has shown that it is effective against cytokine storm and hyper inflammation in COVID-19 infection. It is known to have neuropsychiatric side effects such as depression, mania, agitation, mood disorder, anxiety, sleep disorders, catatonia, depersonalization, delirium and psychosis due to corticosteroid use in the past. It induces cytochrome 3A4 and 2C19 enzymes in the liver. Psychotropes metabolized by these enzymes may decrease plasma level.

**Interferon (IFN)**

IFNs, being glycoproteins with immunomodulatory, antiproliferative and hormone-like activities, have been recognized as a potential treatment for COVID-19. It is warned that IFN use may have side effects related to fatigue, mood disorders, increased risk of suicide, anxiety, emotional ability, apathy, sleep disorders and cognitive impairment. Close psychiatric follow-up of patients using IFN is recommended. A pharmacokinetic interaction has not
been reported regarding its combined use with psychotropes, but when used with carbamazepine, valproate and clozapine, warning is made about the risk of bone marrow suppression.

Our knowledge about the interactions between psychotropic drugs and Covid-19 infection and drugs used in its treatment is limited. The information we have is presented to us in the light of the findings revealed to date.

**IMPACT OF PANDEMIC ON CHRONIC PSYCHIATRIC DISEASES**

Pandemic process has also negatively affected individuals with chronic psychiatric diseases and caused them to experience many disruptions in their treatment process. These patients have higher risk of catching and transmitting COVID-19, having severe process of COVID-19 disease, need to get in patient treatment and risk of death with respect to average risk of community. The reasons for this situation include the difficulties of patients receiving psychiatric treatment in adapting to self-care, hygiene, nutrition, sleep and other necessary measures, inadequacy in impulse and behavior control, cognitive disorders, and access to treatment. In addition, metabolic diseases that develop due to the side effects of psychiatric treatments and inflammatory processes associated with psychiatric diseases increase this risk.

Life expectancy in psychosis patients is shorter than the population average. This difference is about 15 years and the cause of death is 90% physical diseases such as cardiovascular diseases, diabetes and respiratory diseases. It has been shown that the risk of deep vein thrombosis and pulmonary embolism increases 2-3 times in patients with psychotic disorders such as schizophrenia. Frequent observation of smoking and less physical activity in these patients are also factors that increase the disease burden and deteriorate their general health status.

It is not emphasized that there is a need to change the treatment strategies of these diseases during the pandemic process. However, new applications are suggested for the use of clozapine and depot antipsychotics. These are as follows;

**USAGE OF CLOZAPINE**

Clozapine, which is frequently preferred in the treatment of resistant schizophrenia, is a drug recommended to be used by monthly complete blood count
against the risk of agranulocytosis. However, this practice increases the risk of COVID-19 transmission in patients during the pandemic process. A new consensus has been published by Siskind et al in 2020. According to this report, it is stated that frequency of neutrophil count could be reduced to once in a quarter in patients

1. a. Patients having been on clozapine therapy for more than 1 year. b. Patients whose neutrophil count had never fallen below 2000 before. c. Patients without safe and practical access to neutrophil count analysis. It is said that the frequency of checking the neutrophil count in these patients can be reduced to every 3 months (if medicine for 3 months can be obtained).

For patients who are just starting clozapine treatment, it is recommended to follow country-specific protocols for the first 6 months. It is stated that for patients who are on clozapine treatment continuously for 6-12 months, decisions regarding complete blood count follow-up can be made on a case-by-case basis, and regardless of hemogram follow-up, patients using clozapine should continue to receive regular mental status and potential drug side-effect assessments through face-to-face or online interviews.

2. Clozapine is associated with an increased risk of pneumonia. This risk increases due to sialorrhea and aspiration side effects. Therefore, patients using clozapine should be informed about applying to a health care institution in case of signs of infection. And upon application, detailed systemic examination and detections of the patient, including complete blood count, should be done.

3. During the course of COVID-19 infection, an increase in the plasma level of clozapine can be seen. In a fever and flu-like picture, it is recommended to reduce the clozapine dose to half against the risk of clozapine toxicity. After the fever subsides, the lower dose should be continued for 3 days and then the dose should be increased gradually. Clozapine should be discontinued in case of toxicity.

Clozapine use can lower the seizure threshold. In case of seizure during acute infection, the dose of clozapine should be reduced, and an antiepileptic should be added to the treatment if necessary.
It is recommended that patients using long-acting depot antipsychotics can switch from 1 month injection to 3 months injections if the clinical course is stable for more than 4 months.

CONCLUSION

As a result, the COVID-19 pandemic affects the entire world, including our country, both physically and spiritually especially health care workers, those with chronic physical illnesses, children, the elderly, immigrants and those with chronic mental illness come out to be groups that are much more risky. COVID-19 besides the effects of acute infection, restrictions applied to prevent spreading of disease, quarantine, closure of schools and workplaces, social isolation, economic burdens give rise to fear, worry, sleep disorders in people and increase risk of anxiety disorder, depression and TSSB. It has also increased the psychological burden of patients who had previously had a psychiatric disorder and received support, and caused many disruptions in their treatment. In this process, it may be necessary to use COVID-19 drugs and psychotropes together. In this case, it is necessary to be careful about drug interactions.

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