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Mini Review

Repurposing Anti-Depressants and Anti-Psychotics for SARS-Cov2 Infection: A Mini-Review of Current Evidence

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Abstract

Due to ongoing Coronavirus Disease 2019 pandemic, drug repurposing is widely used as a strategy for finding suitable treatments for the disease. Worldwide quarantine situations can cause different levels of mental health problems. Two groups of drugs namely, anti-depressants and anti-psychotics have shown antiviral effects besides their approved indications. In this mini review we have looked over the present evidence for their antiviral effects.

Keywords: *Anti-Depressants; Anti-Psychotics; Drug Repurposing; COVID19; Mental Health*

Introduction

Since the start of Coronavirus Disease 2019 (COVID19) pandemic, the number of infected people has been growing. According to the who.int website, though in the last days of July 2020, there are more than 14 million confirmed cases all around the world, still, there is not an approved medication for the treatment of SARS-CoV2 infection [1].

One of the strategies that has been gaining attention in recent decades is drug repurposing or repositioning. Novel discovery strategies being time-consuming and high cost brings incentive for pharmaceutical companies to reposition the clinically failed medications as well as approved ones to new indications in a considerably shorter time. Such drugs enter clinical trials thanks to their previously shown safety profiles along with successfully passed pre-clinical experiments [2,3]. Molecular screening methods aiming to repurpose available drugs for uses other than their labelled indications has become a detour strategy of brand preservation for companies as well as for academic groups to develop their small-molecule libraries [4].

Various groups of drugs have been under investigation for drug repositioning, namely anti-depressants, and anti-psychotics, which besides their possible proposed anti-viral effects, gains more attention in difficult psychosocial situations such as isolation and quarantine.

Isolation and loneliness being accounted as risk factors of diseases such as depression and schizophrenia, are resulted due to quarantine and lockdown. These factors which nowadays are inevitable in patients with COVID19 infection, result in different levels of psychological symptoms such as depression and anxiety [5-7].

Since a successful repurposing would be a meeting point of basic and clinical sciences [8], in this mini review, we have tried to gather the present basic and clinical evidence for antiviral effects of some of the anti-depressants and antipsychotic drugs. Some of these medications that are under investigation in ongoing clinical trials for the management of COVID19 infection might be considered as candidate drugs with antiviral effects suitable for quarantined patients with mental health problems.

Antipsychotics

In a screening study aiming to reposition medications by finding approved drugs that are effective against Ebola virus infection, Aripiprazole, Piperacetazine were found to block the entry of Ebola virus to cells *in vitro* by inhibiting internalization of the virus from the cell surface and acidification of endosomes consecutively [9].

Olanzapine and Quetiapine as atypical antipsychotics can inhibit IL6 levels through their anti-histaminic effects. This mechanism of action is suggested to be a beneficial strategy in managing COVID19 in clinical trials [10].

Flupentixol, a thioxanthene antipsychotic medication, was shown to reduce the viral RNA and protein synthesis in enterovirus infected cells, however, possible hematologic adverse reactions, limit its use as an antiviral agent [11].

Haloperidol, an antipsychotic that is used to relieve patients' delirium, seems to have an inhibitory effect on cytokine storm and could be considered as another investigational drug candidate in severely ill COVID19 patients [12].

Phenothiazines with antipsychotic effects, along with their various indications, have been shown to inhibit hepatitis C virus entry to the cells [13]. As examples of a phenothiazine derivative antipsychotics, Chlorpromazine and Trifluprom azine's inhibitory effect on MERS-CoV and SARS-CoV have been shown *in vitro* previously [14] and structural similarity of SARS-CoV19 and SARS-CoV has made them an investigational drug candidate in clinical trials for COVID19 patient [15].

Recently, patients receiving chlorpromazine have shown a lower prevalence of COVID19 [15]. Inhibition of clathrin-mediated endocytosis is the proposed mechanism of this drug's antiviral activity [16] which alongside with the clinically observed potential benefit in reducing prevalence, became the rationale for the hypothesis of its efficacy in viral infections [15]. The clinical trials currently studying chlorpromazine include NCT04366739 and NCT04354805 [15]. The beneficial effects of chlorpromazine are not limited to its inhibitory effects on virus entry to cells. The drug's effect on decreasing the pro-inflammatory interleukins suggests its benefit in relieving the inflammation in later stages of COVID19 disease. Moreover, high distribution rate to lungs, saliva and brain highlights the possible unique effects on decreasing the viral load and preventing neurological complications consecutively [15].

Antidepressants

Research on antiviral effects of serotonin reuptake inhibitors is done in HIV patients as well. Among the studied drugs, Sertraline, Citalopram, and Trazodone have shown efficacy on the reduction of viral replication in cerebrospinal fluid which makes them promising candidates for repositioning [17]. Moreover, Sertraline showed an inhibitory effect on Ebola virus entry [9].

Fluoxetine, an FDA-approved selective serotonin reuptake inhibitor, was shown to reduce the viral RNA and protein synthesis in enterovirus infected cells. With a relatively safe profile, it was suggested as a candidate for enterovirus infections [11]. Besides this mechanism, fluoxetine can block IL6 [18] and consequently, the cytokine storm which is being studied in a clinical trial with code NCT04377308. In addition to the proposed mechanisms, it has been shown that fluoxetine in among the drugs that can disrupt the endocytosis by making changes to the pH of endomembrane system which is a crucial strategy in inhibition of SARS-CoV2 infection [19].

Next, fluvoxamine is being used in a trial in mild covid19 patients to prevent further respiratory complications (NCT04342663). The effect of this drug on inhibiting the production of IL-6 has been shown *in vitro* [20]. Also, the potential for endosomal pH disruption has been proposed for fluvoxamine [19].

Conclusion

COVID19 pandemic has brought unavoidable situations like quarantine, isolation and lockdowns which, as a result, could cause various psychological problems. While different groups of people react to the burdens of pandemic differently and the effects may even continue for years [21], the undeniable importance of mental health in society highlights the necessity of considering applicable plans to prevent and ameliorate such consequences. The discussed groups of medication might provide a better chance of controlling psychological problems alongside management of COVID19 infection.

Conflict of Interest

Nil.

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