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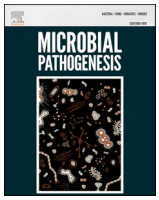
Microbial Pathogenesis 168 (2022) 105608

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath



Repurposing of antiviral drugs for COVID-19 and impact of repurposed drugs on the nervous system

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Antiviral therapy
Repurposing drugs
Neuropsychiatric effects

ABSTRACT

The recent pandemic, Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has devastated humanity and is continuing to threaten us. Due to the high transmissibility of this pathogen, researchers are still trying to cope with the treatment and prevention of this disease. Few of them were successful in finding cure for COVID-19 by including repurposed drugs in the treatment. In such pandemic situations, when it is nearly impossible to design and implement a new drug target, previously designed antiviral drugs could help against novel viruses, referred to as drug repurposing/redirecting/repositioning or re-profiling. This review describes the current landscape of the repurposing of antiviral drugs for COVID-19 and the impact of these drugs on our nervous system. In some cases, specific antiviral therapy has been notably associated with neurological toxicity, characterized by peripheral neuropathy, neurocognitive and neuropsychiatric effects within the central nervous system (CNS).

1. Introduction

Infectious diseases caused by viruses cause high morbidity and mortality throughout the world and mostly affect developing countries. At present, there are >200 known species of virus, capable of causing human infections. On average, three to four emerging or re-emerging viruses are reported annually and more than half either originate and/or are directly transmitted from animals [1,2]. As per the World Health Organization (WHO), 60% of the agents accepted as human pathogens find their source in the animal kingdom. In the past three decades, 75% of new human pathogens detected, have the potential to cross the animal human interface [3]. Most of the epidemic and pandemic outbreaks in the 21st century, including Influenza A (H1N1, H5N1), SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), Ebola, Nipah and the recent COVID-19, have animal origins.

The recent pandemic, Coronavirus Disease 2019 (COVID-19) that has been caused by a 2019-Novel coronavirus (2019-nCoV) was named as severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) [4]. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus from the family Coronaviridae (genus *Betacoronavirus*). This virus is a close phylogenetic relative of the SARS virus, which was responsible for the SARS outbreaks during 2002–2004, and the MERS virus, which has been responsible for MERS outbreaks since 2012 [5–7]. Initially, the SARS-CoV-2 outbreak began in Wuhan, China and consequently started spreading all across the world. According to the COVID-19 global case dashboard published by the WHO, as of December 13, 2021, this virus has infected around 270 million people and resulted in more than five million deaths [8].

Over the past three decades, outbreaks resulting from emerging or re-emerging species of viruses have led to the discovery of many antiviral targets and consequently, to the development of several antiviral agents. The initial stages of such outbreaks are particularly challenging due to the urgency of finding an effective treatment plan to curb the spread of infection and developing an efficient therapy. The need for new antiviral drugs in the treatment of chronic viral diseases motivates researchers to find newer targets and mechanisms for the development of new antivirals. However, it should be noted that the process of drug development is tedious and requires several years to reach its intended beneficiaries. Even if a suitable drug candidate is developed, the large-scale production in a short time is usually challenging [9]. To overcome this situation, previously designed antiviral drugs are tested against novel viruses, referred to as drug repurposing/redirecting/repositioning or

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https://doi.org/10.1016/j.micpath.2022.105608
Received 20 December 2021; Received in revised form 11 April 2022; Accepted 28 May 2022
Available online 30 May 2022
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Abbreviations

ACE	Angiotensin-converting enzyme
ALT	alanine transaminase
AST	aspartate transaminase
BBB	blood-brain barrier
CC	cytotoxic concentration
CDC	Centers for Disease Control and Prevention
CES	carboxylesterase
CNS	central nervous system
CoV	Coronavirus
COVID-19	Coronavirus Diseases 2019
DDIs	drug-drug interactions
DRV	Darunavir
EC	effective concentration
EMA	European Medicines Agency
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
FMO	flavin-containing monooxygenase
GI	gastrointestinal; gp-glycoprotein
HA	hemagglutinin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ICMR	Indian Council of Medical Research
ICTV	International Committee on Taxonomy of Viruses
IFN	interferon
LPV/RTV	Lopinavir/ritonavir
MERS	Middle East Respiratory Syndrome
mRNA	messenger RNA
MRP	multidrug resistance protein
NA	neuraminidase
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIV	National Institute of Virology
NPAE	neuropsychiatric adverse events
OAT	organic anion transporter
OC	oseltamivir carboxylate
OP	oseltamivir phosphate
PNS	peripheral nervous system
RdRp-	RNA-dependent RNA polymerase
RDV	Remdesivir
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SARS	Severe Acute Respiratory Syndrome
SLC	solute carrier
WHO	World Health Organization

re-profiling. Side-effects ranging from mild to severe are common with consumption of any drugs, not the least with antiviral agents. The vast majority of the commercially available drugs may have mild side effects, such as allergic reactions, nausea and some gastrointestinal symptoms that are most often self-limiting and/or might require minimal medical management. However, in some cases, specific antiviral therapy has been notably associated with neurological toxicity, characterized by peripheral neuropathy, neurocognitive and neuropsychiatric effects within the central nervous system (CNS) [10]. For instance, oseltamivir, an antiviral agent, has been extensively documented to be associated with neurological toxicity [11–13]. Similar effects have also been observed in the case of COVID-19 infection where psychiatrists are being consulted to assist with the treatment of infected individuals, some of whom display challenging neuropsychiatric comorbidities [14].

In this review, we will first highlight the current landscape of the repurposing of antiviral drugs for COVID-19. Further, we will discuss some of the studies which have highlighted the neuropsychiatric effects caused as a result of treatment by certain antiviral drugs. Finally, given the vast amount of data available on clinical studies and the associated adverse effects for oseltamivir, we will discuss studies involving this drug and their reported consequential neuropsychiatric effects in detail.

2. Methods

The literature in this area is limited and a non-systematic narrative review was therefore undertaken. We used a structured PubMed search using the following search terms, ((“Antiviral Agents"[Mesh]) AND (“Antiviral Agents/administration and dosage"[Mesh] OR “Antiviral Agents/adverse effects"[Mesh] OR “Antiviral Agents/classification"[Mesh] OR “Antiviral Agents/poisoning"[Mesh] OR “Antiviral Agents/therapeutic use"[Mesh])) AND “Respiratory Tract Infections/virology"[Mesh] for articles in all languages from the year 2010–2021 (2,078 results).

We selected the following antiviral drugs for COVID-19 which are most commonly used in healthcare settings and some of them are known to cause neuropsychiatric effects; Lopinavir and ritonavir, oseltamivir, zanamivir, peramivir, remdesivir, ribavirin, darunavir, arbidol, favipiravir, and molnupiravir.

3. Repurposing of COVID-19 antiviral drugs

The drug repurposing approach suggestively reduces the cost and timeline of drug discovery for novel pathogens [15]. One of the important advantages of drug repurposing over the traditional drug development process is that the repurposed drug offers a considerable amount of existing data through a significant number of studies, the safety of that specific drug is known, and the risk of failure is reduced [16]. Several *in vitro*, preclinical and clinical trials have demonstrated the anti-COVID efficacy of known repurposed drugs [17]. For instance, in October 2020, the US Food and Drug Administration (FDA) authorized the administration of Remdesivir for the treatment of hospitalized COVID-19 patients. However, at present, the drug is no longer recommended by the WHO [18]. Remdesivir was previously under development for the treatment of Ebola virus disease in 2014–2016 [19].

4. Repurposed drugs and their potential side effects on CNS

COVID-19 patients are currently receiving a variety of supportive treatments, which are determined by their symptoms [20]. However, many clinical professionals prescribe medications or drugs which are previously being used for specific diseases, including antiviral drugs, anti-parasitic drugs, or immunotherapeutics. Given the continuing course of the COVID-19 pandemic, we are focusing this review on reporting the potential CNS side effects of the antiviral drugs that are currently and/or those that were repurposed during this ongoing pandemic for the treatment of COVID-19.

4.1. Lopinavir and ritonavir

Lopinavir/ritonavir (LPV/RTV) is a combination drug of a nucleoside analogue and a protease inhibitor used for the treatment of human immunodeficiency virus (HIV) type 1, approved by the FDA in 2000 [21,22]. There are many antiretrovirals (protease inhibitors), currently used against coronaviruses for treatment such as lopinavir, darunavir, and atazanavir [23]. LPV/RTV treatment is common and found to be effective against MERS-CoV and SARS-CoV, and it subsequently went into a clinical trial for treatment against SARS-CoV-2. In an *in vitro* study by

Kang et al., LPV/RTV was found to be effective against SARS-CoV-2 [24] Initially, LPV/RTV was known to suppress 3-chymotrypsin-like protease which is known to be present in SARS and MERS coronavirus [25]. Whether LPV/RTV efficiently blocks the papain-like protease and 3-chymotrypsin-like protease in the SARS-CoV-2 virus remains debatable [25]. In combination therapy of LPV/RTV for the treatment of HIV infection, LPV is the main antiviral agent, whereas RTV acts as a pharmacokinetic promoter by inhibiting cytochrome P450-3A4 enzymes which leads to increased LPV plasma concentrations [26]. The University of Oxford is conducting a randomised trial for SARS-CoV-2 involving orally administered doses of LPV/RTV (LPV-400 mg and RTV-100 mg), twice a day for 10 days [27]. Liu et al. reported 51 positive COVID-19 patients who underwent treatment with interferon, LPV, RTV, corticosteroids, and conventional Chinese medicine, where 50 patients out of the 51 recovered successfully and were discharged from the hospital [28]. However, in July 2020, the WHO recommended discontinuing the use of LPV/RTV as there was no reduction in the mortality rates of COVID-19 hospitalized patients [29].

LPV/RTV drugs have prominent adverse effects including prolonged QT intervals [30], nausea, vomiting, and diarrhoea [31]. Although there are very few case reports or trials explaining the neuropsychiatric side effects of this combination drug therapy, possible neuropsychiatric side effects include abnormal dreams, agitation, anxiety, confusion, and emotional lability [22].

4.2. Oseltamivir

Oseltamivir has been commonly used in treating Influenza A and B infections. It was approved by the FDA in 2000 [32]. It acts as a competitive inhibitor of the viral neuraminidase restricting the release of viral particles from the host cells. A study by Zhang et al. suggests that the active site of the spike (S) 1 protein of SARS is similar to that of neuraminidase in influenza. Neuraminidase inhibitors may therefore be useful for the treatment of SARS-CoV [33]. Several clinical trials are still investigating the efficacy of oseltamivir in treating SARS-CoV-2 infection. Few *in vitro* and *in vivo* studies have reported that treatment with oseltamivir might not have a beneficial effect on the outcomes among patients with SARS-CoV-2. A study by Tan et al. suggests oseltamivir to not be effective for treating patients, and it should be prescribed only for treating influenza [34]. Wang et al. and Choy et al. in their studies also report oseltamivir to be ineffective at inhibiting SARS-CoV-2 *in vitro* [35,36]. There are ongoing clinical trials where oseltamivir is used in combination with chloroquine, favipiravir, antibiotics (azithromycin), and corticosteroids [37,38]. An ongoing phase 3 clinical trial in Pakistan [39] is evaluating the effectiveness of oseltamivir (75 mg orally twice a day for 5 days) alone or in combination with hydroxychloroquine (200 mg orally 8hr thrice a day for 5 days) and azithromycin (500 mg orally on day 1, followed by 250 mg orally twice a day on days 2–5).

Oseltamivir is ingested in the form of an oral prodrug (oseltamivir phosphate) and it is quickly converted by the hepatic esterases into its active form, that is oseltamivir carboxylate [40]. It is observed that neither oseltamivir nor its metabolite is a substrate for or inhibitor of cytochrome P450 isoforms [41,42]. Davies et al. [42] concluded that oseltamivir is suitable for mostly all age groups and has a predictable linear pharmacokinetic profile. Oseltamivir is generally well tolerated but adverse effects in adults include gastrointestinal disturbances, headache, insomnia, vertigo, bronchitis, and hypersensitive reactions. Few Japanese studies have reported acute onset of neuropsychiatric manifestations and sudden deaths in the children and adolescent population [11–13]. The details of oseltamivir are explained further in the following section.

4.3. Zanamivir

Zanamivir is a competitive inhibitor of viral neuraminidase [43]. It is used in the treatment of Influenza caused by Influenza A and Influenza B viruses [44]. It was approved for use by the FDA in 2006. A 2020 publication by Hall et al. [45] showed Zanamivir as a potential candidate for COVID-19 therapy due to its action as a $3CL^{PRO}$ main proteinase inhibitor, along with Indinavir, Saquinavir, and Remdesivir. However, multiple *in vitro* studies have shown Zanamivir to possess no substantial anti-SARS-CoV-2 activity [36].

4.4. Peramivir

Peramivir is a transition state analogue inhibitor of viral neuraminidase, which prevents the production of viral particles. It was tested during the 2009–2010H1N1 epidemic where it failed to show any benefit as compared to placebo. It was approved in 2014 for the treatment of uncomplicated influenza, with limited use among severely ill patients [46]. Peramivir, along with related neuraminidase inhibitors, is not recommended for use against COVID-19 as the SARS-CoV-2 virus uses mechanisms other than the ones involving neuraminidase to facilitate its way out of the infected cell [23,47].

4.5. Remdesivir

Remdesivir (RDV), a broad-spectrum antiviral which was developed by Gilead Sciences Inc. in 2017, as a potential antiviral agent for Ebola virus infection [48,49]. On October 22, 2020, it was approved by the FDA to treat COVID-19 patients [50]. RDV is an adenosine triphosphate nucleoside analogue. It metabolizes into its active form, GS-441524 and interferes with viral RNA polymerase and inhibits viral nucleotide synthesis [51]. *In vivo* and *in vitro* studies show that RDV is active against several virus families: filoviridae (Ebola virus), paramyxoviridae (Respiratory Syncytial Virus (RSV), Nipah virus), and coronaviridae (MERS-CoV, SARS CoV, and SARS-CoV-2) [51–54]. Another active metabolite of RDV, GS-5734 showed evidence in animal cell cultures, that it can block the replication of both, MERS-CoV and SARS-CoV [53]. A study by Holshue et al. in the USA reported that RDV in intravenous (IV) form, when administered to a COVID-19 patient, showed promising results [55]. Several clinical trials have been initiated to assess the safety and efficacy of RDV in COVID-19 patients. During the primary stages of the COVID-19 pandemic in China, a randomized, placebo-controlled, double-blinded, multicentric clinical trial was launched in February 2020, they recruited an experimental group of 308 patients and a placebo group of 452 patients. A preliminary dose of 200 mg of RDV was given to the experimental group, followed by a dose of 100 mg for 9 consecutive days via intravenous infusion. The results of this trial were expected by April 2020 but, unfortunately, the trial was terminated and the results of this study remain unknown [56]. A recent trial completed by the National Institute of Allergy and Infectious Diseases (NIAID) in December 2020, reported that RDV showed promising results compared to placebo and the recovery time among adults was substantially shortened [57].

Researchers are still trying to understand the pharmacokinetic profile of RDV, however, an anabolic intracellular kinase plays a key role in the metabolism of RDV [19]. According to the FDA, data related to the toxicity and adverse effects is limited as the drug is still being tested in several clinical trials, but so far it is known to cause nausea, increased ALT and AST levels, and hypersensitivity in some individuals [58].

4.6. Ribavirin

Ribavirin (RBV), a purine nucleoside analogue, was approved as a broad-spectrum antiviral drug by the FDA in 2003 [59]. It is mainly used for treating chronic Hepatitis C virus (HCV) infection, originally being approved for the treatment of severe RSV infection in children [60]. For chronic HCV treatment, it is given in combination with peginterferon-alfa. Apart from RSV and HCV, it has demonstrated activity against hepatitis B virus (HBV), Lassa fever [61], Influenza A and B [62], SARS-CoV [63], and MERS-CoV [64]. The binding activity of RBV triphosphate within the nucleotide-binding pocket of the enzyme

inhibits the synthesis of viral mRNA polymerase, which eventually results in the reduction of the viral load [65]. RBV inhibits mRNA capping which induces mutation in the viral replication. This mechanism of action makes RBV a potential candidate in the treatment of SARS-CoV-2 [66]. Several clinical trials are being conducted to check the efficiency of RBV in COVID-19 patients [67–70]. In a retrospective cohort study involving severe COVID-19 patients, Tong et al., reported that ribavirin was well tolerated by the patients and that there were no significant adverse effects observed [71]. Contrary to this, previous studies suggested that RBV is known to cause severe adverse effects, it is teratogenic and known to affect the nervous system causing depression, suicidal thoughts, insomnia and dyspnoea [40].

One way through which RBV is metabolized is a reversible phosphorylation pathway in nucleated cells, the alternative being a degradative pathway involving deribosylation and amide hydrolysis which results in a triazole carboxylic acid metabolite [72]. *In vitro* studies have reported that ribavirin alone is not a substrate of CYP450 enzymes [73]. However, Simeprevir (a combination of ribavirin and peginterferon-alfa) is metabolized by the cytochrome P4503A4 (CYP3A4) pathway [74]. In COVID-19 patients, RBV with a dose of 500 mg, 2–3 times a day in combination with LPV/RTV or IFN-α is given for ten days [75].

4.7. Darunavir

Darunavir (DRV) is a protease inhibitor that has been extensively used for the treatment of HIV-1 in combination with ritonavir. It was approved by the FDA in 2016 for treating HIV positive pregnant women [76]. Currently, it is being tested against SARS-CoV-2 infection, several clinical trials are underway and some of them are labelled as completed. Cell culture studies demonstrated that DRV tends to inhibit the replication of SARS-Cov-2 virus particles at a concentration of 300 μM [77]. A clinical trial in Qatar [78] is under process for studying the efficacy and safety outcomes of DRV/Cobicistat (cobicistat is a CYP3A4 inhibitor) with a dosage regimen of 800mg/150 mg, one tablet once daily. The studies by De Meyer et al. [79]and Chen et al. [80]suggest that DRV and cobicistat showed no antiviral activity against SARS-CoV-2.

CYP3A is a common metabolizing agent of DRV, and this metabolism is extensive in individuals who have not received any booster (ritonavir for example). The metabolism involved is primarily via isobutyl aliphatic hydroxylation, carbamate hydrolysis, and aniline aromatic hydroxylation. It may also occur via benzylic aromatic hydroxylation and glucuronidation [81]. The most reported adverse reactions to DRV include diarrhoea, nausea, rash, headache, abdominal pain, and vomiting [82].

4.8. Umifenovir

Umifenovir or Arbidol is a broad-spectrum antiviral drug and is currently licensed in Russia and China for the prophylaxis and treatment of influenza. But it is not yet approved by the FDA. It inhibits the fusion of the viral envelope with the host cell membrane, thereby blocking the entry of the virus into host cells and preventing viral infection and replication [83]. Its efficacy has been reported against several viruses; flaviviruses, foot and mouth disease, Lassa virus, herpes simplex virus and the Ebola virus [84–86]. Arbidol acts by binding to the hemagglutinin (HA) protein of the influenza virus. Comparative protein sequence analysis has demonstrated that a short region of the S2 domain of SARS-CoV-2 spike glycoprotein resembles influenza A H3N2 HA protein [87]. Hence, it is currently being studied as a treatment for COVID-19 [88]. Some recent small scale clinical studies with smaller sample sizes have drawn controversial conclusions about the efficacy of umifenovir for COVID-19. Wang et al. reported that treatment with umifenovir showed a high recovery rate and decreased mortality rate in their cohort [89]. However, Lian et al. reported no improved outcomes associated with umifenovir treatment [90].

The pharmacokinetics profile of umifenovir in *in vitro* studies explained that CYP3A4 is the major enzyme involved in metabolism, whereas other enzymes from P450 and a few flavin-containing monooxygenase (FMO) enzymes have minor contributions in metabolism pathways [91]. The detailed data on the adverse effects of umifenovir is not yet available.

4.9. Favipiravir

Favipiravir (Avigan) is a purine base analogue with a pyrazine carboxamide structure and was developed in 2014 in Japan as a treatment for the influenza strains that are resistant to neuraminidase inhibitors [92]. It has also been used against other RNA viruses like Ebola and norovirus [93]. Favipiravir targets RNA-dependent RNA polymerase (RdRp) enzymes, that interfere with the transcription and replication processes of viral genomes [94]. Due to its mechanism of action, researchers are using favipiravir against SARS-CoV-2, targeting its RdRp gene. Initially, favipiravir was used in Wuhan. As the pandemic spread to the rest of the world, it received approval for emergency use in several countries. Shannon et al. concluded that nucleoside analogues (favipiravir) are promising drugs for COVID-19 treatment [95]. Favipiravir is being evaluated in combination with other antivirals such as umifenovir to see whether these drugs interact in a complementary or collaborative manner [96]. Favipiravir showed efficacy in *in vitro* studies with half-maximal effective concentration (EC50) of 61.88 μM and half cytotoxic concentration (CC50) of around 400 μM, indicating that high concentration is required for effective treatment [97]. Both dose-dependent and time-dependent pharmacokinetics are exhibited by favipiravir. It is not metabolized by the cytochrome P450 system but has been shown to inhibit one of its components (CYP2C8) [98,99]. During the last few months, many clinical trials are being conducted in several countries for testing favipiravir against SARS-CoV-2. In China, a prospective open-label multicentric trial conducted by Chen et al. [100] compared two treatment arms; conventional therapy in combination with umifenovir (200 mg thrice a day) or favipiravir (1600 mg twice daily followed by 600 mg twice daily) for 7 days (extendable to 10 days). The recovery rate of both groups did not differ significantly. *Posthoc* analysis illustrated that favipiravir-treated patients showed clinical improvement on day seven. Another study from China [101] found that favipiravir had an enhanced antiviral action compared to LPV/RTV.

The adverse effects pertaining to this drug include increased uric acid level, diarrhoea, neutropenia, increased liver transaminases, teratogenicity, QT prolongation and possible psychiatric symptoms [102].

4.10. Amantadine

Amanatdine, an ion channel blocker was introduced in the 1960's as an antiviral drug against influenza A and accidently it showed activity against Parkinsonian (Parkinson's disease). The FDA licensed the use of amantadine in 1976 for the treatment and prophylaxis of influenza A [103,104]. The antiviral activity of amantadine prevents the release of viral nucleic acid into the host cell by interfering with the viral M2 protein [105]. Similarly, researchers are claiming that amantadine may interrupt the E-channel of coronavirus and thus prevent the release of the viral nucleic acids [106,107]. A retrospective cohort study evaluated amantadine among COVID-19 patients and did not find any significant effect in the treatment [108]. However, an *in vitro* study by Fink et al., reported that amantadine inhibits the replication of SARS-CoV-2 in Vero E6 cells [109]. A hospital-based cohort study represented the antiviral effect of amantadine in COVID-19 patients with known comorbidities (Parkinson's disease and multiple sclerosis) [110]. Clinical trials of amantadine against SARS-CoV-2 are under process at Copenhagen University Hospital [111] and Noblewell [112].

The most common adverse effects concerning to this drug include hypersensitivity, nausea, dizziness, insomnia [113]. Other complications include cardiotoxicity, CNS toxicity (seizures, blurred vision,

suicidal thoughts), renal and respiratory toxicity [105].

4.11. Molnupiravir

Molnupiravir (EIDD-2801 or MK-4482) is a prodrug of β-D-N4-hydroxycytidine (NHC), which is a ribonucleoside analogue and acts as a broad-spectrum antiviral against HCV, Ebola virus, coronaviruses, RSV and influenza viruses [114,115]. Molnupiravir has been shown to have antiviral effects against SARS-CoV-2 in both *in vitro* as well as *in vivo* (animal models) studies [116–118]. Studies suggest, the levels of viral RNA are lowered once this particular medicine is used. The drug was successful in completing the first two phases of clinical studies and is currently in Phase 3 clinical trial [119,120]. There were no possible investigations of neuropsychiatric effects of this drug, and the adverse events included headache and diarrhoea in a few patients [121].

List of experimental evidence for efficacies of above mentioned drugs is summarised in Table 1.

5. Neuropsychiatric side effects and drug-drug interactions of potent antivirals used to treat COVID-19

Emerging reports from patients suffering from COVID-19 note the effect of the virus on multiple organs and associated vasculature, especially the vasculature around the brain [124]. Particularly concerning the central nervous system (CNS), stroke, delirium, lethal clot formation, and rare cases of encephalitis are reported. Effects in the peripheral nervous system (PNS) are also reported in the form of loss of taste, smell, vision, and neuropathic pain [125]. *In-vitro* studies suggest that the SARS-CoV-2 viral spike protein could have significant effects on the integrity of the blood-brain barrier by interacting with vascular Angiotensin-converting enzyme 2 (ACE2), which is upregulated in cases of dementia [126], conditions that are largely seen in the ageing population. The spike protein has also been shown to elicit an inflammatory response in brain endothelial cells, which could contribute towards altered integrity of the blood-brain barrier (BBB) [127]. This could, in a clinical setting, increase the permeability of the CNS with respect to antiviral agents. This carries the potential of emergence of deleterious effects from antivirals, or the worsening of known effects in the CNS. It is therefore also imperative for healthcare workers and drug researchers to be knowledgeable with respect to the mechanisms of antiviral treatments, neuropsychiatric effects, and the possible drug-drug interactions (DDIs) with psychotropic medication. The brief summary of the proposed antiviral drugs for COVID-19 was explained in an earlier section of this review, but to understand the neuropsychiatric side effects and drug-drug interactions, refer to Table 2. Drug interactions with common therapeutics used in COVID-19 treatment are explained. Therapeutic recommendations from National Institutes of Health (NIH) [128] include: Dexamethasone (corticosteroid), Remdesivir (antiviral), antithrombotic drugs (e.g. Warfarin), Chloroquine or Hydroxychloroquine (antimalarial drugs) with or without Azithromycin (antibiotic), Lopinavir/Ritonavir (antiviral), and Ivermectin (antiparasitic drug), tocilizumab or baricitinib (immunosuppressive drug). Among these recommendations, the use of chloroquine or hydroxychloroquine with/without azithromycin has gained significant attention and currently remains debatable.

Table 1
Comparison of *in vitro* and *in vivo* efficacies of existing antiviral agents against SARS CoV-2 from the published literature.[a].

Drug	*In-vivo* study and trial result	*In-vitro* study result
Lopinavir/ ritonavir**	Not efficient [122] Trial results awaited [27]	Anti-SARS CoV-2 activity reported at concentration of LPV- 7 μg/mL and RTV- 1.75 μg/mL [24]
Oseltamivir**	Not efficient [34] Trial results awaited [39]	Not efficient [35,36]
Zanamivir	Anti-SARS CoV-2 activity reported [45]	Not efficient [36]
Peramivir	Not efficient [23,47]	Not efficient [23,47]
Remdesivir	Anti-SARS CoV-2 activity reported [55,57]	Anti-SARS CoV-2 activity was reported in Vero E6 cells at 1.76 μM concentration [97]
Ribavirin**	Anti-SARS CoV-2 activity reported [71] Trial results awaited [67–70]	NA
Darunavir**	Not efficient [79,80] Trial results awaited [78]	Anti-SARS CoV-2 activity at a concentration of 300 μM [77]
Umifenovir***	Anti-SARS CoV-2 activity reported [89]	Anti-SARS CoV-2 activity at a concentration of 21–36 μM [123]
Favipiravir*	Anti-SARS CoV-2 activity reported [100,101]	Anti-SARS CoV-2 activity at a concentration of around 400 μM [97]
Amantadine**	Anti-SARS CoV-2 activity reported [110] Trial results awaited [111,112]	Anti-SARS CoV-2 activity at a concentration of 83–119 μM [109]
Molnupiravir**	Anti-SARS CoV-2 activity reported [117,118] Trial results awaited [119,120]	Anti-SARS CoV-2 activity at a concentration of 3.4 μM and 5.4 μM [117].

[a] * trials completed; ** trials underway still; *** trials contradictory.

6. Lessons from oseltamivir

Oseltamivir (Tamiflu) was approved by the US FDA in 1999 to treat influenza within the first 48 h of the onset of symptoms [139]. The drug was also approved by the European Medicines Agency in 2002. The drug was generally described as safe with less than a 1% rate of discontinuation due to adverse effects in patients, based on two trials with 849 enrolled patients [140]. Based on these reports, concerns of an outbreak of avian flu, fuelled by the 2009–2010 H1N1 pandemic, countries around the world stockpiled enormous quantities of oseltamivir for their respective healthcare systems [141]. In 2010, in the wake of the H1N1 pandemic, WHO added Oseltamivir to the list of essential medications, cementing its place among the essential drug inventories, around the world [142]. However, several shortcomings in reporting around the safety of oseltamivir at individual patient levels from agencies such as the EMA, CDC and WHO were highlighted later in great detail [142].

A large-scale analysis of data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) revealed reports of neuropsychiatric adverse events (NPAE), described as 'abnormal behaviour', 'hallucination', and 'convulsion' associated with oseltamivir treatment [143]. Occurrence of 'abnormal behaviour' among male patients within the age range of 10–19 years was reported. It was also found that 59.4% of the adverse events were observed among people under the age of 16. This was attributed to the higher use of the drug in Japan among the paediatric population as well as a few other temporal reasons. In 2018, Kang et al. [144], reported a large case-crossover research from Korea which found a 1.2–8 times greater incidence of NPAEs 14 days following oseltamivir exposure compared to controls. The association was found to be consistent when the data was controlled for seasonality, age, sex, the Charlson comorbidity index, or the presence of Influenza related high-risk complications, indicating the contribution of oseltamivir to the NPAEs. These aforementioned findings fall in line with other studies and case reports from around the world, which demonstrates the increased risk of NPAEs, associated with the use of Oseltamivir. Suzuki et al. [145] demonstrated that oseltamivir sialylated a serum glycolipid that induced jump down behaviour via stimulation of D2 receptors in the brain. This effect on the dopaminergic

Table 2
Antivirals with their associated neuropsychiatric effects and drug-drug interactions (DDIs).

Proposed antiviral treatment	Contraindications	Common Adverse effects	Neuropsychiatric side effects	Drug-drug interactions	Sources
LPV/RTV	Hypersensitivity	Diarrhoea, vomiting, nausea, hypercholesterolemia, hypertriglyceridemia, pancreatitis	–	Drugs requiring high CYP3A dependence for clearance, CYP3A inducers	[22]
Oseltamivir	Hypersensitivity	Nausea, vomiting, diarrhoea, abdominal pain	Increased risk of confusion, abnormal behaviour, delirium, delusion, hallucination	Not a substrate nor does it affect CYP450 isoenzymes	[11–13].
Zanamivir	Hypersensitivity	Sinusitis, bronchitis, dyspnea, fever or chills, diarrhoea, arthralgia, and articular rheumatism	Headache and dizziness in adults Seizures, confusion, abnormal behaviour among the pediatric age group	Not a substrate nor does it affect CYP450 isoenzymes	[129]
Peramivir	Hypersensitivity	Skin reactions	Depression, hallucinations, confusion, delirium, restlessness, abnormal behaviour, anxiety, and nightmares	Can alter the efficacy of live attenuated influenza vaccines.	[130–132]
Remdesivir	Hypersensitivity	Increased transaminase levels	–	Chloroquine/Hydroxychloroquine co-administration may reduce the anti-viral activity	[58,133]
Ribavirin	Monotherapy: Hypersensitivity, pregnancy, haemoglobinopathies heart disease Combination therapy with pegylated interferon alfa-2a: autoimmune hepatitis, hepatic decompensation, pancreatitis, organ transplant	Monotherapy: Itching and rash Combination therapy with pegylated interferon alfa-2a: autoimmune and infectious disorders, suppression of bone marrow function, haemolytic anaemia, diabetes, pulmonary dysfunction, pancreatitis, dyspnoea, pulmonary infiltrates, sarcoidosis, pneumonitis	Depression, suicidal ideation, dizziness, confusion, somnolence, insomnia	does not inhibit CYP450 enzymes. - Zidovudine - Stavudine - Didanosine	[134,135]
Darunavir	Acute/cytolytic hepatitis, skin reactions, sulfonamide allergy	–	–	Alfuzosin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, oral midazolam, triazolam, St. John's Wort, lovastatin, simvastatin, rifampin and sildenafil (for treatment of pulmonary arterial hypertension)	[82]
Favipiravir	Pregnancy	Hyperuricemia, diarrhoea, reduced neutrophil count	Abnormal behaviour, anxiety, insomnia, so on (Very rare)	Pyrazinamide, Pyrazinamide, Theophylline, Famciclovir, sulindac, Acyclovir	[102,136]
Amantadine	Hypersensitivity, Pregnancy	Cardiotoxicity, arrhythmias, tachycardia, Acute respiratory failure, pulmonary edema, hypersexuality, elevated serum creatinine, alkaline phosphatase, bilirubin, etc.	Delirium, seizures, hypokinesia, delusions, aggressive behaviour, blurred vision, depression, agitation, hallucinations, etc.	Anticholinergic drugs, Acetaminophen Can alter the efficacy of live attenuated influenza vaccines.	[105,137, 138]

system may be associated with 'abnormal behaviours'. Additionally, the presence of an inflammatory state associated with Influenza has been shown to increase the level of IL-6 expression, leading to the increase in the relative concentration of unmodified oseltamivir by inhibiting its carboxylation in the liver [146]. This prodrug usually has limited penetration across the BBB (Fig. 1) due to the presence of P-glycoprotein (P-gp), as demonstrated in murine models. However, the infection and inflammation also alter the activity of the P-gp at the BBB [147]. The combined effect of these phenomena could lead to an increase in the concentration of unmodified oseltamivir in the brain as well as the serum, which may cause a sudden onset of NPAEs within 24 h of the administration of the drug [148]. The lack of expository data analysis, and the joint action of the infection as well as the drug molecule, provide an exemplary blueprint against the haphazard use of drugs in the current as well as future pandemic situations.

7. Conclusion

In this review, we compiled and discussed the *in vitro* and *in vivo* efficacies of various antiviral agents against the SARS-CoV-2 virus. We also emphasized the reported drug-drug interactions and neuropsychiatric effects of the available antiviral agents. A large section of the literature on antivirals focuses on studies performed on murine models, and the effects of antivirals on the human brain must be thoroughly investigated in order to establish reliable treatment regimens for COVID-19 and other emerging and re-emerging viral infections. Optimizing the use of antiviral agents either as mono or in combination therapy after careful consideration of the potential adverse side-effects is warranted.

Funding

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Madhura Punekar: Writing – original draft, Conceptualization. **Manas Kshirsagar:** Writing – original draft, Conceptualization. **Chaitanya Tellapragada:** Writing – review & editing. **Kanchankumar Patil:** Writing – review & editing.

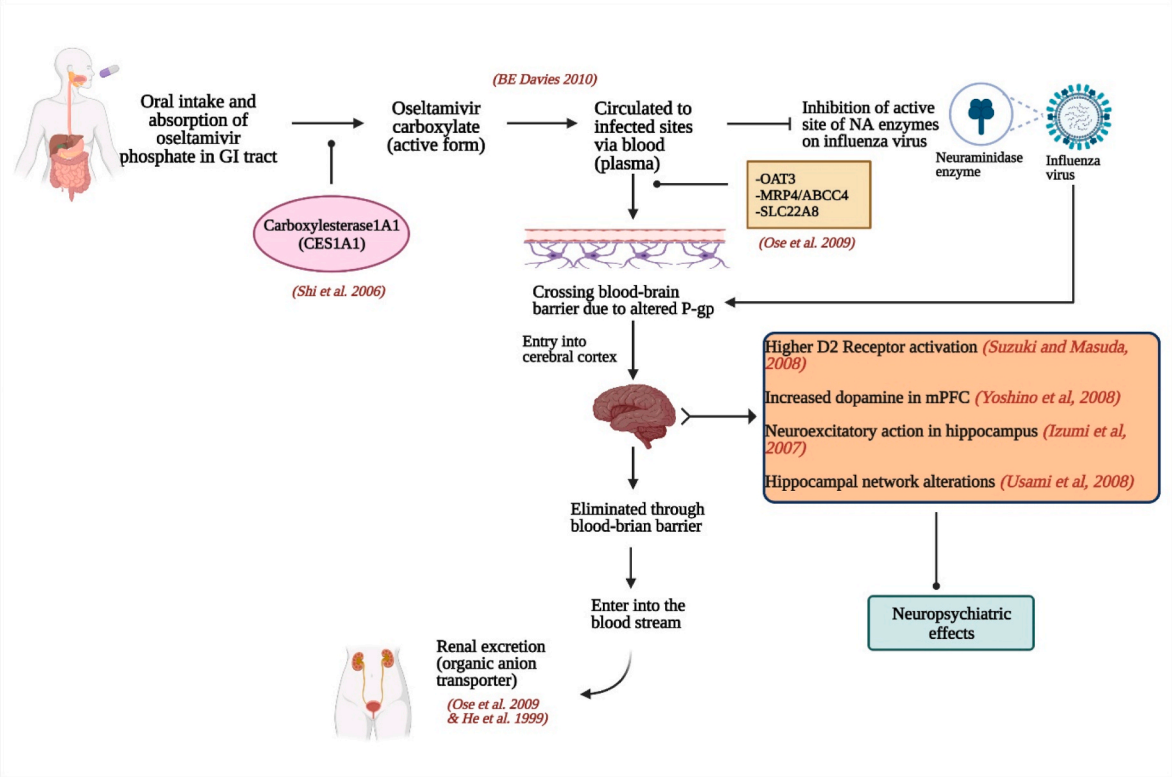

Fig. 1. Probable mechanism of Oseltamivir causing NPAEs Oseltamivir is ingested in the form of an oral prodrug (oseltamivir phosphate; OP), which is then absorbed in the gastrointestinal (GI) tract and metabolized to the active form, oseltamivir carboxylate (OC) by hepatic esterases-carboxylesterase1A1 (CES1A1) [42]. OC is then circulated in the blood and is distributed to the infected sites via plasma to inhibit the neuraminidase (NA) enzyme present in the influenza virus. The distribution of oseltamivir in the brain is attributable to the active efflux at the BBB via the transporter proteins- OAT3 (organic anion transporter 3), MRP4 (multidrug resistance protein 4) and SLC22A8 (solute carrier family 22 member 8) [149]. The efflux takes place because of alteration in the P-gp gene [147]. The function of P-gp is to guard the BBB by not allowing the drug to cross the BBB [149]. The drug then enters the cerebral cortex where the neuropsychiatric effects are observed. Eventually, oseltamivir is eliminated through BBB with the help of MRP4 and OAT3 in the bloodstream. And finally, the drug is excreted from the body via renal excretion by organic anion transporter proteins [150].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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