Review Article

Hacettepe University Journal of the Faculty of Pharmacy
Volume 42 / Number 3 / September 2022 / pp. 187-198

Antiviral Activity of Approved Centrally Acting Drugs: A Narrative Review

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Received date : 27.12.2021
Accepted date : 12.08.2022

DOİ: 10.52794/hujpharm.1047842

ABSTRACT

The emerging and re-emerging of viral infections represent serious problems with many of them affecting the nervous system; many of these viral infections still lacks an effective vaccine or treatment. To overcome viral infections three major approaches are being followed which are developing effective vaccines, de novo antiviral drug discovery and drugs repurposing to be used for viral infections. . Regarding drug repurposing approach, many drugs from different classes were documented as candidates for repurposing for antiviral use, moreover drugs that showed antiviral activity while being already used for nervous system purposes present promising candidates for repurposing, having an advantage of being able to pass through the blood-brain barrier and easily reaching the nervous system. This narrative review article was written as a part in the effort to overcome viral infections, the review summaries the researches that focused on the antiviral activity of drugs originally approved for their effect on the nervous system. And in order to help other researchers to relate between the effect of the drugs on members within thhe same family and the effect on viruses of different families, the findings were arranged in sections based on the classification of viral families to which viruses used in the studies documented belong.

Keywords: Antiviral activity, Drug repurposing, Central nervous system, Approved drugs.

Introduction

Many viral infections are still causing important threats to human being, with the challenging fact that there are no efficient conventional medications or vaccines for most of these viral infections [1]. In the past years, drug repurposing combined with proper drug screening models and approaches significantly contributed to the identification of new antiviral molecules and targets for therapeutic intervention [2]. However, there are still only a few successful examples for drug repurposing in antiviral drug discovery. However, it was also stated that the drug repurposing approach provided promising drug candidates for various viral infections such as Ebola, ZIKA, dengue, influenza, human immunodeficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV) infections, and other infectious diseases [3].

Several viral diseases affect the human central nervous system (CNS), resulting in considerable damage when viruses replicate in the tissues of the nervous system, such as rabies, polio, and West Nile fever which are perhaps the most recognized diseases [4]. These viruses are considered one of the causes of aseptic meningitis, encephalitis, or meningoencephalitis [5]. Regarding the treatment of infections targeting the nervous system, it was mentioned that it is important to find drugs that are able to pass easily through the blood-brain barrier (BBB) and diffuse largely in the CNS at therapeutic concentrations to prevent brain inflammation and reduce neurological complications of SARS-CoV-2 infection [6]. This fact can be generalized to infections that affect the nervous system, and drugs initially approved for their rule in CNS have this condition. It assumes that drugs that act by altering virus-neuron interactions will also affect clinically apparent and clinically unapparent recurrent infections [7]. The following sections will summarize the research results conducted to evaluate the antiviral activity of drugs approved originally for their effect on the central or peripheral nervous system, structured according to the families of the viruses involved in the studies. Figure 1 and Table 1 demonstrated the possible mechanisms for antiviral activity of approved CNS drugs.

1. Drugs affecting bunyaviridae viruses

Members of the bunyaviridae family are single-stranded negative-sense RNA viruses with pleomorphic morphology, the large family of bunyaviruses is a pool for many emerging and re-emerging viruses, such as Rift Valley fever virus, Crimean-Congo hemorrhagic fever virus (CCHFV), and the hantaviruses, and also for recently emerged pathogens, such as severe fever with thrombocytopenia syndrome virus [5].

Chlorpromazine which is an approved neuroleptic drug that have antipsychotic action due to blocking dopamine receptors in the mesolimbic system of the brain, was found able to inhibit CCHFV replication in vitro when used alone, and also showed that CCHFV titer was still markedly reduced when chlorpromazine was added up to 24 hours post-infection, suggesting another post entry inhibitory effect, besides when used in combination with ribavirin, the pharmacodynamics interaction was synergistic as observed in Vero cells. However, this study also stated that the low selectivity index of chlorpromazine diminished its potential clinical use, particularly if this drug is used alone [8].

2. Drugs affecting coronaviridae viruses

Coronaviridae family viruses are huge, enveloped, single-stranded RNA viruses divided into two subfamilies, the Coronavirinae, which includes the coronaviruses (CoVs) and the Torovirinae [9]. Many approved CNS drugs were evaluated for their effect on coronaviridae viruses.

Chlorpromazine hydrochloride strongly inhibited MERS-CoV and SARS-CoV in vitro in Vero E6 cell line with micromolar EC50 and low toxicity [10]. It also showed strong anti-MERS-CoV activity in monocyte-derived macrophages (MDMs) and dendritic cells (MDDCs), but it was associated with high cytotoxicity [11]. Additionally, in vivo study in the MA15 strain of SARS-CoV mouse-adapted virus model showed that chlorpromazine did not inhibit SARS-CoV replication in mice lungs, but significantly reduced weight loss and clinical signs proving that the drug was able to protect mice from signs of disease following infection [12]. Another drug studied for its therapeutic effect against infections induced by coronaviridae viruses is clomipramine, a tricyclic antidepressant that showed in vitro activity against MERS-CoV and SARS-CoV in a primary screening experiment in the Vero E6 cell line [10]. Furthermore, in silico study of the antipsychotics drug pimozide showed that it displayed a potent inhibitory effect on

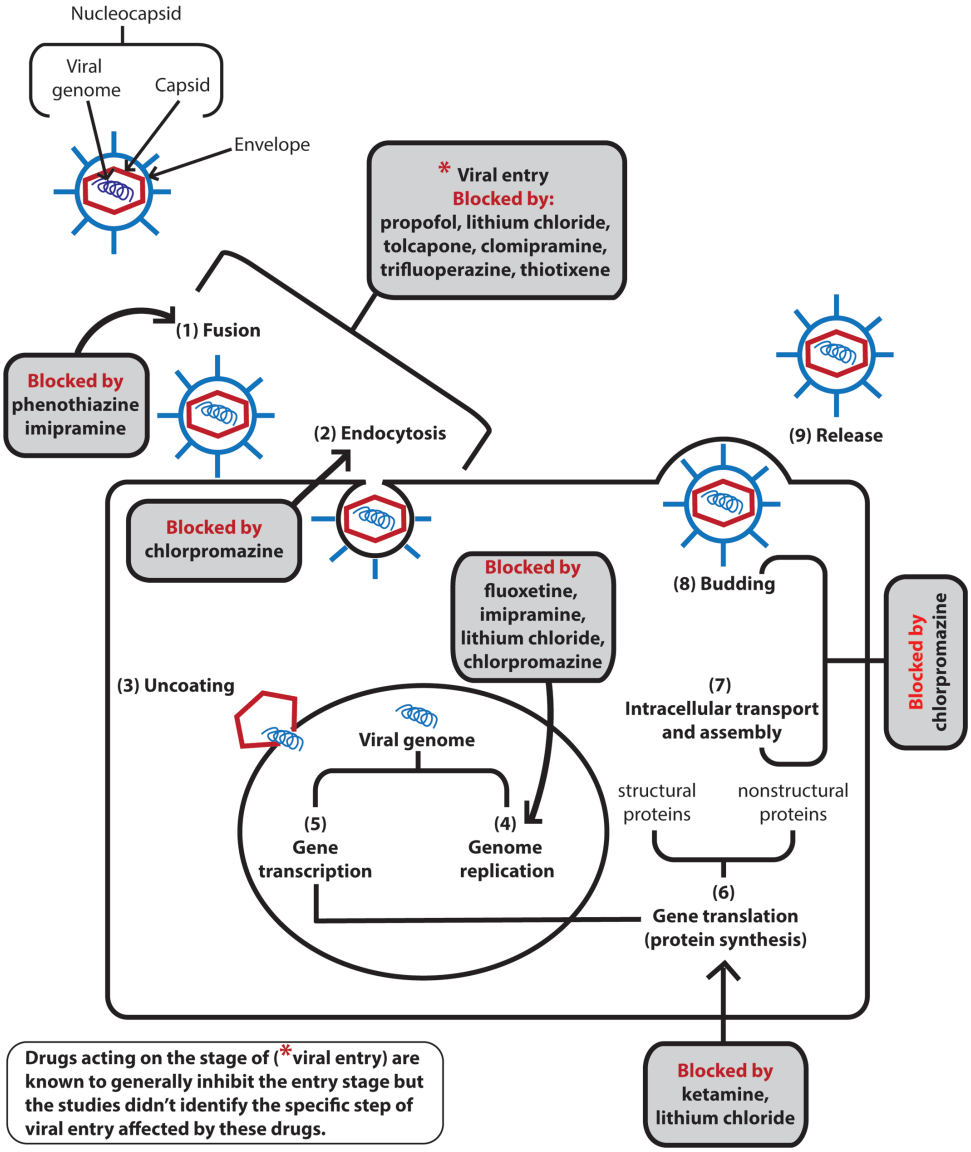

Figure 1. Illustration for suggested stages of viral infection at which approved CNS drugs exerts their antiviral effect according to the studies that focus on the antiviral mechanism of action.

SARS-CoV-2 main protease (Mpro) and the ability to raise the pH of endosomes; however, the cytopathogenic effect was clearly observable with pimozide in vitro at all tested concentrations [13]. The antipsychotic drug Flupentixol which was approved for treatment of schizophrenia and other psychoses and depressive illness was also identified as an important candidate for drug repositioning against SARS-CoV-2, as it showed probability for interaction with the catalytic site of both SARS-CoV-2 (Mpro) and RNA-dependent RNA polymerase (RdRp) enzymes [14]. Flupentixol was also able to down-regulate SARS-CoV-2 gene expression in silico, whereas naltrexone which is an opioid-receptor antagonist showed the ability to revert the transcriptional signature induced by SARS-CoV-2 infection [15].

Memantine which is a blocker of the N-methyl-D-aspartate (NMDA) receptor channels and is approved for management of Alzheimer's disease showed the ability to improve the clinical condition and exert a neuroprotective effect on human coronavirus strain OC43 (HCoV-OC43) infected mice, a decrease in mortality rates and body weight loss and reduction in HCoV-OC43 replication in the central nervous system in a dose-dependent manner [16]. Another in

ISSN: 2458 - 8806

silico study documented that memantine has a potential inhibitor of the SARS-CoV-2 E protein, which is essential for virus virulence [17]. Propofol, a sedative-hypnotic agent, showed the ability to inhibit SARS-CoV-2 pseudovirus (SARS2-PV) entry in an in vitro study [18].

While knowing that Lithium salts are used mainly for prophylaxis and treatment of mania, hypomania and manic-depressive disorder, and in the prophylaxis and treatment of recurrent unipolar depression, one of its salts which is lithium chloride inhibits the avian coronavirus infectious bronchitis virus (IBV) in cell culture, as treatment with lithium chloride reduced IBV progeny virus production in both Vero and DF-1 cells in a dose-dependent manner, and the results indicated that the inhibition was due to cellular rather than a virucidal effect [19]. Also, lithium chloride effectively inhibits entry and replication of porcine epidemic diarrhea virus (PEDV) in Vero cells, the expression of viral RNA and protein of PEDV in Vero cells was suppressed in a dose-dependent manner by lithium chloride. Moreover, adding lithium chloride inhibited both early and late cell apoptosis induced by PEDV [20].

A special focus on SARS-CoV-2

Centrally acting drugs showed ability to interfere with SARS-CoV-2 infection at different stages of this virus life cycle, starting from cell entry which was subjected to inhibition by pimozide which showed the ability to raise the pH of endosomes, this drug was also able to interfere with viral rreplication by inhibiting SARS-CoV-2 main protease (Mpro) [13]. SARS-CoV-2 replication was also a subject for inhibition by flupentixol which can result from affecting to important enzymes, namely SARS-CoV-2 Mpro and RdRp [14]. Additionally naltrexone was predicted to have the ability to reverse the gene expression of the virus hence reverting the transcriptional signature induced by SARS-CoV-2 infection [15], wereas memantine was suggested to be able to reduce viral virulence by inhibiting SARS-CoV-2 E protein [17]. Finally propofol was expected to have inhibitory effect on SARS-CoV-2 infection since it showed ability to inhibit SARS-CoV-2 pseudovirus [18].

3. Drugs affecting filoviridae viruses

Filoviruses are pleomorphic viruses, they are long, filamentous, enveloped particles that may be branched, and they include the Marburg virus and Ebola virus (EBOV), which cause severe hemorrhagic fever [21].

In vitro studies showed that the catechol-O-methyltransferase (COMT) inhibitor tolcapone which is used in management of Parkinson's disease, has the ability to inhibit the EBOV in seminal amyloid fibrils; it was also suggested that tolcapone inhibits viral entry, possibly through binding with critical residues in EBOV glycoprotein. Moreover, tolcapone combined with bepridil and sertraline exhibited synergistic anti-EBOV effects [22]. On the other hand, sertraline which is originally a selective serotonin reuptake inhibitor used for treatment of depression showed antiviral activity against EBOV in both in vitro and in vivo studies [23,24]. However, it was documented that high dose sertraline monotherapy provided no benefit for preventing EBOV disease in rhesus macaques with regards to reducing viral load, morbidity, or survival [25]. Another in vitro study documented that three antipsychotic drugs, namely clomipramine, trifluoperazine, and thiothixene, have inhibitory effects on EBOV virus-like particle (EBOV-VLP) entry [24].

4. Drugs affecting flaviviridae viruses

The flaviviridae are a family of positive, single-stranded, enveloped RNA viruses which include imperative human pathogens like yellow fever virus (YFV), dengue virus, Japanese encephalitis virus (JEV), West Nile viruses (WNV), Zika virus, and hepatitis C virus (HCV) [26]. The antiviral activity of different CNS medications such as flupentixol, chlorpromazine, fluoxetine, and imipramine was evaluated against flaviviridae viruses.

Phenothiazines exhibited antiviral effect against HCV in in vitro study with flupentixol exhibiting the most potent activity with an IC50 of 0.25 μM and a selectivity index (SI) of 20, and the study suggested that flupentixol and phenothiazines inhibit HCV cell entry by increasing target host cell membrane fluidity and inhibit the fusion of these membranes with HCV [27]. On the other hand, chlorpromazine characteristic inhibitory effect for clathrin-dependent endocytosis, which enables it to block an early step in the viral entry process, was documented in vitro against JEV and WNV [28, 29].

Furthermore, a previous in vitro study showed that fluoxetine which is a selective serotonin reuptake in-

hibitor that is mainly used for major depression, bulimia nervosa and obsessive-compulsive disorder, was able to HCV infection in human hepatoma cell line beside promoting IFN-a-mediated inhibition of HCV through the signal transducer and activator of transcription (STAT)-1 and c-Jun amino-terminal kinases (JNK) dependent pathways, suppressing lipid accumulation through JNK and peroxisome proliferator-activated receptor (PPARβ/γ) mediated action, and blockade of ROS production [30]. Fluoxetine was also identified as a dengue virus replication inhibitor in an in vitro screening assay [31]. Whereas the approved antidepressant drug imipramine strongly inhibited, in a dose-dependent manner, the replication of WNV, dengue virus, and Zika virus in human skin fibroblasts in vitro without secondary cytotoxic effects [32].

5. Drugs affecting herpesviridae viruses

Human herpesviruses are DNA viruses that include herpes simplex virus (HSV), B virus, varicella-zoster virus (VZV), cytomegalovirus (CMV), and other pathogenic viruses [33]. Some approved drugs acting originally on the CNS and local anesthetics showed antiviral activity against herpesviruses such as lamotrigine, lithium chloride, sodium valproate, and local anesthetics.

Lamotrigine which is originally used for its antiepileptic effect which results from blocking sodium channels as well as voltage dependent calcium channels showed the ability to produce a moderate inhibition of human herpesvirus-6 (HHV-6) replication in an in vitro study [34]. Lithium chloride also showed antiviral activity as previous in vitro studies documenting that it does not only have an inhibitory effect on HSV but also protects against virion-associated inhibition of host protein synthesis [35], and further studies showed that lithium chloride interferes with DNA synthesis [36,37]. Furthermore, a randomized, double-blind, placebo-controlled study of the effect of oral lithium carbonate on patients with at least four recurrent HSV infections in a year found that lithium treatment reduced the mean number of episodes, the average duration of each episode, and the severity of the symptoms [38]. In addition, a retrospective clinical investigation found that chronic lithium carbonate medication reduced the mean rate of recurrent labial herpes infections significantly [39].

On the other hand, there was inconsistency in in vitro studies targeting the effect of the antiepileptic drug sodium valproate on HSV-1, as a study showed that combined treatment of infected cells with acyclovir and sodium valproate potentiated the antiviral activity of acyclovir in a manner dependent to sodium valproate concentration [40], while another one documented that sodium valproate stimulates HSV-1 replication. However, this study also stated that the inhibitory or stimulatory effect of sodium valproate could not be confirmed until appropriate in vivo assessments were done [41].

Chlorpromazine also showed the ability to influence HSV infection as it was able to inhibit the hemadsorption of HSV-infected cells in vitro [42]. Another in vitro study showed that chlorpromazine inhibited intracellular HSV expression in a concentration-dependent manner [43]. The drug was also able to block Epstein-Barr virus (EBV) infectivity of isolated adult human B cells in vitro, suggesting that the effect is due to inhibiting of EBV endocytosis into B cells resulting from antagonizing calmodulin and calmodulin-regulated cellular enzyme [44]. Chlorpromazine also inhibited clathrin-mediated endocytosis of human herpesvirus 8 (HHV-8) human foreskin fibroblasts in vitro [45].

Additionally, capsaicin, a neuro-pharmacological agent, showed the ability to inhibit viral anterograde transportation in vivo [46]. Also, the treatment of HSV infections in a guinea pig model with cis-capsaicin which originally have analgesic properties resulted in a long-lasting reduction in recurrent genital herpes skin disease, with a significant reduction in the severity of the disease, especially when given in primary infection rather than latent infection. It was also indicated that an infrequent suppressive maintenance therapy by cis-capsaicin against HSV infection might be potential [7].

Herpes simplex viruses also showed sensitivity towards local anesthetics such as lidocaine, as topical application of lidocaine showed inhibitory effects on HSV infection resulting in faster recovery as observed in previous clinical reports [47]. Also, other local anesthetics such as bupivacaine and mepivacaine demonstrated the ability to inhibit HSV-1 replication in vitro when concentrated solutions are used with adrenaline [48].

6. Drugs affecting orthomyxoviridae viruses

Orthomyxoviridae members are spherical, enveloped viruses with a segmented, negative-strand RNA

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genome; these viruses are divided into influenza A, B, and C, with only influenza A and B strains being of medical importance [21].

In a previous study, naltrexone inhibited viral replication of influenza A viruses in vitro in a dose-dependent manner without causing toxicity. It showed high activity against both H1N1-PR8 and H1N1-pdm09 viruses but was less efficient against the H3N2 virus; however, it had no significant effect on viral replication when evaluated in vivo [49]. Chlorpromazine also demonstrated the ability to inhibit influenza A virus replication in vitro [50].

7. Drugs affecting paramyxoviridae viruses

The paramyxoviridae members are RNA viruses divided mainly into three subgroups: paramyxoviruses, pneumoviruses, and morbilliviruses, and they include many pathogenic viruses [51]. An in vitro study showed that chlorpromazine effectively blocked the assembly and budding of Sindbis and vesicular stomatitis virus from chicken embryo fibroblast cells without greatly inhibiting general protein synthesis [52].

8. Drugs affecting picornaviridae viruses

The picornaviruses are small non-enveloped viruses with a single-stranded RNA genome, and the species that causes clinical syndrome in humans belonging to the enteroviruses, rhinoviruses, and hepatoviruses subfamilies [21].

Fluoxetine was identified as a potent inhibitor of coxsackievirus replication, and it was shown able to markedly reduce the synthesis of viral RNA and protein [53]. This finding could be augmented with another study that documented the inhibitory effect of fluoxetine against coxsackievirus in both in vitro and in vivo models [54]. Fluoxetine was also found to inhibit the replication of human enterovirus B (HEV-B) and HEV-D in vitro, and it was documented that the drug interferes with viral RNA replication, and the drug was identified as a viral protein 2C-targeting molecule [55]. The thioxanthene antipsychotic neuroleptic drug Zuclopenthixol which exerts its antipsychotic effect by antagonizing dopamine receptors, also showed an inhibitory effect against coxsackievirus B3 (CV-B3) in in vitro screening, although it was documented that mutations in viral protein 2C resulted in resistance to zuclopenthixol (56). Chlorpromazine which was documented as a clathrin-dependent endocytosis inhibitor, also showed activity in vitro against Human parechovirus 1 (HPEV-1) [57].

9. Drugs affecting polyomaviridae viruses

Polyomaviruses are small, non-enveloped, double-stranded DNA viruses, human illnesses associated with these viruses include progressive multifocal leukoencephalopathy (PML) which is caused by JC polyomavirus (JCV) and is a frequent complication in individuals with HIV/AIDS [5].

An in vitro study showed that chlorpromazine has antiviral activity against JCV, possibly by inhibiting virus entry by disrupting clathrin-mediated endocytosis [58]. Moreover, a further study confirmed that chlorpromazine has the ability to inhibit JCV multiplication and spread in nontoxic doses in vitro [59]. Chlorpromazine also showed antiviral activity against simian virus 40 (SV 40) in vitro, and it was documented that the drug has a strong ability to inhibit the pre-elongation step of SV 40 DNA replication [60].

10. Drugs affecting retroviridae viruses

The family retroviridae includes several pathogenic viruses with clinical importance to humans; members of this family are characterized by the presence of the reverse transcriptase enzyme, which converts a single-stranded RNA viral genome into double-stranded viral DNA, and HIV and human T-cell lymphotropic viruses (HTLV) represent the two main genera of human interest [21].

An ex vivo study that evaluated the antiviral effect of the selective serotonin reuptake inhibitor citalopram which is originally approved for treatment of depression and panic disorder, the study suggested that the drug may inhibit HIV entry and replication in T-cells and monocytes/macrophages by increasing extracellular serotonin concentrations, which in turn may decrease expression of CD4, CCR5 and CXCR4 receptors on the immune cells on peripheral blood, in addition to increasing the release of anti-HIV chemokines such as CCL3, CCL4, and CCL5, which block CD4, CCR5, and CXCR4 receptors, further limiting HIV infectivity [61]. Another drug that showed activity against HIV-1 is diazepam which is a benzodiazepine drug that exterts its anxiolytic, skeletal muscle relaxants and anticonvulsant effects by bind to GABA inhibitory receptors in the CNS to reduce firing rate. Diazepam exhibited inhibitory ef-

fect HIV-1 p24 antigen expression in acutely infected human brain cell and enriched microglial cell cultures, it also suppressed HIV-1 expression in chronically infected promonocytic (U1) cells and acutely infected monocyte-derived macrophages, and it was stated that the antiviral activity of diazepam was associated with decreased activation of nuclear factor kappa B [62].

Memantine was also found able to display a significant anti-HIV effect at a concentration of 1 μg/ml on enriched cultures of glial fibrillary acidic protein (GFAP+) cells in vitro, and the drug was able to return the growth rate of the HIV-infected cells back to normal [63]. Naltrexone, on the other hand, was found able to potentiate the anti-HIV-1 activity of antiretroviral drugs in CD4+ lymphocyte cultures in vitro [64]. Similarly, a clinical trial found that using a combination of sodium valproate as a deacetylase inhibitor with peg-IFN as an immunomodulator, and prednisolone as an anti-inflammatory medication resulted in a significant reduction in HTLV-1 proviral load, anti-HTLV-1 antibody titer, HTLV-1 basic leucine zipper factor (HBZ) and Tax mRNA expression, and a significant improvement in motor disability and spasticity in patients with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) after six months of treatment [65].

11. Drugs affecting rhabdoviridae viruses

Rhabdoviridae family is a large and ecologically diverse group of viruses; it consists of single-strand RNA viruses. The viruses affecting vertebrates are divided into well-known (classical) vertebrates rhabdoviruses, such as vesicular stomatitis virus (VSV) and rabies virus, and novel rhabdoviruses with complex genomes [66]. Reviewing researches regarding this family shows that ketamine, a drug approved as an anesthetic which exerts its effect due to its NMDA antagonistic action, has been investigated in many researches for its therapeutic effect in rabies infection.

Ketamine demonstrated in vitro and in vivo inhibitory activities against rabies virus production. It inhibited the rabies virus production in neuroblastoma cells in vitro and the viral infection in the thalamus, cortex, and hippocampal formation in the rats model [67]. Another study also confirmed the antiviral effect of ketamine on the rabies virus. It stated that ketamine affected nucleoprotein and glycoprotein syntheses. The study's finding suggests that the antiviral effect is at the level of rabies virus genome transcription since there was no observation for modification of cellular protein or mRNA synthesis [68]. However, clinical observations were not consistent as some clinical findings supported using ketamine to treat rabies infection [69,70]. On the other hand, a case report showed failure in the treatment of rabies with ketamine along with other drugs [71].

12. Drugs affecting togaviridae viruses

The togaviruses are enveloped viruses that contain a single-stranded RNA genome and generally three structural proteins, which are the capsid protein and two glycoproteins that form the hemagglutinin-containing viral spikes that project from the lipid bilayer; examples for viruses from this family include chikungunya virus and rubella virus [21].

Imipramine showed the ability to inhibit chikungunya virus replication in human skin fibroblasts, and it was demonstrated that the drug exerts its inhibitory effects on the chikungunya virus at least at the stages of viral fusion and RNA replication step, suggesting the drug's utility in both preventing infection of new target cells and reducing the virus's reproduction rate in cells already infected [32]. Another drug that was documented to have antiviral activity against the chikungunya virus is pimozide, which demonstrated high in vitro activity, with low toxicity, it also showed a therapeutic effect in vivo when combined with the fatty acid synthesis inhibitor 5-tetradecyloxy-2-furoic acid (TOFA) [72].

Perspectives and conclusion

While taking into account the risk of viral infections on the nervous system directly or indirectly by targeting and replicating in the tissues of the nervous system, or resulting in inflammation and attracting the immune response, many researches were done to evaluate the antiviral effect of drugs originally approved for their neurological effect on both peripheral and central nervous system. A justification for this approach of antiviral drug research may be that it is logical to seek drugs that have an antiviral effect and have the ability to reach the nervous system peripherally or centrally easily bypassing blood-brain barrier. Drugs that originally approved for their effect on the nervous system can be considered as promising candidates for repurposing if they showed antiviral

ISSN: 2458 - 8806

Table 1. Possible mechanism for antiviral activity of approved drugs used for CNS purposes

Drug	Suggested mechanism of action	Type of study	Susceptible virus	References
Chloropromazine	Inhibiting viral endocytosis	In vitro	Japanese encephalitis virus	[28]
		In vitro	West Nile virus	[29]
		In vitro	Epstein-Barr virus	[44]
		In vitro	Human herpesvirus 8	[45]
		In vitro	Human parechovirus 1	[57]
		In vitro	JC virus	[58]
	Inhibiting intracellular viral expression	In vitro	Herpes simplex virus	[42]
	Blocking viral assembly and budding	In vitro	Sindbis virus and vesicular stomatitis virus	[52]
	Inhibiting the pre-elongation step of DNA replication	In vitro	Simian virus 40	[60]
Clomipramine	Inhibiting viral entry	In vitro	Ebola virus like particle	[24]
Diazepam	inhibitory effect HIV-1 p24 antigen expression	In vitro	Human immunodeficiency virus	[62]
Fluoxetine	Suppressing lipid accumulation through JNK and (PPARβ/γ) and block ROS production	In vitro	Hepatitis C virus	[30]
	Interfering with viral RNA replication	In vitro	Coxsackievirus	[53-54]
		In vitro	Human enterovirus –B and –D	[55]
Flupentixol	Inhibiting viral entry	In vitro	Hepatitis C virus	[27]
Imipramine	Inhibiting viral entry and viral RNA replication	In vitro	Chikungunya virus	[32]
Ketamine	Inhibiting viral genome transcription	In vitro	rabies virus	[68]
Lithium chloride	Inhibiting viral entry and replication	In vitro	Porcine epidemic diarrhea virus	[20]
	Interfering with herpes simplex virus DNA synthesis	In vitro	Herpes simplex virus	[36-37]
Memantine	Inhibiting SARS-CoV-2 E protein	In silico	SARS-CoV-2	[17]
Pimozide	Increasing pH of endosomes and inhibiting viral main protease (Mpro)	In vitro	SARS-CoV-2	[13]
Propofol	inhibiting viral entry	In vitro	SARS-CoV-2 pseudovirus	[18]
Thiothixene	Inhibiting viral entry	In vitro	Ebola virus like particle	[24]
Tolcapone	inhibiting viral entry	In vitro	Ebola virus	[22]
Trifluoperazine	Inhibiting viral entry	In vitro	Ebola virus like particle	[24]

activity with sufficient evidence for their therapeutic effect and safety during their use for antiviral effect. Although the originally known effects of these drugs on the nervous system may result in adverse effects which represents a disadvantage for their repurposing, they also have the advantage of easily reaching the nervous system. Hence it is suggested to consider further and evaluate the ratio between the risks and benefits of this approach, and also to consider the possibility of regarding these approved drugs with

antiviral activity as lead compounds and trying to optimize their antiviral activity them rather than their original effect on the CNS without losing their ability to transport through the body and reach the nervous system.

From the collected and summarized mechanistic studies it could be noted that centrally acting drugs exerts their antiviral effect using the traditionally known antiviral mechanisms, i.e. inhibiting cell entry, interfering with uncoating process, affecting transcription and translation of viral genome, causing post-translational modifications or interfering with assembly of virion components or new viruses release. Although there were many centrally acting drugs that were studied for antiviral effect, yet not many researches were done for those that exhibited activity. For those drugs that were subjected for mechanistic studies it can be noted that antipsychotic drugs generally acts by interfering with virus entry although for many of the antipsychotic drugs it was not specified if the effect was exerted at the attachment or penetration step of cell entry, but looking back at the available information for the members of this class that were studied more deeply it can be ruled out that inhibition of viral entry is related to their original effect on antagonizing dopamine since they showed diverse mechanisms by which they could inhibit viral entry such as inhibiting receptor dependent endocytosis, increasing host cell membrane fluidity, raising host cell pH which enterferes with viral entry and some drugs were documented to affect late stages of viral entry.

Antidepressant drugs on the other hand had diverse effects on viral life cycle, for instance the tricyclic antidepressant clomipramine showed ability to inhibit virus entry along with imipramine which was also able to inhibit viral entry and viral RNA replication, where as fluoxetine which is a selective serotonin reuptake inhibitor exerted its activity mainly by interfering with viral RNA replication which could be attributable to its ability to inhibit lipid accumulation in the host cells, the importance of interfering with lipid accumulation is that some viruses such as HCV production is highly dependant on intracellular interaction between viral core protein and lipid droplets in host cells, this suggested mechanism by which fluoxetine exerts its antiviral effect could be related to the ability of selective serotonin reuptake inhibitors to alter hepatic lipid biosynthesis which is originally considered as an adverse effect for members of this class.

Sedative drugs also showed diverse mechanis of action, propofol as one of the sedative drugs showed ability to inhibit viral entry step, while diazepam on the other hand affect viras life cycle at post entry steps by interfering with viral capsid production and viral RNA replication. The rest of the drugs that were studied for their mechanism of antiviral action were two of the NMDA antagonists and a COMT inhibitor with each of them affecting viral life cycle at different stage, ketamine which is one of the NMDA antagonists affected viral genome transcription while memantine the other NMDA antagonist showed ability to inhibit SARS-CoV-2 E protein ion channel activity resulting in reduction in viral virulence, since E protein is an iron channel then this antiviral effect of memantine could be related to its original effect as ion channel blocker, lastly tolcapone which is a COMT inhibitor showed ability to interfere with viral infection at entry stage.Regarding the researches summarized there are some facts to be pointed out; firstly some of the stated studies documented the affinity and the strong ability for interaction between some drugs to certain important enzymes and proteins according to in silico studies, such as the interaction between pimozide and flupentixol and the SARS-CoV-2 Mpro, and the interaction between memantine with SARS-CoV-2 E protein. However, these results cannot be used alone to make conclusions but they should also be considered and evaluated using further in vitro and in vivo studies. Secondly, there are some drugs that showed inconsistency in their antiviral activity assessment; either in in vitro study such as the antiviral effect of sodium valproate against herpes simplex virus, or in clinical observations such as the antiviral effect of ketamine against rabies virus, such conflicts needs further studies to confirm if these drugs actually have or lack antiviral effect. Thirdly, it is rational to recommend further studies that focus on the mechanism of antiviral action as they could reveal drugs that act on known favorable targets such as the action of chlorpromazine on viral endocytosis rather than the fusion of the virus with the cells, a fact that makes chlorpromazine less susceptible to viral resistance and can be a model for further drug researches, or drugs that targets more than one step of viral infection which is also an advantageous characteristic, as seen with some drug such as lithium chloride, chlorpromazine, and imipramine. Finally, considering that members

ISSN: 2458 - 8806

within a viral family may have common characteristics and have their special criteria, having a drug that affects a member of the viral family may indicate that it could affect other members of the same family. Hence it is recommended to consider broadening the antiviral screening of the drugs among members of families within which they originally showed activity before investigating the effect on viruses of other families.

Acknowledgement

The authors received no financial support for this review.

Conflict of 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.

Statement of Contribution of Researchers

E.E., F.A., L.A. designed the methods, literarture search and interpret the data, wrote the manuscript draft; E.A. critically reviewed the manuscript and approved the final draft; B.Y. conceptualization, supervising the research work, critically reviewed the manuscript and approved the final draft. All the authors have read and approved the manuscript.

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