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Repurposing of Adamantanes for the Potential Prevention or Treatment of COVID-19

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Repurposing of Adamantanes with Transmitter Receptor Antagonist Properties for the Prevention/Treatment of COVID-19

Keywords: COVID-19; Coronavirus; Adamatanes; Amantadine; Memantine; SARS-CoV-2; Re-purposing, NMDA receptor antagonist; a7-nAChR; Viral replication; Lysosomotropic; ACE-2

Abstract

Members of the adamantane family of agents in general and two such members, amantadine and memantine, in particular, have established beneficial actions across a wide range of infectious diseases including those caused by coronaviruses. Increasing evidence suggests that the protective effects of these agents is the result of actions on neurotransmitter systems namely the NMDA receptor subclass of the glutamatergic system and by the a7-nACh subclass of nicotinic cholinergic receptor. The potent NMDA receptor antagonist, memantine, prevents motor disabilities and reduces replication of the neuroinvasive/neurotropic human respiratory virus HCoV-OC43 dose-dependently. Moreover, the lysosomotrophic adamantanes amantadine and memantine also limit viral replication. Known lysomotrophic agents such as ammonium chloride inhibit cellular entry of SARS-CoV-2 on laboratory testing. Inhibiting clathrin-mediated endocytosis (cellular entry) of the SARS-CoV-2/ACE2 complex by amantadine or rimantadine may block viral entry into vulnerable cellular populations, and also reduce platelet activating factor-priming of Polymorphonuclear [PMN] cells, potentially lessening PMN cell-mediated tissue damage and excess Neutrophil Extracellular Traps [NETs] seen in advanced cases of COVID-19. Rimantadine has inhibitory effects of SARS-CoV-1, a closely-related virus to SARS-CoV-2, which may indicate the need for further evaluation as a treatment for COVID-19. Amantadine increases Dopamine [DA] release and blocks its reuptake, increasing its action on DA receptors on T cells thus activating resting effector T cells and suppressing regulator T cells, which may have a beneficial immunomodulating function in infectious diseases. Proposed adverse effects of smoking on COVID-19 outcomes are attributed to the effects of nicotine via the a7-nACh receptor located on bronchial and alveolar epithelial cells. As an antagonist of this receptor, memantine has the potential to prevent the entry of SARS-CoV-2 into these cells. Independent case reports provide evidence of protective effects of amantadine and/or memantine against COVID-19. Additional epidemiologic studies however indicate a lower incidence of smoking in hospitalized patients, stimulating investigations of nicotine-related aspects, and amino acid sequence analysis indicate homologous sequences with those of neurotoxins seen in snake venoms blocking the a7-nAChR suggesting that COVID-19 may be a disease of the nicotinic cholinergic system; a7-nAChR is involved in the cholinergic anti-inflammatory pathway or reflex. COVID-19 is a biphasic disease, the initial aspect involved with the initial infection and viral replication which stimulates a prominent innate immune response. This then transitions to the adaptive immune response with suppression of infection and recovery, while the innate response is suppressed via the cholinergic anti-inflammatory pathway. Severe disease may occur when the initial innate immune response continues, the cholinergic anti-inflammatory pathway being arrested by the neurotoxin inherent in the viral amino acid sequence, causing a runaway innate immune response. Memantine, being an inhibitor of a7-nACHR, could possibly make COVID-19 worse should it be a7-nACHR inhibitor. Tilorone, a lysosomotrophic agent and a7-nACHR agonist could also have potential as a treatment for COVID-19. Further studies are necessary to determine whether repurposing of adamantanes is beneficial in COVID-19, and for further investigations of pharmacological and pathophysiological properties of SARS-CoV-2.

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Introduction

Several members of the adamantane family of agents manifest potent non-competitive antagonist properties at the NMDA subclass of glutamate receptors that are effective for decreasing excess glutamatergic activity in the CNS that may, if unchecked, result in the phenomenon known as excitotoxicity that is widely recognized to be responsible for a range of neurological disorders including the epilepsies as well as the common neurodegenerative Alzheimer's Disease [AD] and Parkinson's Disease [PD] [1,2]. For example, the adamantane derivative and potent NMDA antagonist amantadine is widely employed for the treatment of the disturbances of motor function in PD and for the control of L-Dopa-induced dyskinesias in PD patients [2]. The mechanism of action involves its action as a non-competitive antagonist of the NMDA receptor the net result of which is to redress the imbalance between afferent dopaminergic projections from substantia nigra with those of corticospinal glutamatergic inputs as shown in a simplified schematic manner in Figure 1. Amantadine, is also increasingly being prescribed for the treatment of traumatic brain injury and its associated cognitive and behavioral complications effects that have been also ascribed to its NMDA receptor antagonist properties [3]. Another adamantane-related NMDA antagonist, memantine, is currently employed for the management and treatment of AD [4] (Figure 1).

Dopamine [DA], with increased release and concomitant blockade of re-uptake by amantadine, besides being a principal neurotransmitter, is also a 'neuroimmunotransmitter', having multiple effects on most if not all immune cells and activator of resting effector T cells through DA receptors. DA activation of resting effector T cells and suppression of regulatory T cells may be beneficial in immunotherapy of infectious diseases as well as cancer and medications having a dopaminergic effect on T cells include amantadine, as well as L-dopa, bromocriptine, haloperidol, reserpine, pergolide, pimozide and others [5].

Established anti-viral properties of the adamantanes

Inhibition of viral replication has been demonstrated for a number of adamantanes. For example, both amantadine and

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rimantadine have been shown to be active against the influenza A virus [6]; tromantadine is active against the Herpes Simplex virus and the adamantine derivative bananin manifests activity against SARS coronavirus HCoV-1 where it was shown to be a potent inhibitor of the helicase activities and to limit replication of the virus [7,8].

Amantadine did not show detectable inhibition of SARS-CoV-1 in a fRHK4 cell line, however rimantadine did show detectable inhibitory activity by neutralization tests with 9 isolates of the coronavirus along with leukocytic interferon-alpha, interferon-beta-1a, ribavirin, lopinavir, and baicalin [9]. When tested in a Vero-E6 cell line, rimandatine, along with glycyrrhizin, leukocytic interferon-alpha and interferon-beta were more active, with activity at 72 h. Rimantadine was also active in a plaque reduction assay, however it wasn't as effective as interferons, activity reduced after 72 h and it was concluded that it was unlikely to have significant in vivo activity [9].

Memantine relieves the neuronal impairment and damage caused by the neurotropic Japanese Encephalitis Virus (JEV) where survival times in JEV-infected mice were significantly prolonged, inflammatory cell infiltrates and intravascular cuffing were significantly reduced and mouse brain JEV content was reduced [10]. Memantine is also able to prevent neuronal cell death due to ZIKA virus infection by blocking NMDA receptors but had no effect on viral replication [11].

Adamantanes and human coronaviruses: experimental studies

Human Coronaviruses [HCovs] are respiratory pathogens with potent neuroinvasive properties. The HCoV-OC43 strain can infect human neural cells resulting in activation of neuroinflammatory and neurodegenerative mechanisms and this strain of HCOv is neurovirulent in susceptible mice leading to encephalitis [12]. Moreover, a viral mutant with a single point mutation in the viral surface S protein induces severe hind-limb paralysis that appears to involve glutamate excitotoxicity *via* NMDA receptors in susceptible animals. Treatment with memantine resulted in improvements in clinical scores related to paralysis and other motor disabilities. In addition, memantine attenuated body weight losses and mortality rates and led to reduction in HCoV-OC43 viral replication rates in the CNS in a dose-dependent manner [13].

In order to further elucidate the mechanism of action responsible for this antiviral action of memantine, use was made of two well established cell lines namely i] mouse primary CNS cell cultures [known to express NMDA receptors] and ii] a human epithelial cell line commonly employed to amplify HCoV-OC43 [that does not express NMDA receptors]. Memantine was found to reduce viral replication rates in both cell types leading to the suggestion that the antiviral action of memantine against this strain of coronavirus were not solely dependent on the antagonism of NMDA receptors [14]. Moreover, the authors proposed that, given the fact that memantine produced a significant anti-viral activity following primary infection of susceptible host cells was indicative of the notion that inhibition of viral replication had occurred following viral attachment to the host cell receptor as had been shown for other adamantine derivatives [4,6,7].

Adamantanes for COVID-19: evidence to date

It has been suggested that the Acute Respiratory Distress Syndrome [ARDS] in COVID-19 may be the consequence of the migration of SARS-CoV-2 trans-synaptically from the lungs and nasal epithelium to the medullary cardio-respiratory center via the peripheral nervous system from the lungs and through the cribriform plate from the nasal epithelium [14]. Loss of sense of smell and taste are common features of COVID-19 and are probably associated with the CNS. The virus may be neurotrophic with the latent period from infection to development of complications being the result of virus propagation from the lungs and nasal epithelium to the CNS. It has been proposed that memantine could be considered as a potential treatment for COVID-19 by virtue of its ability to interfere with the NMDA receptor leading to inhibition of excess glutamate release in the medullary brainstem, a potential neurotoxic effect from depletion of ACE2 contributing to ARDS [15].

Other proposed mechanisms whereby amantadine appears to result in inhibition of coronavirus replication include interaction of the agent with the viral E protein and by disruption of lysosomal gene expression [16,17]. Moreover, being itself a lysosomotropic agent [18], memantine could conceivably mimic the effects of amantadine. Along this same line of reasoning, a recent short report described the results of studies suggesting that the E protein, an essential protein of coronaviruses including SARS-CoV-2, is a potential ion channel and that memantine is a potent E protein inhibitor with the potential to curb viral virulence and abate COVID-19 [19].

SARS-CoV-2 virus entry into cells is inhibited by ammonium chloride, which elevates endosomal pH blocking Cathepsin B and L. [20]. Besides a laboratory study investigating lysosomal dynamics and SARS-CoV-2, an epidemiologic study also may be applicable, since widespread consumption of ammonium chloride, (NH_4Cl, salmiak) a known lysotrophic agent, enriched confectioneries, primarily in Northern European countries (primarily Scandinavian), may, along with bacillus Calmette-Guérin (BCG) immunization, be associated with a significantly associated lower rates of COVID-19 related deaths [21].

SARS-CoV-2 enters cells via clathrin-mediated endocytosis, which is inhibited by amantadine, and rimantadine [22,23]. Excess neutrophil extracellular traps, formed by neutrophils in response to COVID-19 infection may cause the severe multi-organ effects in multiple systems involving vasculature, immunity and coagulation [24]. Platelet activating factor induces the release of neutrophil extracellular traps [25]. Platelet priming of neutrophils likely requires clathrin-mediated endocytosis of the platelet activating factor receptor, and amantadine, along with a more potent inhibitor, rimantadine, inhibits clathrin-mediated endocytosis, which inhibits platelet activated factor priming of neutrophils [25]. Amantadine or rimantadine may be able to reduce polymorphonuclear mediated tissue damage in humans [26], and possibly reduce the production of excess neutrophil extracellular traps through reduced priming of neutrophils.

The nicotinic cholinergic receptor and COVID-19

Results of a recent systematic review of the evidence suggest that smoking is associated with an increase in progression and adverse outcome of the disease in patients with COVID-19 and that current smokers along with patients with COPD had increased airway epithelial cell expression of the viral entry receptor ACE-2 [27]. A robust mechanistic explanation was proposed involving nicotine

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exposure as the likely mediator acting specifically through the alpha-7 subtype of nicotinic cholinergic receptor [α7-nAChR] that is localized widely in airway cells such as bronchial epithelial cells, type II alveolar epithelial cells and in interstitial lung fibroblasts in addition to various cells of the CNS. Increased expression of ACE2 receptors is mediated by the stimulation of α7-nAChR and any receptor agonist would have the potential to promote the entry of SARS-CoV-2 into the respiratory epithelium via ACE2 [28,29] (Figure 2).

Therefore, it is likely that antagonists of α7-nAChR could have the potential, by virtue of their ability to decrease ACE2 receptor expression in respiratory epithelium and prevent SARS-CoV-2 invasion of pulmonary epithelial cells. Searches for such agents are currently ongoing and, interestingly, memantine, in addition to its well-established action as a non-competitive antagonist of NMDA receptors, is a very potent antagonist of α7-nAChR [30]. It also exerts protective anti-inflammatory effects by suppression of cytokine expression as shown in an experimental model of lung injury [31]. Whether memantine is able to meaningfully alter ACE2 expression and prevent SARS-CoV-2 entry into the airway epithelium must surely be an important next step that is well worth further evaluation at pace (Figure 2).

There is interplay between inflammatory and anti-inflammatory mediators and α7-nAChR has been referred to as the anti-inflammatory reflex, mediated through the vagal nerve. This nicotinic receptor subunit is essential for inhibiting cytokine synthesis by the cholinergic anti-inflammatory pathway [31]. The SARS-CoV-2 virus, while using the ACE-2 receptor for cellular entry, may also interact with additional receptors. While observations [described above] of smoking worsening COVID-19, conversely, there have been clinical observations of lower smoking incidence among hospitalized COVID-19 patients [32], stimulating further studies of the viral genome, which identified a "toxin like sequence", in the receptor binding domain of the Spike Glycoprotein of SARS-CoV-2 (amino acids 375-390) which is homologous to a sequence of a neurotoxin NL2, a neurotoxin contained in Chinese (Taiwan) Cobra venom, one of the snake venom toxins which interacts with nicotinic acetylcholine receptors [33,34]. Blocking α7-nACHR through interaction with the cobra venom-like neurotoxin would permit unrestrained inflammation, while stimulating or protecting α7-nAChR with nicotine and/or nicotinic cholinergic agonists could be anti-inflammatory [34]. Memantine's interaction with α7-nAChR, would likely have some influence on such SARS-CoV-2 spike glycoprotein/α7-nAChR interactions, possibly protecting the receptor from viral spike glycoprotein interaction with the acetylcholine receptor.

Memantine has been investigated with reference to developing host-directed therapies as adjuncts to traditional antibiotic drugs, and investigated with reference to promoting the host innate immune defense system against pathogens, through α7-nAChR primarily against bacteria, and it was found to stimulate production of antiseptic protein S100A9, a component of calprotectin, (calprotectin S100A8/S100A9)), the bactericidal enzyme MPO (myeloperoxidase), and DNA in PMN's and accelerates release of depolymerized chromatin fibers in the extracellular space, suggesting or indicating the formation of Neutrophil Extracellular Traps (NETS) [35]. This study was primarily concerning treatment of neonatal meningitis. However, activation of α7-nAChR by nicotine could be protective against NMDA receptor-activated excitotoxic glutamate activation in adults, but possibly deleterious in neonates [36]. Viruses can induce NET formation, entrapping viruses, however disproportionate NET formation in response to viruses can have deleterious effects [37]. Widespread NET release has also been seen in severe COVID-19 post mortem examinations, which is also likely responsible for the widespread thrombosis seen in such patients [36].

Severe COVID-19 patients have a burst of circulating calprotectin that precedes cytokine release syndrome, and emergency myelopoiesis releases immature and dysplastic myeloid cells [38]. The blockage of α7-nAChR with memantine and SARS-CoV-2 spike protein homologous neurotoxin sequences with α7-nAChR, may have some similarities, stimulation of S100A9, a component of calprotectin, and stimulation of the innate immune response, with NET formation. This may indicate some effect on the innate immune response, since rapid onset may inhibit the virus in the early phase of infection. Transcriptome analysis revealed hundreds of genes upregulated by SARS-CoV-2 in infected human bronchial epithelial cells and human post mortem samples as prior analysis of neurons injured by glutamate and normalized by the angiotensin receptor blocker, Candesartan, indicating similar mechanisms in SARS-CoV-2 infection and neurons injured by glutamate including nuclear factor kappa-B translocation [39].

The primary recognized action of memantine is blockade of NMDA channels, a glutamate receptor subfamily [40]. Memantine lowers inflammatory markers, however, including nuclear factor-kappa B, indicating it may act on additional receptors besides NMDA receptors, the insulin receptor and reduction in inflammation in cellular studies of astrocytes [41]. Memantine may be able to inhibit viral glutamate induced inflammation and cell death, since the transcriptome indicates similarities between that induced by glutamate in experimental cellular laboratory studies and that obtained from post mortem examination of patient derived material and viral infected human bronchial epithelial cells.

Memantine or amantadine for prevention of COVID-19: clinical studies to date

Given the fact that the COVID-19 pandemic has only been a matter of everyday discussions and preoccupations for less than one year for the vast part of the world, and given the even more recent interest in the repurposing of members of the adamantine family of agents many of which are known to possess antiviral potential, it is not surprising that there have, to date been no published results of randomized controlled trials to assess the efficacy of these agents to say nothing of systematic reviews or meta-analyses of any published findings. Consequently, much reliance and activity is devoted for the moment on the reports of individual cases that are, by necessity, generally uncontrolled and observational in nature. However, results of three published reports have appeared so far involving a total of 24 patients in which there is subjective evidence of a protective effect of amantadine or memantine against COVID-19 including patients with comorbidities or severe neurological disorders [42-45]. In a group of 15 patients [10 with multiple sclerosis, 5 with Parkinson's disease] whilst undergoing treatment with amantadine [100 mg qd] for several months' duration, tested positive for COVID-19. SARS-CoV-2 infection was confirmed by RT-PCR in upper and lower respiratory specimens. All patients had been quarantined for 2 weeks

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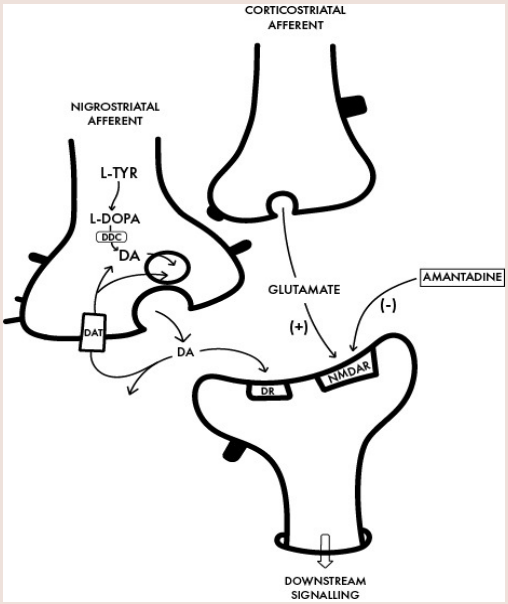

Figure 1: Schematic representation of the interface between a dopaminergic nerve terminal on an afferent fibre from substantia nigra with a glutamatergic terminal from the corticospinal tract.
Synthesis of Dopamine [DA] from L-Tyrosine [L-TYR] to L-DOPA via the enzyme DOPA Decarboxylase [DDC] is followed by vesicular storage, release into the synapse and/or uptake by the Dopamine Transporter [DAT] followed by activation of the post-synaptic Dopamine Receptor [DR]. Activation of the NMDA subclass of glutamate receptor [NMDAR] on the post-synaptic neuron is indicated. Several adamantanes such as amantadine are non-competitive antagonists of NMDAR thus restoring the balance between the nigrostriatal and corticostriatal pathways in favor of increased DA synthesis.

following documented exposure but none of them went on to develop clinical manifestations of infectious disease [43]. Similar findings were subsequently independently reported in a patient with type-2 diabetes and members of his immediate family all of whom tested positive for COVID-19 and were being treated with amantadine as well as in a further case of an amantadine-treated patient with Parkinson's disease [44,45]. In a related study, treatment with memantine [10 mg bid] was reported to manifest apparently protective effects in a group of 7 patients with cognitive impairment who tested positive for COVID-19 [42].

A retrospective study of a national database of 5726 patients, 140 of whom subsequently died, did not reveal any statistical difference in mortality of a group of patients between COVID-19 associated mortality and ongoing treatment with memantine for dementia, indicating it's not likely to have therapeutic effects on patients with COVID-19, however it did not seem to have any deleterious effects [45].

It is likely that a vigorous innate immune response initially is able to arrest viral replication preventing widespread viremia with multi-system and multi-organ involvement. Later in the course, the cholinergic anti-inflammatory pathway could suppress or inhibit the innate immune response. Likely adamantane medications such as amantadine and memantine could be helpful early in the course of the illness, during the initial infection phase when a robust innate immune response is necessary to arrest viral replication as well as inhibition of viral entry into cells by inhibition of clathrin-mediated endocytosis. Interestingly, chlorpromazine is a well-known inhibitor of clathrin-mediated endocytosis, and a study is ongoing on the repurposing of chlorpromazine for COVID-19: the reCoVery study [46].

Conclusions

The adamantanes may have a number of effects on COVID-19, previously seen in patients being treated with adamantanes for a range of neurological diseases who also became infected with COVID-19.

Immune T cells, and essentially all immune cells express DA receptors which are instrumental in activation. T cell activation would be important in the immune response in COVID-19. DA levels are altered in diseases such as PD and also may be decreased in aging, which is one of the primary risk factors for severe disease in COVID-19. Amantadine is known to increase the synthesis of DA (Figure 1).

COVID-19 may also increase glutamate and inflammation, as has been inferred in transcriptome analysis. Memantine, being an NMDA receptor antagonist has the capacity to reduce glutamate-induced inflammation and cell death.

Being lysomotrophic agents, adamantanes such as amantadine, rimantadine and memantine appear to have the potential to manifest direct inhibitory effects on viral development. For example, the lysomotrophic agent, ammonium chloride, appears to have a strong inhibitory effect on SARS-CoV-2 entry into experimental cell lines by blocking the endosomal cysteine proteases, cathepsin B and L and the transmembrane protease serine TMPRSS2 is also involved in viral spike protein processing for binding to ACE2 enabling the virus to enter vulnerable cells [20].

Amantadine and rimantadine may be able to inhibit viral entry due to clathrin-mediated endocytosis, which is the method SARS-CoV-2 utilizes for cellular entry, and also reduce polymorphonuclear [PMN] priming by platelets, possibly reducing cellular injury and

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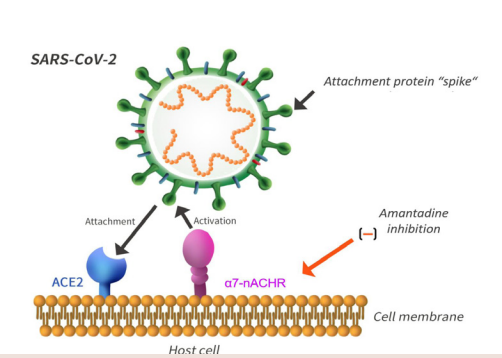

Figure 2: Inter-cellular mechanisms involving the promotion of the entry of SARS-CoV-2, the coronavirus responsible for COVID-19 into the host cell via the interaction with ACE2.
Activation of the alpha-7 subtype of the nicotinic cholinergic receptor [α7-nAChR] has the potential to result in protease activation, increased pro-inflammatory signaling and cell death. Memantine has the capacity to mitigate these effects with the potential to provide an approach to the prevention and treatment of COVID-19.

inflammation, since much of the tissue destruction in viral infection is due to tissue destroying factors released by PMN cells.

Besides blocking NMDA receptors, memantine is also a potent inhibitor of α7-nACHR which is important in the regulation of inflammation and possibly in inducing the inflammatory response, including NETs, which are released in excessive amounts in severe cases of COVID-19.

As a cautionary note, considering the possible nicotinic relationship of COVID-19, medicines which inhibit the α7-nAChR, such as memantine, could in theory worsen or propagate cytokine storm and have deleterious effects on treatment of COVID-19. This issue requires further investigation.

Tilorone, a known interferon inducer and selective α7-nAChR agonist could be of value in reducing inflammation through the anti-inflammatory reflex [47], since severe inflammation or immune system overshoot, resulting in "cytokine storm", is a crisis event in COVID-19. Tilorone also acts as a lysosomotrophic agent in cell culture system of fibroblasts, increasing pH in acid compartments of cells [48,49], so could act in multiple pathways, since it is known to induce interferon and is a prospect as a wide spectrum antiviral agent. Tilorone is among the 10 medicines recommended for repurposing for COVID-19 in the CovidX Network algorithm for drug repurposing recommendation [50,51].

Enhancing the initial innate immune response, inhibiting viral entry, likely through clathrin- mediated endocytosis through the plasma membrane, inhibiting viral development in the endosomal/lysosomal system, and replication in the cytoplasm, are processes which may be inhibited by medications. Adamantanes such as amantadine, rimantadine and memantine could be repurposed with the potential to interfere with some aspects of these features of viral infection. Rimantadine was noted to have some degree of SARS-CoV-1 inhibitory effect on laboratory cell lines [9], which could translate into an inhibitory effect on the SARS-CoV-2 as well, since they are closely-related viruses. They may be compared with other medications such Tilorone, which have a lysosomotrophic effect, and even food items such as ammonium chloride (salmiak) in confections such as liquorices with up to 7.99% food grade ammonium chloride enjoyed on a daily basis, primarily in the Nordic countries, which appear to have a reduced death rate for COVID-19 [20]. Controlled clinical trials to further evaluate these interesting observations are now urgently required in order to confirm and amplify the evidence base in favour of the value of repurposing of adamantanes for the prevention and treatment of COVID-19.

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