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Adamantanes for the Treatment of Neurodegenerative Diseases in the Era of the COVID-19 Pandemic

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1. Abstract

Neurodegenerative diseases constitute co-morbidities along with diabetes, cardiovascular disease and obesity leading to worsening of clinical outcomes in patients infected with COVID-19. Adamantanes have established benefits in the treatment of neurodegenerative disorders including Parkinson's disease (PD), Alzheimer's disease (AD) and multiple sclerosis (MS). Systematic reviews with meta-analysis confirm the efficacy of amantadine for the treatment of the motor signs of PD and for L-Dopa-induced dyskinesias. COVID-19 may result in worsening of the symptoms of PD and conversely, certain features of COVID-19 may aggravate tremor, gait disturbances, dyskinesias and the efficacy of L-Dopa. Antibody responses to coronaviruses have been observed in CSF samples of PD patients. Interestingly, amantadine is potentially effective for the treatment of COVID-19 *per se* via the down-regulation of host cell proteases and inhibition of protein E ion channel activity resulting in decreased viral replication. Three reports appeared of possible COVID-19 prophylaxis by long-term treatment with amantadine in patients with PD infected with SARS-CoV-2. In the case of AD, meta-analyses reveal the efficacy of memantine leading to its approval by US-FDA for treatment of moderate-to-severe forms of AD. Both AD and COVID-19 are functionally linked to amyloid and to activation of NMDA receptors. Indeed, both conditions derive clinical benefit from treatment with memantine or amantadine both of which are non-competitive NMDA receptor antagonists. A case of COVID-19 prophylaxis is described in a report of 7 patients with severe cognitive impairment treated for several months with memantine and subsequently exposed to SARS-CoV-2. None of the 7 treated patients developed symptoms of infectious disease. Amantadine is also effective for the treatment of fatigue in MS and for the cognitive and neurobehavioral complications of traumatic brain injury (TBI) where amantadine, rimantadine and memantine are employed.

2. Introduction

Several members of the adamantine family have established beneficial actions in a number of neurodegenerative disorders including Parkinson's disease (PD) [1, 2]. Alzheimer's disease (AD) [3], traumatic brain injury (TBI) and its cognitive and neurobehavioral complications [4] and for the treatment of fatigue in multiple sclerosis (MS) [5]. Key adamantanes implicated in these disorders include amantadine, rimantadine and the structurally-related memantine all of which are effective against coronaviruses including SARS-CoV-2 the viral entity responsible for the COVID-19 pandemic. Molecular structures of these adamantanes are shown in Figure 1.

Neurodegenerative conditions represent co-morbidities in patients infected with SARS-CoV-2 impacting on treatment strategies as well as on treatment outcomes in patients with COVID-19.

2.1 Amantadine for the treatment of PD and associated complications

Amantadine started life as an effective agent against influenza A but a serendipitous observation in a 58-year-old female patient with moderately severe PD given amantadine for her influenza noted a remarkable improvement in her tremor and cogwheel rigidity that re-appeared upon cessation of amantadine. A controlled clinical trial confirmed the efficacy of amantadine in a group of 163 patients with PD [2]. US-FDA approval for amantadine as a treatment for the motor signs of PD followed a short time thereafter. A subsequent systematic review with meta-analysis [1] of the results of 9 randomised clinical trials (RCTs) involving 298 PD patients confirmed the efficacy of amantadine for treatment of the motor signs assessed using UPDRS III as shown in Figure 2.

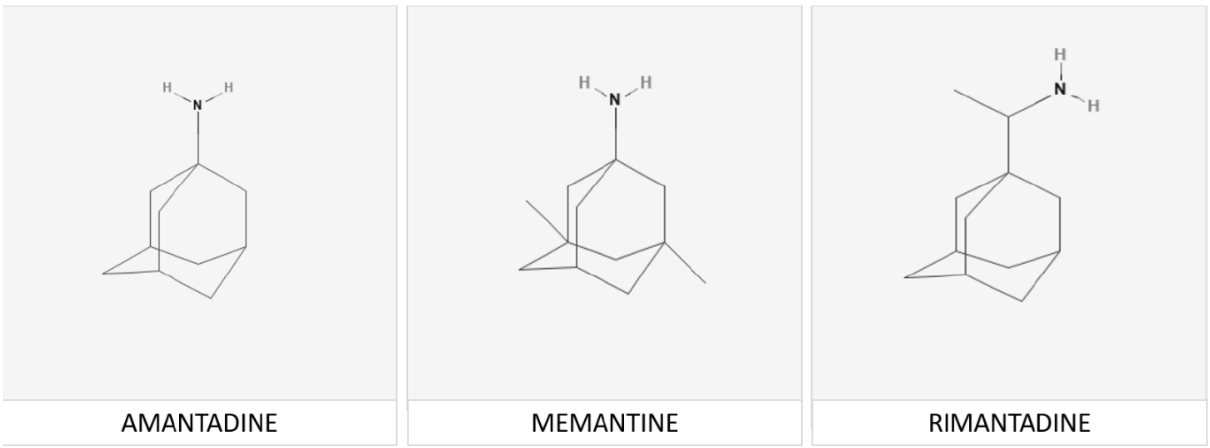

Figure 1: Molecular structures of members of the adamantine family of antiviral agents all of which are effective against coronaviruses. In the case of amantadine and memantine, beneficial effects against SARS-CoV-2 the virus responsible for COVID-19 have been reported in both in vitro studies and in initial clinical studies in patients with PD or MS who became subsequently infected with COVID [7].

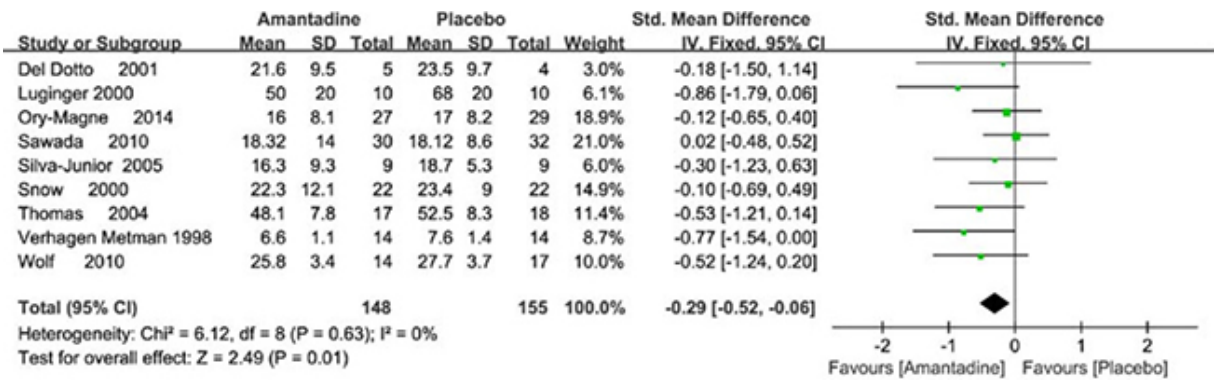

Figure 2: Forest plot of motor symptoms of PD assessed using UPDRS III scores [Mean ± SD by Fixed Odds ± 95% CI] following treatment with amantadine versus placebo. Individual trials are identified by 1st author's name and year [1].

Characterised neuropathologically by selective degeneration of dopaminergic neurons in substantia nigra, PD is currently treated by L-Dopa the precursor amino acid for the synthesis of dopamine (DA) where it is effective for the treatment of the motor signs and symptoms characteristic of PD. However, long-term use of L-Dopa frequently results in dyskinesias that occur at high plasma levels of the amino acid. Results of a systematic review with meta-analysis, published in 2017 of 5 RCTs involving 218 PD patients with L-Dopa-induced dyskinesias confirmed that amantadine was beneficial [1] as assessed by UPDRS IV with MD: -0.97 [95% CI: -1.41, -1.54], test for overall effect: Z=4.36, p<0.0001 as shown in Figure 3.

Both PD and COVID-19 are age-related disorders with common co-morbidities. Moreover, the presence of COVID-19 has the potential to result in worsening of the symptoms of PD and vice versa [6]. Worsening of PD symptoms is known to occur during systemic infections and certain features of COVID-19 such as fever, stress and fatigue aggravate tremor, gait disturbances and dyskinesias in PD and may compromise the efficacy of L-Dopa [7].On the other hand, evidence suggests that amantadine is beneficial for the treatment of COVID-19 *per se*. Functional links between coronaviruses and PD include enhanced antibody responses to coronaviruses in CSF samples from PD patients [8] and lesions in basal ganglia structures occur in some viral encephalides [9].

A report describes the effects of COVID-19 infection in five PD patients who had been treated with amantadine [100mg/d] for at least 3 months. None of the patients went on to develop clinical signs of infectious disease (no fever or cough, no anosmia) while control of extrapyramidal motor function persisted suggesting that amantadine may have potential for COVID-19 prophylaxis [10]. Similar findings were reported subsequently in a case report [11] and in a hospital-based cohort study of patients with PD treated with amantadine [12]. Several mechanisms have been proposed to explain the beneficial effects of amantadine against COVID-19 including down-regulation of host cell proteases leading to impaired release of the virus into the host cell [13], inhibition of protein E ion channel-mediated activity resulting in decreased viral replication and infectivity [14] in addition to antagonist actions at glutamate (NMDA) [15] and nicotinic cholinergic [16] receptors.

2.2 Memantine for the treatment of AD

Results of a systematic review with meta-analysis of the results of 30 RCTs involving 7567 patients confirmed the efficacy of memantine for the improvement of cognitive function in patients with AD compared to placebo with SMD: -0.24, 95% CI:-0.34, -0.15, p=0.0001 [2] and when administered in combination with cholinesterase inhibitors, memantine was superior to the inhibitors alone with p<0.006. Memantine currently has US-FDA approval for the treatment of moderate-to-severe AD.

A number of pathophysiologic links between AD and COVID-19 have been identified. Not only is AD a co-morbidity for COVID-19. Both conditions are functionally-linked to Amyloid Precursor Protein (APP) and AD is strongly linked to the morbidity and mortality of COVID-19 [6]. Amyloid-beta oligomers may cross the plasma membrane leading to the formation of pores that permit the passage of Ca^{2+}resulting from the activation of NMDA receptors.

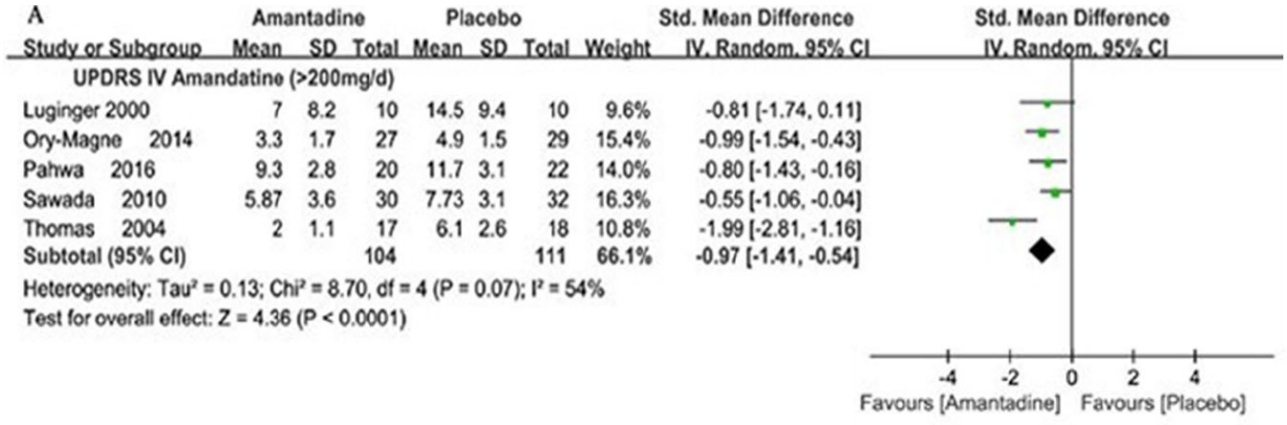

Figure 3: Subgroup analysis: Forest plots of L-Dopa-induced dyskinesias in PD assessed using DRS scores [Mean ± SD by Random Odds ± 95% CI] following treatment with amantadine versus placebo as a function of the dose of amantadine [greater than 200mg/d]. Data from 5 individual trials are identified by 1st author's name and year [1].

Memantine exerts dose-dependent antiviral actions against coronaviruses associated with neuroprotection in certain cases such as that of the neuroinvasive human respiratory coronavirus HCoV-OC43 that is known to activate neurodegenerative mechanisms [17]. Other members of the adamantine family amantadine and rimantadine are effective for the treatment of bovine coronavirus as well as for SARS-Co-V-1, the virus responsible for the 2002 SARS epidemic. On the other hand, studies in a mouse model of COPD reveal that the benefit of memantine was related to its antagonist action against the alpha-7 subtype of nicotinic cholinergic receptor [16]. While there is no direct evidence that this receptor is implicated in the pathogenesis of selective neuronal cell death in AD and given the continuing interest in agents with the ability to manipulate central cholinergic systems, further evaluation of this receptor system may be worthwhile.

A report of potential relevance to AD involved seven patients with severe cognitive impairment all of whom had been treated for several months with memantine [100mg bid] who became infected with SARS-CoV-2 verified by RT-PCR. Remarkably none of the memantine-treated patients went on to show clinical symptoms of infectious disease while the beneficial effects of memantine on their cognitive impairment were maintained [10].

2.3 Memantine for the treatment of fatigue in MS

Fatigue is a common disabling complication of MS with a negative impact on the severity of disability and on patient's quality of life. Patients with primary or secondary-progressive forms of MS are at particularly high risk for development of severe fatigue. Results of neuroimaging and spectroscopic studies implicate a disorder of the striatal-thalamic-frontal cortical neuronal network involving the dopaminergic system [18]. An alternative mechanism involves the pro-inflammatory cytokines [5].

In a questionnaire-based study, ten patients with MS treated with amantadine [100mgqd] for periods in excess of 3 months became infected with SARS-CoV-2 verified by RT-PCR. None of the amantadine-treated patients went on to develop clinical manifestations of infectious disease [10]. Results from11 RCTs and the ensuing 6 systematic reviews with meta-analyses support the efficacy of amantadine for the treatment of fatigue in MS compared to placebo or to alternative agents such as modafinil, pemoline or ondansetron [5]. Clinical Practice Guidelines from NICE [UK] and the German MS Society recommend that amantadine be employed for the pharmacological management of MS-related fatigue.

2.4 Amantadine for the treatment of TBI and its neurological complications

SARS CoV-2 infection results in the detection of virus in the central nervous system [CNS] along with a characteristic pattern of cytotoxic damage consisting of focal neuronal cell death and glial hyperplasia with a distribution of changes that closely resembles that reported in TBI. Systematic reviews of the results of RCTs demonstrate that treatment with amantadine [100-300 mg/d] is effective for the rate of improvement in levels of consciousness and cognitive function in both the acute and chronic care phases of TBI for up to 6 months post-injury (Figure 4) [4]. These findings led to an update of clinical practice guidelines for the treatment of disorders of consciousness by the American Academy of Neurology.

3. Summary and Conclusions

Members of the adamantine family of agents particularly adamantine and memantine have been shown in randomises controlled clinical trials and their associated systematic reviews and meta-analyses to be effective for the treatment of a range of neurodegenerative disorders that include PD and AD, MS for the treatment of fatigue as well as for the complications of TBI. Amantadine is approved by US-FDA for the treatment of moderate-to-severe forms of AD and is also effective in the management of the symptoms of COVID-19 by virtue of its antiviral properties involving the inhibition

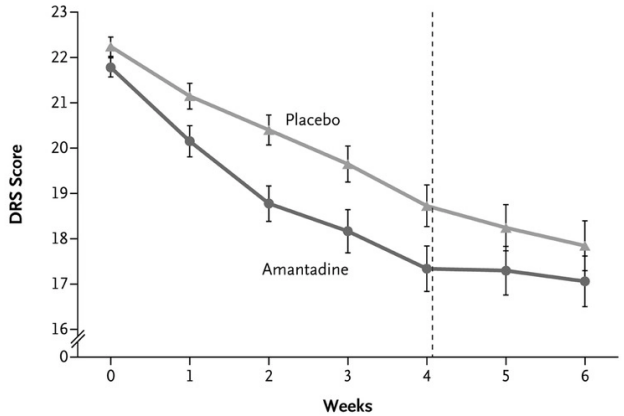

Figure 4: Rate of functional recovery (DRS score) as a function of duration of treatment with amantadine compared to placebo in patients with severe TBI. DRS scores were improved significantly more rapidly following amantadine during the 4-week treatment period compared to placebo. On weeks 5 and 6 (washout interval), recovery rate in the amantadine group were significantly slower. Error bars indicate mean values ± SE [4].

of protein E ion channels and host cell proteases leading to impaired viral replication. There are physiopathologic links between PD and COVID-19. Antibody responses are found in CSF of PD patients and COVID-19 is known to cause worsening of PD symptoms and impairment of the efficacy of L-Dopa. Initial clinical investigations reveal that the long-term treatment of neurodegenerative disease with amantadine or memantine prevents clinical signs of infection should patients subsequently contract PCR-verified COVID-19. These reports of possible COVID-19 prophylaxis by adamantanes now merit confirmation in randomised controlled clinical trials.

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