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RESEARCH ARTICLE

Auvelity as a Potential Treatment for Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is the most common form of dementia affecting older adults. Alzheimer's disease also shares a significant association with Major Depressive Disorder. Glutamatergic excitotoxicity via NMDA receptors is believed to be a key mechanism underlying neurodegeneration in Alzheimer's Disease. Blockade of NMDA receptors by NMDA antagonists like Memantine appears to inhibit glutamatergic excitotoxicity. Memantine also increases dopaminergic activation through agonism of sigma-1 receptors. The combination of these two mechanisms is believed to underlie Memantine's improvements in memory, cognition and general functioning in AD patients. Auvelity was recently approved by the FDA for the treatment of Major Depressive Disorder in adults. Auvelity's relevant mechanism of action is a combination of its blockade of NMDA receptors with consequent antagonism of the glutamatergic neurotransmitter pathway, and its agonism of the sigma-1 receptor. Because Auvelity and AD medications like Memantine employ the same mechanism of action, it is hypothesized that Auvelity might be a potential medical treatment for reducing the symptoms of Alzheimer's disease.

Keywords: Auvelity; Alzheimer's Disease; aging; NMDA antagonist; glutamatergic excitotoxicity

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by ongoing declines in memory, language and problem-solving.[1] It is the most common form of dementia affecting older adults.[2] Currently, 6.5 million of the 58 million Americans over the age of 65 (about one in nine) have been diagnosed with AD.[2] The risk of dementia increases with advancing age, and about one third of people over the age of 85 have AD.[3] As the number and proportion of Americans age 65 and older continues to grow, the number and proportion of Americans with AD and/or other dementias will also increase. The number of Americans over the age of 65 is expected to grow from 58 million in 2022 to 88 million by 2050, with the increasing number of AD patients significantly impacting quality of life for AD patients and their families, as well as the economics of healthcare systems.[2,4]

AD is also associated with a Major Depressive Disorder (MDD). In a systematic review of 30 studies on AD, depressive and psychotic symptoms were observed in up to 40% of AD patients.[5] A separate meta-analysis indicated that a history of depression is associated with increased risk for developing AD, and might be an independent risk factor for AD.[6] Variables including gender, the progression of dementia and declines in general functioning appear to increase the association of depression with AD.[7]

In 2022, the U.S. Food and Drug Administration (FDA) approved Axsome Therapeutics, Inc.'s new medication, Auvelity (Dextromethorphan HBr - Bupropion HCl) extended-release tablets for the treatment of MDD in adults.[8] Based on research suggesting that N-methyl-D-aspartate (NMDA) antagonists can reduce the symptoms of MDD, the medication's formulation represents a novel approach to the treatment of MDD.[9] The purpose of this paper is to examine similarities between the mechanism of action of Auvelity and that of Memantine, a memory-sparing agent used for the treatment of AD, and based on those similarities, to suggest that Auvelity might be considered as a potential treatment for the symptoms of AD.

Mechanism of action in AD: The glutamatergic excitotoxicity hypothesis

AD is characterized by an accumulation of extracellular amyloid β peptide (Aβ) and the intracellular neurofibrillary tangles (NFTs) associated with large scale neuronal cell death.[10] Over 40% of neuronal synapses in the brain are glutamatergic, and brain health relies on regulation of glutamate levels through metabolite exchange in neuronal, astrocytic and endothelial cells.[1] Glutamate receptor proteins occur on the surface of cells that appear to be activated externally, where glutamate performs its neurotransmitter function from the extracellular fluid. Regulation of glutamate receptor activation appears to be accomplished by releasing glutamate into extracellular fluid, from which glutamate is then removed. There are no extracellular enzymes capable of degrading glutamate, so its removal from extracellular fluid requires cellular uptake.[11] Various transporter proteins at the cell surface of both astrocytes and neurons catalyze glutamate uptake.[12] Although the processes involved in glutamate regulation are numerous and complex, the pathological mechanism of AD appears at least in part to be NMDA receptor-mediated glutamatergic excitotoxicity leading to synaptic dysfunction and neuronal death.[10,11]

Treatment of AD: NMDA antagonists: Memantine

Because excessive excitatory glutamatergic neurotransmission via NMDA receptors promotes neural cell death, blockade of NMDA receptors by NMDA antagonists like Memantine is believed to inhibit glutamatergic excitotoxicity, sparing synaptic responses required for normal behavioral functioning, cognition and memory.[13] Specifically, Memantine is thought to induce blockade of current flow through channels of NMDA receptors. NMDA receptors are a glutamate receptor subfamily involved in numerous brain functions including mood regulation and incorporation of memory.[14] Memantine exerts minimal inhibitory effects on the isoenzyme cytochrome P450-2D6 (CYP2D6), and is not believed to significantly impact CYP2D6 metabolism.[15]

In addition, Memantine works as an agonist on the sigma-1 receptor, which has been identified as a modulator of dopaminergic transmission.[16] Memantine's agonistic effect on the sigma-1 receptor, combined with glutamatergic inhibition, is believed to be the mechanism through which Memantine serves as a memory-sparing agent for AD patients. Accordingly, Memantine has become a medication of choice for the treatment of AD.[13,17]

Treatment of AD: cholinesterase inhibitors

The other family of medications consistently used for the containment of AD symptoms is the cholinesterase inhibitors (ChEIs). The cholinergic pathway, essential to the incorporation of memory, is also compromised in AD patients. Boosting cholinergic activity through the use of ChEIs has demonstrated efficacy for reducing AD symptomatic impairments to general functioning, cognition and memory. The three ChEIs currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD are donepezil, rivastigmine and galantamine.[18]

Other NMDA antagonists

Other NMDA antagonists that might theoretically be used to treat mood disorders or AD exhibit potentially difficult side-effects. An example increasingly discussed for the treatment of mood disorders is Ketamine.[13] Ketamine's potential side-effects include sedation, a dream-like state, colorful dreams, feelings of intense strength and power, decreased focus, agitation, anxiety, dizziness, hallucinations, difficulty thinking, out of body experiences, alterations in discernment, amnesia, confusion, reduced awareness of environment, disorientation, drowsiness, dissociation, decreased ability to feel pain, forgetfulness, decreased coordination, physical side effects, double vision, involuntary eye movements, seizures, impaired motor function, nausea, vomiting, slowed breathing, cessation of breathing, elevated blood pressure, decreased heart rate, tachycardia, irregular heartbeat, motionlessness, excessive salvia production, and garbled speech.[19] Although Memantine shares the mechanism of NMDA inhibition with Ketamine, Memantine's effects on gating of blocked channels is different from Ketamine's. Memantine's more subtle mechanism of action includes binding to two sites on NMDA receptors, where modulation of NMDA receptor activity can inhibit glutamatergic activity without significantly inhibiting other neuronal pathways.[13]

The oldest family of oral antidepressants, the Mono Amine Oxidase Inhibitors (MAOIs) were thought to treat depression through a mechanism of action inhibiting the oxidation of serotonin (5-hydroxytryptamine, or 5-HT) and norepinephrine (NE).[20] MAOIs, specifically MAO type-A-specific inhibitors, are known to inhibit glutamatergic excitotoxicity, but only at concentrations much higher than those used for classical type-A MAO inhibition, often leading to numerous and sometimes life-threatening side-effects.[21] For this reason and due to the many food restrictions associated with their use, MAOIs have not been used as a drug of choice for the treatment of AD, although MAO type-B-specific inhibitors have been used to treat various Parkinsonian symptoms in Parkinson's Disease (PD).[22]

Potential difficulties with current treatments

Memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is widely used for the treatment of moderate to severe Alzheimer's disease.[23] Memantine's relevant mechanism of action is the inhibition of glutamatergic excitotoxicity in NMDA glutamate receptors.[24] Although widely used for treating cognitive and memory deficits in AD, the use of Memantine has been associated with exacerbation of psychotic symptoms in some AD patients.[25]

Memantine has FDA approval for the treatment of moderate to severe AD, but it is also frequently used off-label for the treatment of mild AD. There is little evidence to support the efficacy of Memantine for treatment of mild AD, for which ChEIs are the FDA-approved drugs of choice.[26-28] However, due to their mechanism of action, ChEIs also have a range of potential side-effects presenting as symptoms of overstimulation of the parasympathetic nervous system, including vomiting, falling, nausea, increased confusional state, dizziness, pneumonia, diarrhea, hallucinations, malaise, bradycardia, syncope, convulsion and death.[29,30] The respective limitations of Memantine and the ChEIs leave the door open for novel medical approaches to the treatment of dementia symptoms in patients diagnosed with AD, especially mild AD.

Auvelity: A Novel Antidepressant

On August 19, 2022, Axsome Therapeutics, Inc. announced that the FDA had approved Auvelity (Dextromethorphan HBr -Bupropion HCl) extended-release tablets for the treatment of MDD in adults.[8] The medication's formulation is based on research suggesting that NMDA antagonists and sigma-1 receptor agonists can reduce the symptoms of MDD.[9,16]

Auvelity: Mechanism of action

The Dextromethorphan component of Auvelity works as an antagonist on the NMDA receptor, an ionotropic glutamate receptor, and as an agonist on the sigma-1 receptor in the brain. The Bupropion component of Auvelity increases blood levels of Dextromethorphan by competitively inhibiting CYP2D6, catalyzing a major biotransformation pathway for Dextromethorphan.[31]

NMDA receptors are glutamate-gated cation channels with high calcium permeability.[32] The role of the glutamatergic neurotransmitter pathway in mood regulation has long been the focus of research. Significantly higher serum levels of glutamate are found in patients diagnosed with MDD than the general population.[33] Glutamate is necessary for the normal development of dendritic branching, and excessive glutamatergic neurotransmission is thought to induce dendritic retraction and loss of dendritic spines.[33] The growing body of evidence has led researchers to suggest that the glutamatergic neurotransmitter pathway is a 'primary mediator of psychiatric pathology'.[34] Auvelity's inhibition of the glutamatergic pathway functionally reduces glutamatergic excitotoxicity.

In addition, Auvelity works as an agonist on the sigma-1 receptor, which has been identified as a modulator of dopaminergic transmission.[16,35] Auvelity's agonistic effect on the sigma-1 receptor, combined with glutamatergic inhibition, is believed to be the mechanism of action through which Auvelity works as an antidepressant.[9,16,31]

Auvelity: Hypothetical novel application for treatment of AD

Auvelity's NMDA antagonism inhibits glutamatergic excitotoxicity, believed to induce neuronal loss in AD.[8,33] Auvelity's agonism of the sigma-1 receptor is believed to increase activity in the dopaminergic neurotransmitter pathway, with consequent improvements in mood and potential improvements in cognition.[16,31] The sigma-1 receptor has been identified as a modulator of dopaminergic transmission whose activity is also increased by Memantine.[16,35] Sigma-1 agonism combined with glutamatergic inhibition is believed to be the mechanism through which Memantine serves as a memory-sparing agent for AD patients.[9,16]

Auvelity's mechanism of action (NDMA antagonism inhibiting glutamatergic activity, combined with sigma-1 receptor agonism leading to increased dopaminergic activity) closely resembles Memantine's mechanism of action. Accordingly, in addition to reducing the symptoms of MDD, Auvelity might provide AD symptom containment (serving as a memory-sparing agent with benefit for cognition, memory and general functioning), without many of the potential side-effects associated with other medications used to treat AD.[9,16,24-28,31]

Discussion and Conclusion

Auvelity's mechanism of action as an NMDA antagonist and sigma-1 receptor agonist so closely resembles the mechanism of action underlying the effect of Memantine that it might be described as the same mechanism of action. Memantine is believed to inhibit glutamatergic excitotoxicity through blockade of NMDA receptors, sparing synaptic responses required for normal behavioral functioning, cognition and memory.[13] Memantine also functions as a sigma-1 receptor agonist, increasing dopaminergic transmission.[16] Memantine's activation of the dopaminergic pathway through its agonistic effect on the sigma-1 receptor, combined with NMDA antagonism reducing glutamatergic excitotoxicity, is believed to be the mechanism through which Memantine improves memory, cognition and general functioning in AD patients.[16] Because of its demonstrated efficacy for improving functioning in these areas, Memantine is a medication of choice for the treatment of AD.[13,17]

Auvelity's Dextromethorphan component functions as a potent NMDA receptor antagonist.[31] Auvelity's NMDA inhibition is amplified by its Bupropion component, which competitively inhibits the isoenzyme CYP2D6, with consequent significant elevation of Dextromethorphan blood serum levels, catalyzing a major biotransformation pathway for Dextromethorphan.[31] Because NMDA receptors are glutamate-gated cation channels with high calcium permeability,[32] NMDA antagonists like Auvelity reduce glutamatergic neurotransmission, including glutamatergic excitotoxicity believed to induce dendritic retraction and loss of dendritic spines associated with Alzheimer's disease.[33]

In addition, Auvelity's agonistic effect on the sigma-1 receptor boosts dopaminergic transmission, which is also believed to mediate mood and cognitive functioning.[16,31] Auvelity's combination of elevated

dopaminergic activity with glutamatergic inhibition is believed to be the mechanism of action through which Auvelity works as an antidepressant.[31] It is also the specific mechanism through which Memantine is thought to be effective for treating the symptoms of AD.[13,17]

Although Auvelity has not been specifically approved for the treatment of AD, it can be prescribed for the significant proportion of AD patients diagnosed with MDD.[5-7,36,37] It is hypothesized that the use of Auvelity for AD patients diagnosed with MDD might produce improvements not only in mood, but also in general behavioral functioning, cognition and memory. Such off-label benefits might eventually lead to AD being added to the list of approved conditions for treatment with Auvelity.

Interestingly, research indicates that Memantine might have efficacy for the treatment of bipolar depression.[38,39] Of even greater interest with regard to Auvelity, a study combining Memantine with Dextromethorphan produced improvements in mood and functioning in patients with bipolar depression.[40] These findings corroborate the overlap between the mechanisms of action found in Auvelity and Memantine, and consequent potential interchangeability for symptom treatment, supporting the hypothesis that Auvelity might be effective for treating the symptoms of AD.

Currently, approximately one in nine, or 6.5 million, of the 58 million Americans over the age of 65 have been diagnosed with AD,[2] and about one third of people over the age of 85 have AD.[3] The risk of dementia increases with advancing age, so the rapidly growing number of older adults (expected to grow to 88 million by 2050) includes an even greater proportional increase in the number of AD patients.[2-4] The growing population of AD patients will have significant impact on the quality of life for AD patients, their families, their care providers, and the healthcare economy.[2,4] The need for efficacious and cost-effective medical interventions for AD will continue to increase, making the potential application of Auvelity as a treatment for AD especially pertinent.

Auvelity's potential adverse effects and consequences of long-term use remain to be seen. Because Auvelity shares mechanisms of action with Memantine, it is possible that Auvelity also has the same limitations and potential for producing adverse side-effects associated with Memantine.[25-28] Clinical observation and data collection from a large number of AD patients treated over time with Auvelity will reveal whether Auvelity has specific benefit for the treatment of AD.

Declarations:

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