Application of Ketamine in Depression in Alzheimer's Disease

Subjects: Medicine, Research & Experimental

Contributor: Amber Edinoff , islam shehata , , Alexandra Anderson , Elyse Cornett , Adam Kaye , Alan David Kaye

Depression is a leading cause of disability globally, with a prevalence of 3.8% among the whole population, 5% of the adult population, and 5.7% of the elderly population over 60 years of age. There is evidence that depression is linked to certain neurodegenerative diseases, one being Alzheimer's disease (AD). The efficacy of conventional antidepressants to treat depression in AD is conflicting, especially regarding selective serotonin reuptake inhibitors (SSRIs). However, ketamine, a nonselective N-methyl-D-aspartate (NMDA) receptor antagonist, can mediate a wide range of pharmacological effects, including neuroprotection, anti-inflammatory and anticancer properties, multimodal analgesia, and treatment of depression, suicidal attempts, and status epilepticus. Recent clinical findings suggest that ketamine may provide neuroprotection and reduce neuropsychiatric symptoms associated with AD.

Alzheimer's disease dementia depression ketamine esketamine

1. Introduction

Depression is a leading cause of disability globally, with a prevalence of 3.8% among the whole population, 5% of the adult population, and 5.7% of the elderly population above 60 years of age [1]. It is characterized by a lack of desire to engage in normal activities or previously desirable activities, persistent sadness, or irritation affecting one's social and professional life [2]. There is evidence that depression is linked to some neurodegenerative diseases; one is Alzheimer's disease (AD) [2][3]. AD is characterized by memory loss, decreased cognitive abilities, decreased visuospatial skills, and personality change. These pathological features are attributed to the accumulation of β-Amyloid (Aβ), which stimulates an inflammatory response causing neuronal damage [4][5]. Depression is reported in 30–40% of patients suffering from AD [6].

Ketamine, a nonselective N-methyl-D-aspartate (NMDA) receptor antagonist, can be used to treat depression [7]. A single sub-anesthetic dose of ketamine can be an alternative to electroconvulsive therapy in treatment-resistant depression (TRD) given its rapid action [8]. Moreover, ketamine has a rapid and prolonged antidepressant effect compared to currently approved antidepressants [9][10]. These studies suggest that ketamine may be an option in treating AD-related depression [11]. Esketamine, which is ketamine formulated as a nasal spray, was approved by the Federal Drug Administration (FDA) in the United States in March 2019 as an adjuvant drug in the treatment of TRD [12].

The unclear role regarding the use of ketamine as a potential therapy for depression in AD is due to ketamine's side effects of dissociation, memory loss, confusion, and the likelihood of abuse. Additionally, the exact mechanism by which ketamine can potentially benefit depression symptoms is largely unknown.

2. Alzheimer's Disease

AD is a progressive neurodegenerative disease that mainly affects older adults.

2.1. Pathogenesis

Pathogenesis mainly involves the progressive loss of cortical neurons related to atrophy and classical positive lesions formed by the accumulation of amyloid plaques, neurofibrillary tangles (NFT), dystrophic neuritis, neuropil threads, and other deposits. Amyloid plaques are created by excess production and decreased clearance of Aβ peptides. The major constituent of NFTs is hyperphosphorylated tau protein.

2.2. Causes and Risk Factors

The risk factors associated with AD include age, genetic predisposition, head injuries, vascular disease, infections, hypertension, diabetes mellitus, dyslipidemia, medications, and environmental factors (e.g., air pollution, heavy metals, pesticides, etc.). There is some evidence that impairment of cholinergic function is a critical risk factor, but others believe that alteration in Aβ-protein production and processing is the main factor.

2.3. Clinical Features

AD is a progressive disease. Life expectancy after diagnosis is about 8–10 years but can vary greatly from 3–20 years [13][14]. Impairment in memory, executive function, judgment, visuospatial ability, language and behavior, and psychological symptoms (apathy, social disengagement, irritability, agitation, aggression, wandering, and psychosis) are the cardinal symptoms of AD. Memory impairment, defined as the specific loss of the memory of a recent event, is an initial and most common symptom [15].

2.4. Diagnosis

Clinically, AD is diagnosed with an insidious onset and progressive cognitive decline in one or more domains. The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) defines these domains as learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition for neurocognitive disorders in general [16]. The scans and biomarkers discussed above help guide the diagnosis, but usually clinical diagnoses. If this decline is seen gradually, AD is probably the cause of the neurocognitive disorder. Definitive diagnosis is completed with histopathology obtained from a brain biopsy, which is rarely done.

3. Current Alzheimer's Treatments and Shortcomings

Evidence suggests that pathological changes can develop in AD decades before individuals begin experiencing symptoms, making certain medications less successful by the point of later diagnosis [17]. Another major challenge exists with risk factor differences between men and women in clinical presentation [17]. Preclinical studies have suggested that menopausal changes may be a risk factor for AD in women [17]. To date, no medications have successfully cured individuals or slowed the progression of AD [17]. All available treatments currently approved by the FDA are designed for supportive care of symptomatic treatment in AD, including behavioral and cognitive deficits [18].

Additionally, there are limited medications available to treat psychiatric symptoms in AD [18]. There are no drugs currently approved to treat psychosis, apathy, or depression in AD [18]. However, the drug pimavanserin is a serotonin receptor antagonist that may soon receive approval by the FDA to treat AD-related psychosis [18]. Standard therapies for major depression have mostly proved unsuccessful in treating depression [18]. AD pathology is very complex, and therefore many standard therapies for other neurological diseases are not effective in treating this disease. The neurobiological basis for these symptoms is still an area of investigation, and if treated, can prevent further decline and behavioral problems in many individuals [18].

Currently, acetylcholinesterase inhibitors and N-Methyl-D-aspartic acid (NMDA) antagonists are the only medications approved for use in AD by the FDA [19]. Acetylcholinesterase inhibitors reduce the breakdown of acetylcholine by the enzyme acetylcholinesterase in the synaptic cleft [19]. These medications are designed to slow the decline in cognition and are most effective when started soon after the time of diagnosis [19]. Galantamine, one acetylcholinesterase inhibitor, is approved for treating mild to moderate AD, while rivastigmine and donepezil can be used in any stage of treatment for AD [19]. Individuals taking these medications may experience symptoms such as nausea, vomiting, and diarrhea [19]. Memantine is an approved medication for AD that works differently from acetylcholinesterase inhibitors by blocking the NMDA receptor and affecting the action of glutamate, which plays a role in memory [20]. Memantine can be used for moderate to severe AD in combination with acetylcholinesterase inhibitors, or on its own [20].

4. Evidence for Ketamine Treatment

Ketamine was developed in the 1960s as an anesthetic agent, and its neurobehavioral effects have been identified over the last 50 years [21]. Ketamine is a racemic mixture comprising equal parts of (R)-ketamine (or arketamine) and (S)-ketamine (or esketamine). Ketamine, a nonselective N-methyl-D-aspartate (NMDA) receptor antagonist, can mediate a wide range of pharmacological effects, including neuroprotection, anti-inflammatory and anticancer properties, multimodal analgesia, and treatment of depression, suicidal attempts, and status epilepticus [22]. One of the non-competitive NMDA receptor antagonists, memantine, showed therapeutic benefits in AD [23]. The theory behind NMDA receptor antagonists in AD treatment lies in implementing NMDA receptor blocking agents in offsetting Alzheimer-related pathological stimulation of these subtypes of glutamate receptors in the central nervous system [24]. The excitotoxic hypothesis is speculated in the pathogenesis of AD, where the overactivation of glutamate, the primary excitatory amino acid, causes neurotoxicity [25]. Comparing ketamine to memantine, the latter exhibits lower affinity to the NMDA receptors with rapid relief of its block, which allows symptomatic

improvement without affecting desirable functions such as memory and learning [5]. However, ketamine showed rapid relief of major depression symptoms in patients with AD [26]. The US FDA and European Medicines Agency recently approved intranasal S-ketamine for treatment-resistant depression in conjunction with an oral antidepressant [27]. At the same time, the data about the efficacy of the conventional antidepressant in AD are still conflicting, especially with regard to the selective serotonin reuptake inhibitor (SSRI) [28].

5. Recent Clinical Findings

A pre-clinical study by Zhang Ke et al. conducted a pre-clinical trial to elucidate the difference between the underlying molecular effects of ketamine and memantine that make the former one more susceptible to generating antidepressant effects. The authors used rats and looked at slices of their hippocampus and analyzed antibody staining of the studied protein via western blot. The study found that only ketamine induces the activation of mTOR and GluA1 expression, thus enhancing the excitatory synaptic transmission and inducing an anti-depressant action [29].

A 2021 randomized controlled trial investigated the efficacy of ketamine in patients suffering from chronic post-traumatic stress disorder (PTSD). This trial was performed after the authors' proof-of-concept trial, which showed a reduction of PTSD symptoms after ketamine infusion after 24 h. In this study, 30 subjects with PTSD were randomized in a 1:1 ratio to receive six infusions of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg), which was used as a psychoactive control, over a two-week period. The authors found that 70% of individuals responded with significant improvement in their symptoms during this period as measured by their clinician-administered PTSD Scale for the DSM-5 from baseline [30].

6. Conclusions

Although there is currently no cure for AD, there are several approved medications and targets for drug therapy in clinical trials for symptomatic treatment. The FDA-approved medications for AD are acetylcholinesterase inhibitors and NMDA antagonists. Recent clinical findings in the last twenty years suggest that the nonselective NMDA antagonist ketamine may be beneficial in providing both neuroprotection and reduction of the neuropsychiatric symptoms in AD. Ketamine may prove to be more beneficial to patients than the standard treatments for AD because it has fewer side effects than acetylcholinesterase inhibitors and more of a broad mechanism of action than the NMDA antagonist, memantine. As a well-known analgesic and anti-inflammatory drug, it acts quickly, has long-lasting effects, and improves psychiatric symptoms with a smaller therapeutic dose than other medications. Ketamine has already proven successful in the treatment of psychiatric symptoms, specifically for treatment-resistant depression. This is important because depression may occur prior to memory loss in AD. In addition, ketamine is less likely to worsen cognition compared to other treatments like ECT for severe depression. Clinical trials have demonstrated that periodic doses of ketamine reduce symptoms such as suicidal ideation and psychosis. However, ketamine can also cause side effects such as dissociation, memory loss, and confusion. Based on these known side effects, the effect on individuals with dementia and depression may simply be

explained as a drug side effect rather than a definitive improvement in symptoms. Additionally, vitals should be monitored closely when treating individuals with ketamine because individuals may experience an increase in blood pressure. This is a factor to consider before treating individuals with ketamine, especially in older individuals with cardiac comorbidities. Ketamine has been shown to act on the cellular level in opposing neurotoxins and protecting glial and neuronal function from the deleterious effects of inflammatory cytokines. Based on present information, it can be summarized that ketamine may have a role in neuroprotection and the improvement of psychiatric symptoms in AD. Further research and clinical trials are warranted to prove or disprove this theory, but it is well worth investigating for a potential chance at improving the quality of life for millions of individuals.

References

1. World Health Organization. Depression. Available online: https://www.who.int/news-room/fact-sheets/detail/depression (accessed on 7 February 2022).
2. Chand, S.P.; Arif, H. Depression. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2022. Available online: http://www.ncbi.nlm.nih.gov/books/NBK430847/ (accessed on 7 February 2022).
3. Ownby, R.L.; Crocco, E.; Acevedo, A.; John, V.; Loewenstein, D. Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. Arch. Gen. Psychiatry 2006, 63, 530–538.
4. Wang, R.; Zhang, Z.; Kumar, M.; Xu, G.; Zhang, M. Neuroprotective potential of ketamine prevents developing brain structure impairment and alteration of neurocognitive function induced via isoflurane through the PI3K/AKT/GSK-3β pathway. Drug Des. Dev. Ther. 2019, 13, 501–512.
5. Ketamine: A Neglected Therapy for Alzheimer Disease. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6667975/ (accessed on 7 February 2022).
6. Wragg, R.E.; Jeste, D.V. Overview of depression and psychosis in Alzheimer's disease. Am. J. Psychiatry 1989, 146, 577–587.
7. Ballard, E.D.; Zarate, C.A. The role of dissociation in ketamine's antidepressant effects. Nat. Commun. 2020, 11, 6431.
8. Zanos, P.; Gould, T.D. Mechanisms of ketamine action as an antidepressant. Mol. Psychiatry 2018, 23, 801–811.
9. Zanos, P.; Piantadosi, S.C.; Wu, H.-Q.; Pribut, H.J.; Dell, M.J.; Can, A.; Snodgrass, H.R.; Zarate, C.A.; Schwarcz, R.; Gould, T.D. The Prodrug 4-Chlorokynurenine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/GlycineB-Site Inhibition. J. Pharmacol. Exp. Ther. 2015, 355, 76–85.

10. Berman, R.M.; Cappiello, A.; Anand, A.; Oren, D.A.; Heninger, G.R.; Charney, D.S.; Krystal, J.H. Antidepressant effects of ketamine in depressed patients. Biol. Psychiatry 2000, 47, 351–354.
11. Lozupone, M.; La Montagna, M.; D’Urso, F.; Piccininni, C.; Sardone, R.; Dibello, V.; Giannelli, G.; Solfrizzi, V.; Greco, A.; Daniele, A.; et al. Pharmacotherapy for the treatment of depression in patients with alzheimer’s disease: A treatment-resistant depressive disorder. Expert Opin. Pharmacother. 2018, 19, 823–842.
12. Choudhury, D.; Autry, A.E.; Tolias, K.F.; Krishnan, V. Ketamine: Neuroprotective or Neurotoxic? Front. Neurosci. 2021, 15, 672526.
13. Wolfson, C.; Wolfson, D.B.; Asgharian, M.; M’Lan, C.E.; Østbye, T.; Rockwood, K.; Hogan, D. A Reevaluation of the Duration of Survival after the Onset of Dementia. N. Engl. J. Med. 2001, 344, 1111–1116.
14. Larson, E.B.; Shadlen, M.-F.; Wang, L.; McCormick, W.C.; Bowen, J.D.; Teri, L.; Kukull, W.A. Survival after Initial Diagnosis of Alzheimer Disease. Ann. Intern. Med. 2004, 140, 501–509.
15. McKhann, G.M.; Knopman, D.S.; Chertkow, H.; Hyman, B.T.; Jack, C.R., Jr.; Kawas, C.H.; Klunk, W.E.; Koroshetz, W.J.; Manly, J.J.; Mayeux, R.; et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging—Alzheimer’s association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimer’s Dement. J. Alzheimer’s Assoc. 2011, 7, 263–269.
16. DSM-IV and DSM-5 Criteria for Dementia—UpToDate. Available online: https://www.uptodate.com/contents/image?imageKey=NEURO%2F91276 (accessed on 13 February 2022).
17. Frozza, R.L.; Lourenco, M.V.; De Felice, F.G. Challenges for Alzheimer’s Disease Therapy: Insights from Novel Mechanisms Beyond Memory Defects. Front. Neurosci. 2018, 12, 37.
18. Cummings, J. New approaches to symptomatic treatments for Alzheimer’s disease. Mol. Neurodegener. 2021, 16, 2.
19. Yiannopoulou, K.G.; Papageorgiou, S.G. Current and Future Treatments in Alzheimer Disease: An Update. J. Cent. Nerv. Syst. Dis. 2020, 12, 1179573520907397.
20. Raina, P.; Santaguida, P.; Ismaila, A.; Patterson, C.; Cowan, D.; Levine, M.; Booker, L.; Oremus, M. Effectiveness of cholinesterase inhibitors and memantine for treating dementia: Evidence review for a clinical practice guideline. Ann. Intern. Med. 2008, 148, 379–397.
21. Feifel, D. Breaking Sad: Unleashing the Breakthrough Potential of Ketamine’s Rapid Antidepressant Effects. Drug Dev. Res. 2016, 77, 489–494.
22. Pribish, A.; Wood, N.; Kalava, A. A Review of Nonanesthetic Uses of Ketamine. Anesthesiol. Res. Pract. 2020, 2020, 5798285.

23. Kishi, T.; Matsunaga, S.; Oya, K.; Nomura, I.; Ikuta, T.; Iwata, N. Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis. J. Alzheimer's Dis. 2017, 60, 401–425.
24. Kuns, B.; Rosani, A.; Varghese, D. Memantine. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2022. Available online: http://www.ncbi.nlm.nih.gov/books/NBK500025/ (accessed on 7 February 2022).
25. Memantine in Moderate-to-Severe Alzheimer's Disease—PubMed. Available online: https://pubmed.ncbi.nlm.nih.gov/12672860/ (accessed on 7 February 2022).
26. Rocha, F.L.; de Vasconcelos Cunha, U.G.; Paschoalin, R.C.; Hara, C.; Thomaz, D.P. Use of subcutaneous ketamine to rapidly improve severe treatment-resistant depression in a patient with Alzheimer's disease. Int. Clin. Psychopharmacol. 2021, 36, 104–105.
27. Pharmacodynamic Interactions between Ketamine and Psychiatric Medications Used in the Treatment of Depression: A Systematic Review. Available online: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8538895/ (accessed on 7 February 2022).
28. Rosenberg, P.B.; Drye, L.T.; Martin, B.K.; Frangakis, C.; Mintzer, J.E.; Weintraub, D.; Porsteinsson, A.P.; Schneider, L.S.; Rabins, P.V.; Munro, C.A.; et al. Sertraline for the treatment of depression in Alzheimer disease. Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry 2010, 18, 136–145.
29. Zhang, K.; Yamaki, V.N.; Wei, Z.; Zheng, Y.; Cai, X. Differential regulation of GluA1 expression by ketamine and memantine. Behav. Brain Res. 2017, 316, 152–159.
30. Feder, A.; Costi, S.; Rutter, S.B.; Collins, A.B.; Govindarajulu, U.; Jha, M.K.; Horn, S.R.; Kautz, M.; Corniquel, M.; Collins, K.A.; et al. A Randomized Controlled Trial of Repeated Ketamine Administration for Chronic Posttraumatic Stress Disorder. Am. J. Psychiatry 2021, 178, 193–202.