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Effect of Esketamine on Cognitive Dysfunction in Elderly Patients

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Abstract: *This paper aims to analyze the mechanism of action of esketamine, explore its efficacy in treating cognitive dysfunction in elderly patients, and evaluate its clinical application prospects. This paper focuses on the main molecular pathways of esketamine acting on the central nervous system, and summarizes its efficacy and safety in treating depression and cognitive dysfunction in elderly patients. Esketamine protects and improves the cognitive function of elderly patients by regulating the activity of glutamatergic neurons, promoting the secretion of Brain-derived neurotrophic factor (BDNF), and enhancing synaptic plasticity. Ketamine, as a new drug for the rapid treatment of depression, has great application prospects in clinical practice. However, in the treatment of cognitive dysfunction in elderly patients, it is necessary to strictly grasp the indications and pay attention to the rational use of the drug.*

Keywords: *Cognitive Dysfunction, Antidepressant Effect, Artistic Intelligence, Medical Image Aided Diagnostics*

1. Introduction

Cognitive dysfunction is a common chronic disease of the elderly, and also a common psychiatric disease of the elderly. If symptoms occur, memory decline and executive ability decline usually occur, and even dementia symptoms may occur in severe cases. The decline of cognitive function usually affects a person's daily life, quality of life and life span. Therefore, it is necessary to explore the influencing factors of cognitive function. As a common emotional disorder, depression seriously affects the ability to live and reduces the quality of life of individuals. The occurrence of depression is closely related to age. The prevalence of depression increases with age. Some studies have shown that depression accelerates the progress of cognitive dysfunction in elderly patients, but the specific relationship between them is very complex. Although there are more and more researches on them, due to their complexity, the research on them has become a hot topic in the spiritual field.

With the development of artificial intelligence, medical image aided diagnosis has become an irreplaceable important means in modern medical diagnosis, which has great advantages over other methods. Therefore, medical image aided diagnosis has received extensive attention and research in the medical field. In this regard, this paper analyzes the influencing factors of cognitive dysfunction through medical image aided diagnosis, and tests the patients with cognitive dysfunction based on image technology to verify the impact of antidepressant effect on cognitive dysfunction.

Cognitive dysfunction has always been a concern in the medical field, and many scholars have studied it. Viggiano Davide believed that understanding of other forms of cognitive dysfunction could be improved by understanding the relationship between renal dysfunction and cognitive dysfunction [1]. DeLuca John outlined the treatment of patients with multiple sclerosis (MS), and believed that disease improvement therapy was effective in reducing the recurrence rate of MS. However, this treatment was ineffective in treating cognitive dysfunction [2]. Biessels Geert J believed that cognitive dysfunction was an important comorbidity and complication of diabetes, which greatly affected the treatment of diabetes [3]. Vuralli Doga proved through research that preventive drugs could affect cognitive function, but could not fully explain the cognitive impairment of migraine [4]. Nation Daniel A found that individuals with cognitive impairment suffered from brain capillary damage and the decomposition of the blood brain barrier in the hippocampus, indicating that the decomposition of the blood brain barrier was an early biomarker of human cognitive impairment [5]. Munshi Medha N believed that in the management of diabetes patients, attention should be paid to cognitive dysfunction, because it

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interfered with patients' participation in diabetes management [6]. However, due to the lack of data sources, the above research is still in the theoretical stage and has no practicality.

The relationship between depression and cognitive dysfunction has always been a hot issue. Knight Matthew J studied the latest progress of major depressive disorder, and believed that cognitive dysfunction and major depressive disorder were related to emotional interaction [7]. MacQueen Glenda M believed that cognitive impairment was related to poor overall functional outcomes, and the degree of cognitive impairment in patients with bipolar affective disorder was greater [8]. However, the methods used in these studies are too traditional and not convincing enough.

In order to improve the treatment effect of cognitive dysfunction in elderly patients and enhance the treatment level, this article systematically sorts out the mechanism of action of esketamine, and comprehensively analyzes its targets, efficacy evaluation and possible risks, providing a theoretical basis for future drug development and personalized medication. By integrating the latest research results at home and abroad, this article systematically evaluates the advantages and disadvantages of esketamine as a new generation of rapid antidepressant, and promotes its application in the treatment of cognitive dysfunction in the elderly.

2. Diagnosis of Cognitive Impairment Based on Image Technology

2.1 Cognitive Dysfunction

Cognition is a psychological activity of people, mainly involving a series of social behaviors such as learning, memory and spirit [9-10]. The executive function refers to the ability of people to start and complete an activity according to their own wishes. The executive function involves many contents, mainly reflected in the initiation of plans. Cognitive dysfunction refers to the abnormality of people's learning, memory and other behaviors, which has a great impact on people's life. It is mainly manifested in memory disorder, executive dysfunction, etc. [11-12], as shown in Figure 1.

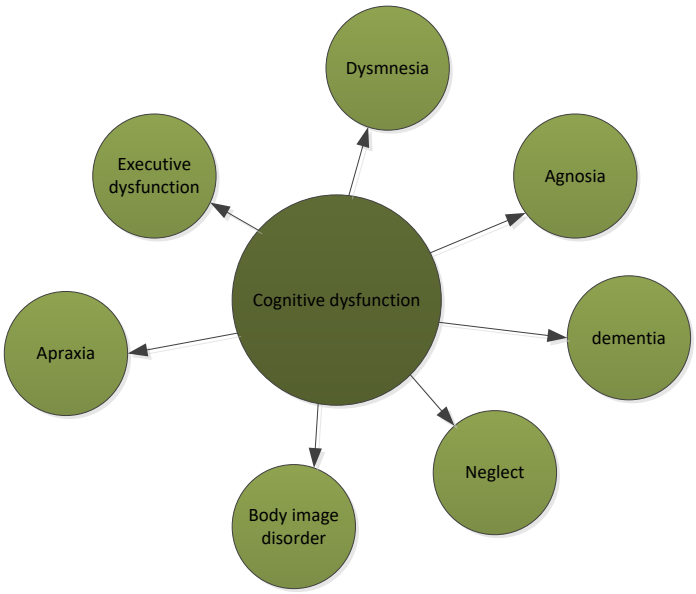

Figure 1 Cognitive dysfunction

Among cognitive dysfunction, memory impairment is the most common manifestation. Memory refers to the process of encoding and extracting knowledge acquired from the outside in the brain, which mainly includes three basic steps: memorization, retention and reproduction [13-15]. Memory can be classified according to different memory time, as shown in Figure 2.

According to different memory time, memory can be divided into long-term, short-term and instantaneous memory [16-17]. Long term memory is kept in the brain for a long time, as long as it can be remembered at any time. Short term memory refers to the ability to retrieve external information after a period of delay, which mainly depends on the storage function of the hippocampus. Instantaneous memory is mainly embodied in the temporary retention of stimulus information in sensory channels. Memory disorders are divided into organic amnesia, mental amnesia and other types

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of memory disorders [18-19].

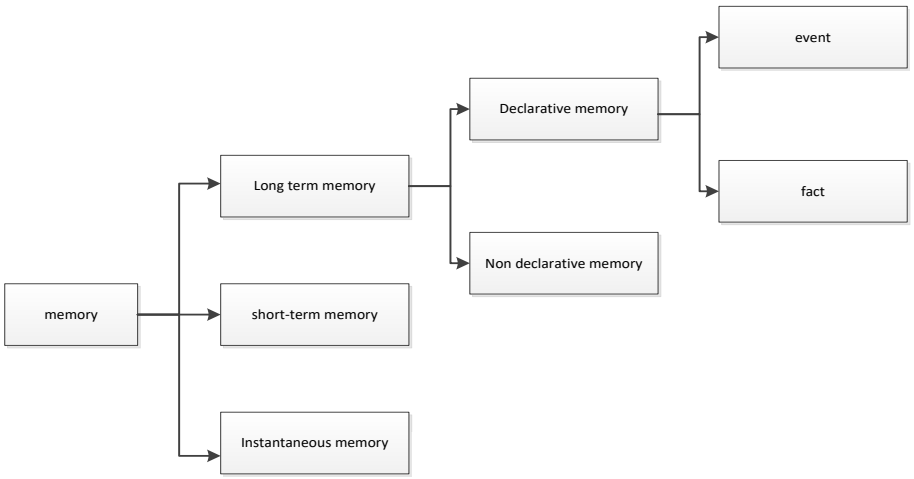

Figure 2 Memory type

2.2 Depression

Depression, also known as Major Depressive Disorder (MDD), is a common mental illness characterized by low mood, decreased interest, decreased appetite, decreased attention, self-denial, and even suicidal thoughts. According to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) (DSM-5), patients must experience 5 or more core symptoms within 2 weeks and seriously affect their social abilities [20]. Clinically, other symptoms of depression include sleep disorders (insomnia or drowsiness). These symptoms not only have an adverse effect on the patient's daily life, but also cause significant damage to the patient's cognitive ability, including memory loss, decreased judgment, and decreased executive function.

In the elderly patient population, depression is not only a common emotional disease, but is also often accompanied by cognitive impairment. The pathogenesis and clinical symptoms of the two are strongly correlated. Studies have shown that patients with Late-Life Depression (LLD) have cognitive dysfunctions such as poor attention and executive function, slow information processing speed, and impaired memory[21]. These functional impairments are not only a manifestation of depression, but may also indicate other neurodegenerative diseases such as Alzheimer's disease.

In terms of neurobiology, elderly depression and cognitive impairment share a number of common pathophysiological bases[22]. First, chronic stress and long-term depression can increase the activity of the hypothalamus-pituitary-adrenal axis (HPA), which in turn causes atrophy of the hippocampus and prefrontal cortex (hippocampus), which are important parts of emotional and cognitive regulation[23-24]. Second, the decrease in nerve growth factor (BDNF), represented by BDNF, not only affects synaptic plasticity, but also aggravates the decline in learning ability. Previous studies have found that elderly depression and patients with cognitive impairment have related inflammatory factors (IL-6, TNF-α, etc.), accompanied by higher levels of oxidative stress[25]. There may be a common immune mechanism between these two diseases. If they cannot be effectively identified and treated, their cognitive ability will decline faster, leading to their transformation to dementia. Therefore, for elderly patients with depression, in addition to alleviating their emotional symptoms, attention should also be paid to improving their cognitive function.

2.3 Pharmacological mechanism of esketamine

Esketamine is an enantiomer of ketamine, has good pharmacological activity, and has good clinical application prospects. Its mechanism of action is mainly binding to N-methyl-D-aspartate (NMDA) receptors, and it also plays an important role in the regulation of synaptic plasticity, neural regeneration,and multiple signaling pathways[26].

First, esketamine is a non-competitive antagonist of NMDA receptors and plays a very critical role in the brain. NMDA receptors are an important class of ionotropic glutamatergic receptors that play an important role in learning and memory. Esketamine can indirectly increase the activity of excitatory neurons by binding to the above receptors, especially the activity of inhibitory interneurons, by

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reducing their activity [27-28]. This regulation can help rebuild the homeostasis of neural networks, alleviate depressive symptoms, and even help repair impaired cognitive abilities. It promotes the activity and expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and plays an important role in synaptic reactions [29]. The enhancement of the AMPA receptor signaling pathway can promote the secretion of BDNF, thereby maintaining the stability of synapses. Therefore, esketamine may promote synaptic remodeling by activating the AMPA pathway, thereby improving the cognitive and emotional regulation of depression.

Secondly, esketamine also shows a certain neuroprotective effect, which is likely achieved through its antidepressant effect. Studies have shown that it can promote the proliferation of nerve cells by activating signaling pathways such as PI3K/Akt and ERK/MAPK [30]. These pathways are closely related to cell survival, proliferation and differentiation. Esketamine can exert a neuroprotective effect by regulating key molecules in the pathway, especially for the occurrence and development of chronic stress and neurodegenerative diseases [31-32]. In addition, esketamine can enhance the newborn capacity of hippocampal neurons, and this process is an important link in maintaining normal emotions. Promoting neural regeneration can promote the damage of neural circuits caused by long-term stress, depression and other factors, and provide new ideas for the prevention and treatment of cognitive impairment in the elderly.

3. The Therapeutic Effect of Esketamine on Cognitive Impairment in Elderly Patients

Esketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor blocker with significant pharmacological activity compared to classic monoamine antidepressants. Studies have shown that esketamine can regulate synaptic plasticity and network connectivity by inhibiting the excitability of glutamatergic neurons on NMDA receptors[33]. Previous studies have also found that esketamine has the effects of promoting BDNF secretion, synaptic remodeling and neural repair, which is an important mechanism for its rapid action[34]. As a new type of antidepressant, its efficacy is better than that of selective serotonin reuptake inhibitors (SSRIs), has a faster efficacy, and can significantly improve patients' emotions and cognitive abilities within 24 hours[35]. This feature gives it a unique advantage in the treatment of elderly depression with cognitive impairment. Esketamine is a dextrorotatory isomer of ketamine, and its analgesic effect is twice that of ketamine[36], so it is widely used in general anesthesia[37]. Recent studies have shown that esketamine has a certain protective effect on brain damage, but the specific mechanism is still unclear and needs further study.

3.1 Effects on Attention and Executive Function

Esketamine can promote functional connections in the prefrontal cortex of the brain, thereby improving the cognitive control level of elderly patients[38]. A meta-analysis based on randomized controlled studies showed that esketamine can significantly reduce the risk of perioperative neurocognitive impairment and improve patients' cognitive abilities[39].

3.2 Effects on memory function

Studies have shown that esketamine can protect and improve memory function to a certain extent[40]. An AI-assisted 3 T and 7 T structural MRI imaging study found that 10 days after ketamine administration, the overall volume of the left amygdala in patients with refractory depression increased significantly. However, there was no significant difference between the normal control group and the refractory depression group[41]. Five medical imaging studies have shown that patients treated with esketamine have improved in processing speed, verbal memory, visual memory, working memory and cognitive flexibility. Studies on esketamine showed that performance did not change. Studies have shown that inattention, slow processing speed and improved working memory are important indicators of antidepressant effects. Esketamine can normalize brain regions related to emotion and reward, such as the amygdala, insula, and orbitofrontal cortex[42].

3.3 Regulatory effect on behavioral symptoms

Cognitive dysfunction is often accompanied by a variety of behavioral symptoms, such as emotional instability, impulsive behavior, or social withdrawal [43-44]. A study combining bioinformatics, network pharmacology, and AI to predict target genes for S-ketamine in the treatment of major depression showed that S-ketamine may alleviate depression by targeting specific genes

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(including TGM2, HSP90AB1, and ADORA3) and signaling pathways (including gonadotropin-releasing hormone and relaxin signaling pathways) [45]. An in vitro study found that esketamine can alleviate depression by downregulating TREK-1 expression and promoting GABAergic neuron activity, but overexpression of TREK-1 can reverse the above effects. Esketamine blocks TREK-1 channels, enhances hippocampal neuron activity, and improves patients' postoperative depressive symptoms, providing a new idea for the prevention and treatment of postoperative depression in patients [46].

3.4 Comparison with other antidepressants

The main advantages of esketamine over traditional SSRIs are rapid onset of action, safe and reliable use, reduced postoperative hemodynamics, reduced postoperative inflammatory response, and shortened general anesthesia time. It can improve postoperative cognitive function with fewer side effects. One study found that propofol + esketamine was significantly better than propofol + sufentanil in anesthesia induction ($P<0.05$) [47]. Another study confirmed the safety and tolerability of esketamine in an elderly woman with cognitive impairment. In terms of cognitive tolerance, ketamine derivatives may become an alternative to electroconvulsive therapy for patients with refractory depression, and may improve short-term cognitive outcomes [48].

4. Conclusions

This article focuses on the efficacy of esketamine on cognitive dysfunction in elderly patients. Combining artificial intelligence medical imaging-assisted diagnosis technology and relevant literature analysis, this article systematically studies the effects of esketamine on attention, memory, behavior, and other aspects, as well as the differences between esketamine and other antidepressants. Esketamine is a new antidepressant with a fast onset and unique pharmacological mechanism. It can regulate NMDA receptors, promote BDNF secretion, enhance synaptic plasticity, and improve cognitive function in the elderly, especially language memory, visual memory, and working memory. At the same time, the drug improves behavioral symptoms caused by cognitive impairment by regulating the activity of brain regions such as emotion and reward. Compared with conventional antidepressants, esketamine has a good clinical application prospect, can shorten the operation time, reduce postoperative inflammatory response, and can provide a better treatment plan for elderly patients. Future studies can further explore the exact mechanism and long-term drug safety of esketamine from multiple levels such as the central and peripheral levels, in order to better guide its clinical application.

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