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Review: Pharmacological Approaches to Cognitive Impairment in Brain Disorders and Injury

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ABSTRACT: Cognitive impairment resulting from brain disease and injury significantly affects patients' quality of life by impairing memory, language, and other cognitive functions. The primary causes include dementia, mild cognitive impairment (MCI), and delirium, as well as cognitive deficits associated with chemotherapy and neurodegenerative diseases like Huntington's disease and multiple sclerosis. Pharmacological interventions play a crucial role in managing these impairments. Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and NMDA receptor antagonists (memantine) are widely used for dementia. Antipsychotics (e.g., haloperidol, clozapine, risperidone) target dopamine receptors to treat cognitive dysfunction in delirium and schizophrenia. Nootropics enhance cognitive performance, while calcium channel blockers (nimodipine, nilvadipine) prevent neurodegeneration by reducing calcium overload. Cognitive enhancers like erythropoietin, SSRIs (fluoxetine), modafinil, and methylphenidate have shown promise in mitigating chemotherapy-induced cognitive decline. A multifaceted pharmacological strategy tailored to the underlying pathology offers potential to improve cognitive outcomes in affected patients.

KEYWORDS: I Cognitive impairment, Dementia, Pharmacological treatment, Cholinesterase inhibitors, Antipsychotics

INTRODUCTION

Cognitive impairments encompass a range of conditions and diseases that result in brain damage and the decline of cognitive abilities, including language and memory [1]. These impairments significantly reduce an individual's ability to perform daily tasks, thereby diminishing their overall quality of life [2]. The primary causes of cognitive impairments include delirium, dementia, and mild cognitive impairment (MCI). Delirium is characterized by acute and fluctuating disturbances in attention and awareness, while dementia involves a progressive decline in cognitive function, most commonly due to Alzheimer's disease [3]. MCI represents an intermediate stage between normal aging and dementia, marked by noticeable but not yet disabling cognitive deficits [4].

A comprehensive approach is essential for managing cognitive impairments. Cognitive rehabilitation aims to enhance specific cognitive functions through targeted exercises, while physical activity has been shown to support brain plasticity and reduce cognitive decline [5]. Pharmacological interventions remain a cornerstone of treatment, with cholinesterase inhibitors and NMDA receptor antagonists widely used to alleviate symptoms and slow disease progression, particularly in dementia [6]. This article explores the underlying causes of cognitive impairments and provides an overview of the primary pharmacological treatments available to manage these conditions effectively.

COGNITIVE IMPAIRMENTS CAUSES

There are several factors that lead to cognitive impairments starting with dementia also known as major cognitive impairment, which is not a specific illness but an overall term to describe different range of progressive organic brain diseases that lead to cognitive difficulties mostly caused by Alzheimer's disease [7]. Vascular Dementia, Mixed dementia, Frontotemporal Dementia

(FTD) and Lewy Body Dementia (LDD) are thought to be common factors for dementia, it should be highlighted that LDD includes both Parkinson disease with dementia (PDD) and dementia with Lewy Bodies (DLB). There are other neurodegenerative diseases may lead to dementia, for example, Huntington's disease and Multiple sclerosis [8]. As well as other factors such as HIV infection, brain injury via stroke or trauma [7]. Additionally, MCI is a cognitive disorder but without any form of dementia, it is considered as intermediate state between cognitive aging and Alzheimer's disease. There are two subtypes of MCI: amnestic and nonamnestic [4].

Cognitive dysfunction can also be associated with acute non-reversible neuropsychiatric syndrome known as delirium, that leads also to disturbance of consciousness, mental status [9]. Patients with delirium experience some symptoms such as disorientation, memory difficulties, illusions, hallucination, hypoactive and mood changes. There are varies factors for delirium, for example, physical illness, anaemia, depression, aging and dementia. It is worth mentioning that the main difference between delirium and dementia is that dementia occurs over time, while delirium occurs suddenly [10].

Furthermore, 70% of cancer survivors have reported amnesia and other cognitive difficulties after chemotherapy treatment. In several studies it has been shown via brain images that chemotherapy leads to a reduction in the white matter, superior frontal gyri and parahippocampal gyrus area. In general, it has been found that chemotherapy drugs are responsible for altering and damaging regions in the brain of cancer survivors. Thus, cancer survivors' are cognitive skills affected. Moreover, it is believed that cancer itself causes cognitive impairments as many patents had some cognitive difficulties even before chemotherapy treatment, because cancer increases cytokines levels and then inflammation occurs in the brain [6].

PHARMACOLOGICAL APPROACHES

Atypical and Typical anti-psychotics

The atypical and typical anti-psychotics can relief cognitive disorders in delirium and schizophrenia via blocking dopamine receptors mainly D2 receptors, since dopamine agonists can affect the five dopaminergic pathways in CNS that control cognitive functions. Typical antipsychotics, for instance, haloperidol has high affinity for D2 receptor and low affinity for D1 receptor at high dose (12 mg/day), so low does (2-4 mg/day) is given intramuscular and intravenous to block only D2 receptors and also to disinhibit cholinergic receptors. Therefore, the risk of Parkinsonism decreases, but still other side effects can happen such as insomnia, dizziness [11].

Atypical anti-psychotics are believed to have fewer side effects as they can be either partial dopamine receptor antagonists, mostly D2 blocker, or multiple receptor antagonists, an example for D2-specific antagonist is remoxipride the first atypical anti-psychotics drug to be used in USA to treat short/long of schizophrenia and the associated cognitive disorders. Sulpiride is another D2-receptor antagonist, which can increase dopamine turnover. Even though sulpiride is less potent than haloperidol, both have the same effectiveness. Sulpiride cannot cross BBB as fast as haloperidol, since it has low lipid solubility. Therefore, the normal does of sulpiride (2000 mg/day) is signifyingly higher than haloperidol [12].

On the other hand, the multiple receptor antagonists are designed to target D2 receptor and other receptors, for instance, clozapine and risperidone. Clozapine was found to be able to improve cognitive function by blocking 5-HT2, 5-HT3, α-adrenergic, muscarinic, histaminergic, D1 and D2 receptors. Moreover, clozapine has 10- folds higher affinity for D3 and D4 receptors [13]. Although, clozapine does not develop tardive dyskinesia, some cardiovascular conditions may occur via blocking α-adrenergic and muscarinic receptors, in addition to blood abnormality, agranulocytosis and other serious side effects. Risperidone is a D2, 5-HT2A, 5-H7, H1, α1-adrenergic and α2-adrenergic antagonist, risperidone is also a weak antagonist at D4 and D1 receptors. Risperidone was suggested to have no cardiovascular risks, but still has some drawbacks such as anxiety and sedation [11].

Nootropics

Nootropics also called cognitive enhancers, which define as a group of various medications that improve cognitive functions in patent with dementia and brain injuries [14]. There are only four nootropics licensed by NICE; three of them are acetylcholinesterase inhibitors (AChEIs), donepezil, galantamine and rivastigmine, and one NMDA receptor antagonist Memantine [15]. AChEIs work by increasing the level acetylcholine, as it has been proved that cholinergic deficits can lead to cognitive disorders mainly in Alzheimer's disease "cholinergic hypothesis" [14]. Tacrine was the first licensed AChEI to treat Alzheimer's disease, and to enhance cognitive abilities by giving it four times a day . However, tacrine has some cholinergic side effects, for example, nausea and abdominal cramps, also hepatotoxicity can occur. On the other side donepezil, galantamine and rivastigmine were found to cause better improvement in cognitive functions with slight side effect [15]. Although donepezil, galantamine and rivastigmine are AChEIs, each drug has different way of inhibition as showin in table Table 1.

Memantine reliefs cognitive disorders via preventing glutamine uptake, as it has been proved that excessive release of glutamate plays a role in neurodegenerative disorders "glutamatergic hypothesis". Moreover, it was found that overactivation of glutamate

receptors, specially NMDA receptors, are responsible for damage of GABA neurones and neuronal toxicity via β-amyloid peptide, which cause cognitive impairments Therefore, memantine can afford neuroprotection by blocking NMDA receptors [16].

Table 1: Acetylcholinesterase inhibitors with there type of inhibition and side effects

Drug	Type of inhibition	Duration of action	Main side effects	Notes
Tacrine	Short acting, reversible affects both AchE and BuCHE	6 hours	Few cholinergic side effects. It can also cause hepatotoxicity	The first AChEl shown to be active in Alzheimer's disease. Monitoring for hepatotoxicity is needed
Donepezil	Short acting, reversible AchE-selective	24 hours	Slight cholinergic side effects	-
Rivastigmine	Slowly reversible affects both AchE and BuCHE	8 hours	Cholinergic side effects that tend to subside with continuing treatment	Gradual dose escalation of minimize side effects
Galantamine	Reversible, non-selective. Also enhances nicotinic ACh receptor activation by allosteric mechanism	8 hours	Few side effects	Dual mechanism of action postulated

Calcium channel blockers

Calcium channel blockers, for instance, nmodipine and nilvadipine have been demonstrated to be able to treat cognitive dysfunctions in dementia, whereas other calcium channel blockers failed. Calcium antagonists inhibit intracellular calcium overload via β-amyloid peptide, in order to prevent neuropathology and cell death. Nmodipine and nilvadipine can also block calcium uptake by both NMDA receptors and L-type calcium channels in postsynaptic by massive release of glutamate. Thus, the rate of cell death by cascade declines and eventually cognitive skills are enhanced [17].

Cognitive impairments, cancer and chemotherapy

Cognitive functions in cancer survivors can be improved by different kind of drugs, including cognitive enhancers, erythropoietin (EPO), selective serotonin reuptake inhibitor (SSRI), modafinil and methylphenidate [18]. Several studies found that EPO can enable an improvement in cognitive functions after chemotherapy, by promoting red blood cell production. Moreover, EPO can afford neuroprotection in patients with brain damage. However, the correlation between blood levels and cognitive skills is not fully understood. In addition SSRIs, for example, fluoxetine increases serotonin levels in the brain by preventing serotonin reuptake, which improve cognitive abilities. Some studies in animals illustrated that cognitive disorders were prevented by administration of fluoxetine before and during chemotherapy treatment with 5-fluorouracil [19].

Modafinil has been shown to enhance cognitive performance in healthy individuals by increasing cortical catecholamine levels and indirectly upregulating cerebral serotonin, glutamate, orexin, and histamine levels [20]. In cancer patients, studies have investigated modafinil's effects on cognitive function before and during chemotherapy. For instance, a study by Kohli et al.[21] analyzed the effects of modafinil on cognitive dysfunction in 82 breast cancer patients who had completed chemotherapy or chest radiotherapy more than one month prior. All participants received modafinil (200 mg daily) for four weeks, and the study found that modafinil improved cognitive function in these patients [22]. Similarly, Lundorff et al.[23] conducted a double-blind, randomized crossover trial assessing modafinil's impact on cognitive function in 28 patients with advanced cancer in a palliative care setting. The study reported that modafinil had a positive effect on cognitive function in these patients.

Methylphenidate is a norepinephrine–dopamine reuptake inhibitor, which is used as medication for both attention-deficit and hyperactivity disorder. Methylphenidate (20-30 mg/day) was found to be able to enhance cognitive performance in patient with primary brain tumors and cancer. Methylphenidate can also treat cognitive disorders in Alzheimer’s disease, vascular dementia and frontotemporal dementia. However, it is unclear if methylphenidate can prevent cognitive impairments after chemotherapy [6].

CONCLUSION

Cognitive impairments can occur in patients with delirium, dementia and mild cognitive impairment, also several cancer survivors had cognitive disorders after chemotherapy. Cognitive enhancers are considered to be effective treatments for cognitive disorders

in cases with dementia and brain injuries, whereas calcium channel blockers are mainly used to improve cognitive performance in patients with dementia.

Anti-psychotics are drugs that improve cognitive functions in patients with delirium and schizophrenia via inhibiting dopamine reuptake, some anti-psychotic drugs can block other receptors. Furthermore, there are other drugs that can prevent cognitive disorders in dementia and after chemotherapy, for instance, erythropoietin, SSRI, modafinil and methylphenidate.

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