Late-Life Depression

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Late-life depression (LLD), compared to depression at a young age, is more likely to have poor prognosis and high risk of progression to dementia. A recent systemic review and meta-analysis of the present antidepressants for LLD showed that the treatment response rate was 48% and the remission rate was only 33.7%, thus implying the need to improve the treatment with other approaches in the future. Recently, agents modulating the glutamatergic system have been tested for mental disorders such as schizophrenia, dementia, and depressive disorder.

Keywords: late-life depression ; glutamatergic system ; NMDA receptor ; IL-6 ; cytokine ; BDNF

1. Introduction

Aging is a global trend. The UN statistics shows that the population over age 65 by 2050 will reach 16% of total population. (https://www.un.org/en/global-issues/ageing?fbclid=IwAR2ut7ufS5ULfFGf4HbXtijNmx2q0VFzzIyBy0Fonznzt87LeIMjJGK21nU (accessed on 9 July 2021). Depression has recently been identified as a pandemic, causing huge social cost and high financial load. The average prevalence of geriatric depression in the community is about 12%, and, in long-term care institutions, 35% of patients have significant depressive symptoms [1].

Unlike depression at a young age, late-life depression (LLD), with high pathogenic complexity caused by physiological and psychosocial issues and chronic disease, can rarely be treated with one antidepressant. A recent systemic review and meta-analysis of the present antidepressants for LLD showed that the treatment response rate and the depression remission rate are 48% and 33.7% [2], respectively. It is thought that biological factors are pathogenically associated with LLD [3]. In the process of aging, structural changes in the brain may be associated with depression. The causes of LLD may include not only neuroendocrine dysregulation and changes in neural circuitry, but also genetic vulnerability and stress due to life events that interact reciprocally [4][5].

According to the 2016 CANMAT guideline, the first-line drug recommendations for adult depression include SSRIs, SNRIs, agomelatine, bupropion, and mirtazapine [6]. For elderly depression, the first-line drug recommendations include duloxetine, mirtazapine, and nortriptyline (level of evidence: level 1), as well as bupropion, citalopram/escitalopram, desvenlafaxine, duloxetine, sertraline, venlafaxine, and vortioxetine (level of evidence: level 2) [7].

In two large-scale studies, IMPACT [8][9] and PROSPECT [10][11] trials for elderly depressed patients, there was a difference in response rate between receiving antidepressant treatment and receiving general care only. The results of the IMPACT and PROSPECT trials showed that the antidepressant group had a better response rate (IMPACT, antidepressant vs. normal care: 45% vs. 19%; PROSPECT, antidepressant vs. usual care: 43% vs. 28%). Compared with young depression, late-life depression displays more somatic symptoms and cognitive deficits. The somatic symptoms include hypochondriasis, general and gastrointestinal somatic symptoms, and agitation [12][13][14].

Moreover, old age may be accompanied by other chronic diseases. When somatic complaints occur, depression may not be the first diagnosis, thus leading to underdiagnosis [15]. In the past, meta-analyses found different response rates of antidepressants between different groups: 53.8% in early-onset depression vs. 44.4% in late-onset depression [16][17]. Coupled with the analysis of subgroups, it was found that depressed people younger than 55 years had a significantly higher response rate to antidepressants than those older than 65 years. In addition, there was no significant difference between the group older than 65 and the placebo group. In the STAR*D trial [18], the overall remission rate in the acute treatment step was 67%. With more treatment steps, the remission rate continued to decrease, from 36.8% in the first step to 13% in the fourth step. Approximately 50% of patients will develop treatment resistance to antidepressants over time. Some studies found that treatment resistance for first-line antidepressants in elderly patients was as high as 55–81% [19]. Some studies suggest that lithium may be effective for treatment-resistant late-life depression [20][21]; however, more replicative studies are warranted. Esketamine is a recent FDA-approved treatment for treatment-resistant

depression, but its efficacy and safety in the elderly have not yet been confirmed. A recent phase 3 clinical trial [22] enrolled treatment-resistant depression patients over 65 years old and randomly assigned them to the nasal spray esketamine/antidepressant or nasal spray placebo/antidepressant group for 4 weeks. According to the change in scores of MADRS as the primary endpoint, there were no significant differences between both groups.

2. Depression and Dementia

Late-life depression is usually considered a chronic course, accompanied by cognitive impairment. Depression is considered to be one of the risk factors of dementia or a prodrome of dementia. Research [23] suggests that late-life depression may increase dementia risk by twofold. A recent meta-analysis [24] showed that depression in later years is associated with dementia in all forms. Further analysis discovered that the risk (2.52, 95% CI 1.77–3.59, $p < 0.001$) of vascular dementia is higher than Alzheimer`s disease (1.65, 95% CI 1.42–1.92, $p < 0.001$).

The two seem to overlap in some neurobiological findings. The theory of the HPA axis is currently the most consistent in depression research. Elevated cortisol level can also cause hippocampus neuronal loss and volume reduction [25][26]. Hypercortisolemia can also be seen in the CSF of patients with Alzheimer's disease (AD) [27]. Vascular depression refers to the appearance or aggravation of depression after the occurrence of cerebrovascular events. In addition to WMHs seen on neuroimaging, there are lesions on small blood vessels (maybe subcortical infarcts, microbleeding, etc.). In addition, in cases of depression, decreased blood flow in the brain may also lead to hyperactivity of the hippocampus and amygdala [28]. Inflammation can be seen in people with AD and depression, due to an increase in activated microglia in the CNS [29] [30]. Microglial cells that are continuously activated have a reduced ability to remove neurotoxic agents, leading to a reduction in neuronal loss and neurogenesis [28]. An increase in peripheral proinflammatory markers is also associated with the severity of depressive symptoms and cognitive impairment [31]. Neurotrophic factors include BDNF, the main function of which is to regulate synaptic plasticity, which plays an important role in learning and memory. It has been found in patients with depression that the use of antidepressants can increase the concentration of BDNF in the blood [24][32]. In patients with AD, the severity of cognitive impairment is related to BDNF and amyloid beta (Aβ1–42) plasma levels in serum [33][34]. Although the current research has found some common neurobiological changes in depression and AD, there are overlaps in symptoms. However, according to the current research, there is insufficient evidence that antidepressants can improve the cognition of depression in the elderly and the depression symptoms of AD [35][36][37][38].

3. Conclusions

Late-life depression (LLD), unlike early-onset depression (EOD), is a geriatric disease caused by a variety of factors. Serotonin is unlikely to effectively treat LLD, as it is thought to be associated with other biological factors. The glutamatergic system, inflammatory markers, and brain-derived neurotrophic factors may contribute to LLD and dementia. Ketamine, as a noncompetitive NMDAR antagonist, is the only officially approved clinical antidepressant; however, insufficient elderly were included in the pre-FDA-approved clinical trials. Therefore, a further clinical trial is needed to empirically prove the validity, safety, and reliability of ketamine as an antidepressant for LLD. The causality among cytokines, BDNF factors, and LLD remains uncertain, and it can likely be ascertained by applying anti-inflammatory agents or BDNF compounds in a clinical trial of the elderly. Clearly, disease arises from a physiological and mental interaction; thus, it is necessary to pay attention to cases of depression in the elderly, since improvements in physiological and psychiatric conditions may occur simultaneously.

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