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Meta-analysis of Clinical Efficacy of Commonly Used Therapeutic Drugs for Depression

Youran Huang

Suzhou Dulwich International High School, Suzhou, China
15821220450@163.com

Abstract. The incidence of depression has been on a continuous rise, which emerges as a major mental illness of concern in the global public health domain. As a primary intervention for moderate to severe depression, pharmacological treatment holds significant importance. Currently, commonly used clinical antidepressants include SSRIs, SNRIs and NaSSAs. However, notable differences exist among these drugs in terms of efficacy, safety, onset time, and patient compliance. How to scientifically select and optimize treatment regimens has thus become a key challenge in clinical practice. In recent years, evidence-based medical approaches like meta-analyses have been widely applied. Network meta-analysis enables indirect comparisons of different antidepressants by integrating data from multiple randomized controlled trials, which provides more comprehensive evidence for clinical medication choices. This article provides a review of depression's pathological mechanisms, which include neural plasticity impairment, neurotrophic factor deficiency, the monoamine hypothalamic-pituitary-adrenal (HPA) axis axis dysfunction, and the monoamine neurotransmitter hypothesis. It also examines the efficacy, safety, and related research progress of three main classes of antidepressants such as SSRIs, SNRIs, and NaSSAs, to provide references for clinical medication selection.

Keywords: depression, SSRIs, SNRIs, meta-analysis

1. Introduction

The incidence of depression has been on the rise continuously, becoming a major mental disorder of concern in the global public health field. Major depressive disorder causes severe damage to patients' emotions, cognition, social functions and substantially increases the danger of suicide and the incidence of chronic comorbidities, which imposes a heavy burden on families and society. As one of the main intervention methods for moderate to severe depression, drug treatment plays an irreplaceable role in improving symptoms, alleviating suffering and preventing relapse [1, 2]. Currently, the commonly used antidepressants in clinical practice mainly include several categories such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine and specific serotonin antidepressants (NaSSAs), and orexin receptor antagonists. Among them, SSRIs such as fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram are widely used due to their high safety and relatively mild adverse reactions. SNRIs like venlafaxine and duloxetine also show good efficacy in treating depression patients with

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somatization symptoms. While numerous antidepressants are available, they vary considerably in efficacy, safety, time to onset, and patient adherence. How to scientifically select and optimize treatment plans has become an important challenge in clinical practice. In recent years, evidence-based medical methods, such as systematic reviews and meta-analyses, have been widely used in the research of the efficacy of psychiatric drugs. Especially, network meta-analysis, by integrating data from multiple randomized controlled trials, can achieve indirect comparisons among various antidepressants, providing a more comprehensive evidence base for clinical drug selection [3, 4].

2. Pathology of depression

2.1. Monoamine neurotransmitter hypothesis

Abnormal monoamine neurotransmitters are one of the earliest proposed pathological mechanisms of depression. Patients with depression often exhibit the following characteristics. First, there is a deficiency in 5-hydroxytryptamine (5-HT). 5-HT is closely related to emotional stability and anxiety regulation. A decrease in its intersynaptic concentration in the central nervous system can lead to depression, loss of interest and sleep disorders. Second, the level of norepinephrine (NE) drops. NE is contained in the regulation of attention, alertness and emotional response. Its deficiency may cause psychomotor retardation and slow response. Thirdly, the function of the dopamine (DA) pathway is low. DA mainly regulates reward and pleasure. The decline in its function in the midbrain-limbic pathway is closely related to anhedonia [5].

2.2. Abnormal function of the HPA axis

Stress is one of the key triggers of depression, and HPA axis overactivity is a common neuroendocrine feature in depressed patients. It manifests in three aspects: increased cortisol secretion, disrupted negative feedback regulation, and neurotoxic effects. When cortisol secretion increases, most depressed patients have elevated morning cortisol levels, indicating a state of chronic stress. When negative feedback regulation is disrupted, the function of glucocorticoid receptors (GR) declines, resulting in insufficient negative feedback inhibition of the HPA axis and forming a vicious cycle of hypercortisolism. The neurotoxic effect refers to the fact that chronically elevated cortisol can inhibit hippocampal neurogenesis, impairing memory and emotional regulation functions [6].

2.3. Deficiency of neurotrophic factors and damage to neural plasticity

Depression is not only a disease caused by neurotransmitter imbalance but also a disorder of neural plasticity. BDNF's level in the cerebrospinal fluid and serum of depressed patients are often decreased. Depression can cause structural changes in the hippocampus and prefrontal lobe. Reduced emotional regulation ability and cognitive impairment have been linked to findings from imaging studies showing that depressed patients exhibit gray matter decreased in the prefrontal lobe alongside reduced hippocampal volume. Moreover, under long-term stress, glutamate excitotoxicity and oxidative stress can further damage neurons [7].

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3. Current meta-analysis of clinical drug

3.1. SSRIs

Selective Serotonin Reuptake Inhibitors (SSRIs) are currently the first-line drugs for the treatment of depression, and numerous studies have conducted in-depth explorations of their clinical efficacy. Montgomery conducted a meta-analysis on the efficacy difference between escitalopram and citalopram, aiming to clarify their relative advantages in the treatment of major depressive disorder (MDD) [8]. The study included 8 randomized controlled trials (RCTs) and 1 naturalistic trial, involving a total of 2009 patients (995 in the escitalopram group and 1014 in the citalopram group). The primary outcome was the change in total score of the Montgomery-Åsberg Depression Rating Scale (MADRS) at 8 weeks, with response rate (symptom improvement ≥50%) and remission rate (MADRS ≤12) as secondary outcomes. The results showed that escitalopram was significantly more effective than citalopram. The mean difference in total MADRS score was 1.7 points (95% CI 0.8-2.6, p=0.0002). The innovation of this study lies in confirming the clinical relevance of the difference between the two through rigorous meta-analysis methods, with a more prominent advantage especially in severe depression patients.

A meta-analysis was carried out by Cipriani et al to thoroughly compare 21 antidepressants including different SSRIs in terms of their efficacy and acceptability [9]. With 522 double-blind randomized controlled trials (RCTs) and 116,477 patients in total, the research used dropout rate for any reason and response rate as its main outcomes. The results showed that all SSRIs were more effective than placebo, among which escitalopram had outstanding efficacy (OR 1.68, 95% CrI 1.50-1.87), significantly outperforming citalopram (OR 1.52, 95% CrI 1.33-1.74); in terms of acceptability, both escitalopram and citalopram performed well with low dropout rates. The innovation of this study is that it systematically included a large amount of unpublished data for the first time and balanced direct and indirect evidence through network analysis, more comprehensively reflecting the differences in efficacy and tolerability among different SSRIs. In summary, both studies indicate that among SSRIs, escitalopram is more effective than citalopram with clinical significance; meanwhile, the study by Cipriani et al. further shows that among various antidepressants, escitalopram has more advantages in balancing efficacy and acceptability, providing an important reference for clinical medication selection.

3.2. SNRIs

With a dual mechanism of action for neurotransmitter regulation, SNRIs play a significant role in treating depression. Venlafaxine and duloxetine are routine choices, while multiple studies have delved deeply into examining their efficacy and safety in clinic. Wang et al compared agomelatine and duloxetine for treating of first-episode depressive disorder, aiming to clarify the performance of duloxetine in treatment-naive patients [10]. The study encompassed six RCT trials with a total of 600 patients. total effective rate, cure rate, HAMD-17 score, total incidence of adverse reactions served as its outcome indicators. After treatment, it was observed that the agomelatine group's HAMD-17 score was lower in comparison to the duloxetine group's. Additionally, the duloxetine group's total effective rate was lower significantly compared to the agomelatine group (OR=0.49, 95% CI 0.30-0.82, P=0.007). No obvious differences were found in total incidence of adverse reactions or cure rate. This study focused on first-episode patients, excluding interference from previous medications, and compared with other studies on patients with mixed disease courses, it better reflects the initial therapeutic effect of duloxetine. Lu et al compared the efficacy of

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escitalopram and duloxetine through meta-analysis, which included 2621 patients in total, spread across 25 RCTs [11]. There were not any significant differences in the total effective rate at weeks 1, 2, 4, 6, and 8 of treatment, and in the cure rate at weeks 4, 6, and 8 between the two groups (P>0.05). However, the incidence rates of constipation (RR=1.69, 95% CI 1.23-2.32, P=0.001), dry mouth (RR=1.54, 95% CI 1.22-1.94, P=0.0004), and nausea (RR=1.47, 95% CI 1.20-1.80, P=0.0002) in the duloxetine group were significantly higher than those in the escitalopram group. Hetrick's network meta-analysis included 21 RCTs to explore the performance of SNRIs in children and adolescents with depression. The results showed that duloxetine could reduce the CDRS-R score (MD=-2.70, 95% CI -5.03 to -0.37, P<0.05). The risk of suicide-related events with venlafaxine was significantly higher than that with placebo (OR=13.84, 95% CI 1.79-106.90, P<0.05) and also higher than that with escitalopram (OR=0.06, 95% CI 0.01-0.56). The research systematically compares multiple antidepressants in the child and adolescent population for the first time, which highlights the safety risks of venlafaxine in young patients compared with adult studies [12]. In summary, duloxetine has efficacy comparable to some SSRIs but with a higher incidence of specific types of adverse reactions; venlafaxine requires vigilance against suicide risk in children and adolescents. Both provide diverse options for different clinical scenarios.

4. Conclusion

Significant progress has been made in depression research. At the level of pathological mechanisms, frameworks such as the monoamine neurotransmitter hypothesis (e.g., dopamine systems, norepinephrine, imbalances in serotonin), HPA axis dysfunction (e.g., elevated cortisol levels and disrupted negative feedback regulation), and impaired neural plasticity (e.g., reduced BDNF levels and structural changes in the hippocampus and prefrontal cortex) have laid the core foundation for drug development. Recent studies have further revealed how gut microbiota metabolites remotely regulate central nervous system function, along with the interaction between neurotransmitter systems and excessive release of TNF-α, IL-6 et al. This has broadened the understanding of disease mechanisms, shifting the focus from a single system to a multi-system interactive network. In terms of clinical treatment, with the refinement of drug categories such as SSRIs, SNRIs, and NaSSAs, treatment options have become increasingly diverse: SSRIs serve as first-line medications due to their safety, SNRIs are more advantageous for patients with somatic symptoms, and NaSSAs exhibit prominent performance in improving sleep and anxiety symptoms. Notably, network meta-analyses have confirmed the advantages of escitalopram in balancing efficacy and tolerability, and the risk warnings of venlafaxine in adolescent populations, providing evidence-based support for individualized medication use. However, disease heterogeneity leads to significant individual differences in treatment responses, with approximately 30% of patients showing poor response to existing drugs; most medications have a delayed onset (usually requiring 2-4 weeks) and some patients experience tolerability issues such as sexual dysfunction and gastrointestinal reactions; meanwhile, research on specific mechanisms and targeted therapies for different subtypes (e.g., melancholic, atypical) remains insufficient. Future research needs to move toward precision medicine: constructing efficacy prediction models by exploring biomarkers such as blood BDNF levels, inflammatory factor profiles, and imaging features; new drug development should break through the limitations of the monoamine system and explore new directions such as glutamatergic modulators and neurotrophic factor mimetics; promoting the synergistic application of multimodal interventions (e.g., SSRIs combined with cognitive behavioral therapy, vagus nerve stimulation), while strengthening specialized research on special populations (e.g., elderly, pregnant and perinatal

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patients), ultimately achieving full-course management from symptom relief to functional recovery and improving patients' long-term quality of life.

References

[1] Maier, A., Riedel-Heller, S.G., Pabst, A. and Luppa, M. (2021) Risk factors and protective factors of depression in older people 65+. A systematic review. PLoS One, 16(5), e0251326.
[2] Monroe, S.M. and Harkness, K.L. (2022) Major Depression and Its Recurrences: Life Course Matters. Annu Rev Clin Psychol, 18, 329-357.
[3] Shorey, S., Ng, E.D. and Wong, C.H.J. (2022) Global prevalence of depression and elevated depressive symptoms among adolescents: A systematic review and meta-analysis. Br J Clin Psychol, 61(2), 287-305.
[4] Beurel, É., Toups, M. and Nemeroff, C.B. (2020) The Bidirectional Relationship of Depression and Inflammation: Double Trouble. Neuron, 107(2), 234-256.
[5] Han, Y., Gu, S., Li, Y., Qian, X., Wang, F. and Huang, J.H. (2023) Neuroendocrine pathogenesis of perimenopausal depression. Front Psychiatry, 14, 1162501.
[6] Oyola, M.G. and Handa, R.J. (2017) Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes: sex differences in regulation of stress responsivity. Stress, 20(5), 476-494.
[7] Vratarić, M., Senk, V., Bursać, B., Gligorovska, L., Ignjatović, D., Kovačevic, S., Velickovic, N. and Djordjevic, A. (2023) Fructose diet ameliorate effects of macrophage migration inhibitory factor deficiency on prefrontal cortex inflammation, neural plasticity, and behavior in male mice. Biofactors, 49(1), 90-107.
[8] Montgomery, S., Hansen, T. and Kasper, S. (2011) Efficacy of escitalopram compared to citalopram: a meta-analysis. Int J Neuropsychopharmacol, 14(2), 261-268.
[9] Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J.P.A. and Geddes, J.R. (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet, 391(10128), 1357-1366.
[10] Wang, Q. and Liu, Y.J. (2024) Meta-analysis of the Efficacy and Safety of Agomelatine and duloxetine in the treatment of first-episode depressive disorder. Shanghai Pharmaceuticals, 45(09), 23-28.
[11] Lu, S.S., Li, W.X., Zhang, B.B., Li, Z.Q., Jin, Y.H. and Hou, N. (2018) Meta-analysis of the Efficacy and Safety of escitalopram and duloxetine in the Treatment of depression. Chinese Pharmacy, 29(10), 1395-1400.
[12] Hetrick, S.E.(2021) New generation antidepressants for depression in children and adolescents: a network meta-analysis. Cochrane Database Syst Rev. 5(5): p. Cd013674.