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Beyond Biology: Assessing the Effectiveness and Limitations of SSRIs in Major Depressive Disorder

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Abstract:

Major depressive disorder (MDD) is a complex condition influenced by biological, genetic, and environmental factors. Selective serotonin reuptake inhibitors (SSRIs) remain one of the most commonly prescribed treatments because of their effectiveness and safety. Research shows that SSRIs significantly reduce depressive symptoms and help prevent relapse when taken consistently. However, since they mainly act on serotonin regulation, their impact is limited to the biological side of depression and does not fully address environmental or cognitive influences. Genetic studies, such as those examining the 5-HTTLPR polymorphism, further suggest that individual differences can affect treatment outcomes. Cognitive therapy (CT), on the other hand, focuses on identifying and changing negative thought patterns that often lead to relapse. When combined, antidepressant medication (ADM) and CT provide both immediate symptom relief and more lasting recovery. ADM stabilizes brain chemistry, while CT helps patients build psychological resilience. This integrated approach not only reduces relapse rates but also addresses the broader causes of depression. Overall, combining pharmacological and psychological treatments offers a more balanced and comprehensive strategy for managing MDD and improving long-term mental health outcomes.

Keywords: Major Depressive Disorder; Selective Serotonin Reuptake Inhibitors; Cognitive Therapy; Combined Treatment

Introduction

Major depressive disorder, or clinical depression, is a mood disorder that causes persistent feelings of sadness and loss of interest. According to the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5), major depressive disorder is identified by persistent low mood, reduced interest or pleasure in activities, feelings of guilt or worthlessness, and recurrent thoughts of death or suicide. If a person has 5

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symptoms, mixed with social impairment or lack of emotion, they can be successfully diagnosed with MDD (Malhi et al., 2018). The etiology of major depressive disorder is thought to be multifactorial, including biological, genetic, environmental, and psychosocial factors. MDD is thought to be primarily due to abnormalities in neurotransmitters, especially serotonin, norepinephrine, and dopamine, leading to secondary disturbances in the neurotransmitter system. Selective serotonin reuptake inhibitors (SSRIs) are a class of drugs most commonly used to treat depression, especially major depressive disorder. Because of their safety, effectiveness, and tolerability, SSRIs are approved for use in both adults and children (DeLucia et al., 2016). However, they focus mainly on the biological side of depression and tend to overlook the role of environmental factors, making their treatment effect less comprehensive.

Effectiveness of SSRIs in Treating Depression

Evidence from a large-scale meta-analysis demonstrates that SSRIs are significantly more effective than placebos in reducing depressive symptoms among adults. This conclusion is based on a comprehensive review of 522 clinical trials involving 116,477 participants. The analysis found that all antidepressants, including SSRIs, produced greater symptom improvement compared to placebo treatments. In studies on the efficacy of antidepressants, the odds ratio (OR) is a statistical measure used to determine the strength of the association between a specific drug treatment and achieving a desired outcome. An OR greater than 1 indicates that the treatment is more effective than a control (usually a placebo). For instance, the OR for amitriptyline, a tricyclic antidepressant, is reported at 2.13 (95% CrI 1.89–2.41), and for reboxetine, an NRI, it is 1.37 (1.16–1.63). These figures underscore the significant efficacy of these drugs compared to placebo. While the excerpt does not provide ORs for SSRIs like fluoxetine, it does mention fluoxetine specifically in terms of acceptability, with an OR of 0.88 (95% CrI 0.80–0.96) for dropout rates compared to placebo. This indicates not only its effectiveness but also its better tolerability, which is crucial for patient adherence to treatment.

Furthermore, in head-to-head comparisons, certain SSRIs such as paroxetine and sertraline are noted to be more effective than other antidepressants, with ORs ranging from 1.19 to 1.96. an OR of 1.19 means that patients treated with an SSRI have a 19% greater chance of experiencing a reduction in symptoms compared with those treated with a placebo, indicating a modest but positive effect. On the other hand, an odds ratio of 1.96 indicates that the likelihood of symptom improvement is 96% higher, reflecting a relatively strong treatment effect. This finding further reinforces the efficacy of SSRIs and highlights their role as a reliable option among antidepressants. Moreover, the large-scale and consistent evidence showing that all antidepressants perform better than placebos strengthen the conclusion that SSRIs are effective in treating major depressive disorder (Furukawa, Cipriani, & Atkinson, 2016).

Limitations of SSRI Treatment

Although SSRIs remain a first-line treatment for Major Depressive Disorder (MDD), they are not capable of fully addressing the environmental factors that significantly impact depression. SSRIs mainly work by regulating serotonin levels in the brain, which addresses only one part of the complex biological and psychological processes involved in depression. However, depression is also influenced by environmental and social factors that SSRIs alone cannot fully address. Research has shown a strong connection between the 5-HTTLPR polymorphism in the serotonin transporter gene (SLC6A4) and MDD. The two main alleles are the short (S) allele and the long (L) allele. Individuals carrying one or two short alleles are often found to be more sensitive to environmental stressors, which may increase their vulnerability to developing MDD in the face of significant life stress or adversity, this highlights the gene-environment interaction in individuals. Neurobiologically, carriers of the short allele may exhibit altered brain function, such as increased amygdala activity, which is associated with emotional processing and stress response, which potentially contributing to their increased risk for MDD. In contrast, carriers of the long allele are generally thought to have a more robust serotonin transporter function, providing them with greater resilience to stress and reducing their risk of developing MDD when faced with environmental influences. Three related studies indicate that both early and recent physiological and environmental activities in individuals can promote the development of MDD. This includes heightened childhood adversity and recent environmental stress, where individuals with the short allele exhibit greater stress vulnerability and increased severity of depression (McGuffin, P. 2011. Nanni, V. 2012. Wendland, J.R. 2006). SSRIs primarily function by increasing serotonin levels in the brain, which is insufficient to influence all the biological and psychological processes involved in depression. Furthermore, the interaction between genetic factors, such as the 5-HTTLPR polymorphism, and environmental stressors means that SSRIs cannot alter an individual's genetic susceptibility or eliminate environmental pressures. Consequently, in scenarios where the risk of depression is influenced by the interaction of genetic and environmental factors, the effectiveness of SSRIs may not meet expectations.

Additionally, an experiment with mice highlighted this limitation. The mice exhibited depressive characteristics after two weeks of chronic stress and were then subjected

to three weeks of treatment in either enriched or stressful environments. The results showed that fluoxetine (FLX), the most commonly used antidepressant, had opposite effects depending on the environment. In an enriched environment, FLX reduced corticosterone levels, whereas it did not have this effect in a stressful environment. Under stress conditions, FLX decreased the mRNA levels of glucocorticoid receptors but did not affect the expression of mineralocorticoid receptors, potentially leading to weakened feedback of the hypothalamic-pituitary- adrenal (HPA) axis, which regulates emotion. Furthermore, in an enriched environment, FLX increased the expression of brain-derived neurotrophic factor (BDNF), which is linked to the increased expression of the protein p11, associated with depression and antidepressant response. However, in a stressful environment, FLX adversely affected the increasing of neuronal progenitor cells (Wong, M.L., Dong, C., & Flores, D.L. 2014). Responding to environmental stress is outside the scope of SSRI's influence, but environmental influences change the effect of FLX. This shows the limitation of SSRI in considering environmental influences.

Effectiveness of Combined ADM and CT Therapy

SSRIs are currently among the most widely used antidepressant medications (ADMs). However, like other ADMs, they primarily alleviate symptoms rather than providing a long-term cure for depression. In other words, while ADMs can effectively treat acute depressive episodes and provide preventive benefits as long as they are used continuously, the risk of relapse increases once the medications are discontinued. Consequently, the efficacy of ADMs in treating major depressive disorder (MDD) is significantly limited. Cognitive therapy (CT) is one of the most well-known and extensively tested interventions in the field of cognitive-behavioral therapy. Similar to ADMs, CT is a safe and effective treatment method for acute episodes of severe depression. The mechanism of CT involves addressing incorrect beliefs and maladaptive information that are causally related to the onset of depression. This "cognitive model" posits that correcting maladaptive thinking can reduce both acute distress and the risk of subsequent symptom recurrence (Hollon et al. 2002).

Combining the two treatment approaches, ADM and CT, has shown significant changes in the extent of treatment for MDD. In a recent CT-ADM placebo-controlled comparison, in order to demonstrate the optimal efficiency of the combined efficacy of CT and ADM, 240 patients with major depressive disorder were randomized and the results showed that patients who received ADM or CT showed comparable rates of change in cognitive and vegetative depressive symptoms (Bhar et al., 2008). This stands in stark contrast to the findings of studies comparing ADMs with other psychosocial interventions. One study reported that ADMs can alleviate vegetative symptoms such as insomnia more quickly than interpersonal psychotherapy. However, as mentioned in the previous paragraph, the sustained efficacy of ADMs is relatively low, leading to a higher relapse rate. Data from Hollon et al. (2005) indicate that 76% of patients who initially responded to antidepressant medication (ADM) experienced relapse after discontinuation, whereas only 31% of those treated with cognitive therapy (CT) relapsed. By the end of the continuation phase, patients who remained stable on ADM and subsequently discontinued the drug showed a 54% relapse rate, compared with only 17% among those previously treated with CT. This shows that CT has a low recurrence rate that ADM does not. Therefore, combining CT and AMD treatment options, ADM helps stabilize mood by changing brain chemicals, while CT provides a significantly lower relapse rate.

SSRIs have long been regarded as a first-line treatment for major depressive disorder (MDD), largely because of their effectiveness and favorable safety profile. Research shows that they increase serotonin availability in the brain, which helps relieve symptoms and supports long-term remission (Feighner, 1999). Patients who continue SSRI therapy are significantly less likely to relapse, particularly those with recurrent depression or comorbid conditions such as PTSD. For example, studies on paroxetine have reported lower relapse rates during follow-up periods of up to a year. Although SSRIs are generally well-tolerated, some patients may experience mild side effects, and their long-term safety has been consistently supported by clinical evidence. While SSRIs indeed have shown to reduce relapse rates, they are not effective for all patients. Individual responses to SSRIs may vary based on genetic and environmental factors, resulting in some patients not being able to achieve adequate relief or being unable to tolerate side effects. In addition, integrating psychological interventions, such as cognitive behavioral therapy (CBT) and interpersonal therapy (IPT), can significantly improve treatment outcomes by addressing underlying psychological issues and providing psychological coping strategies that SSRIs alone cannot provide, thereby reducing the risk of relapse by targeting negative thinking patterns and interpersonal conflicts. Moreover, long-term safety issues with SSRIs, such as weight gain and sexual dysfunction, can affect patient compliance and quality of life. At the same time, the treatment cycle of SSRIs is long, and in order to reduce the relapse rate, even continuous SSRI assistance is required. Therefore, the side effects of SSRI are magnified, and it is difficult for patients to adhere to treatment (American Psychological Association, 2020)

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only when combined with psychotherapy methods like CBT can make the treatment of MDD be more effective.

Conclusion

In summary, SSRIs remain a central treatment for major depressive disorder because of their effectiveness and safety. However, they only target part of the problem and do not fully address the genetic and environmental factors that contribute to depression. This limitation highlights the value of combining SSRIs with cognitive therapy (CT). Together, they not only provide quicker symptom relief but also support longer-term recovery by addressing both the biological and psychological roots of depression. CT helps patients identify and change negative thought patterns, reinforcing the benefits of SSRIs and reducing the risk of relapse. Therefore, a holistic approach that includes both medication and therapeutic interventions provides a more comprehensive strategy for managing MDD, ultimately improving long-term outcomes for patients.

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