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Research Article

Long-Term Side Effects of Prescription Drugs for Mental Health: An Organ-Specific Analysis and Exploration of Healthy Alternatives

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Abstract

The use of prescription drugs for mental health disorders has become increasingly prevalent, with millions of individuals relying on pharmacotherapy for conditions such as depression, anxiety, bipolar disorder, and schizophrenia. While these medications can provide substantial relief to patients, their long-term use raises concerns about potential side effects, particularly on vital organs including the central nervous system (CNS), cardiovascular system, liver, kidneys, and endocrine system. This paper aimed to comprehensively analyze the long-term side effects of commonly prescribed mental health medications on various organs. Additionally, non-pharmacological alternatives as potential strategies were investigated to mitigate the adverse outcomes caused by mental health medications. By highlighting the risks associated with prolonged pharmacotherapy and providing evidence-based alternatives, the main aim of this paper is to provide a comprehensive understanding of the risks and offer a balanced approach to mental health treatment that prioritizes both efficacy and safety.

Keywords

Antipsychotics, Mental health, Antidepressants, CNS, Psychotherapy.

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Introduction

Mental health disorders are among the leading causes of disability worldwide, affecting over 970 million people as of 2019, with depression and anxiety being the most prevalent conditions [1]. Depression is a chronic and recurring mental disorder that can take lifelong treatment procedures. Mental health disorders encompass a variety of illnesses including depression, mood disorders, schizophrenia, eating disorders, anxiety, bipolar disorders, Post-Traumatic Stress Disorders (PTSD), addictive disorders, and dissociative and neurodevelopmental disorders [2]. Mental health disorders are reported to be number 3 in the top 10 causes of disabilities in individuals between the ages of 15-44 [3]. Individuals with childhood trauma history are more prone to develop some mental disorder at later stages of their lives [4].

With the emergence of COVID-19 in 2020, the number of people suffering from depression and other mental disorders has skyrocketed [1]. Globally, the economic burden of mental disorders has been estimated to be around $5 trillion in 2022 [5]. In the United States, the annual cost of mental health inequities alone is estimated at $477.5 billion. If current trends continue, this figure could rise to an estimated $1.26 trillion annually by 2040 [6]. According to a survey, approximately 16% of U.S. adults have reported using antidepressants for several mental health issues, with higher rates observed among older adults and women [7].

The burden of these mental health disorders has led to the widespread use of pharmacotherapy, with antidepressants, antipsychotics, mood stabilizers, and anxiolytics being some of the most commonly prescribed medications. Antidepressants (monoamine oxidase inhibitors (MAOIs) and SSRIs (Selective Serotonin Reuptake Inhibitors)) are commonly used to treat depression, anxiety, and other mood disorders [8]. Antipsychotic drugs (haloperidol and atypical antipsychotics) were initially reported back in the 1950s for treating the symptoms of psychosis including bipolar disorders and schizophrenia [9]. Psychosis is usually caused by the dysregulation of dopamine at the central mesolimbic pathway, and the therapeutic purpose of the antipsychotic drugs is to block this pathway [10]. These are used to manage psychosis, including disorders like schizophrenia and bipolar disorder. Stimulants like methylphenidate and amphetamine are primarily used to treat Attention Deficit Hyperactivity Disorder (ADHD) [11]. Anxiolytics and Benzodiazepines (diazepam and alprazolam) are used primarily for anxiety disorders, panic disorders, and sometimes insomnia [12].

Although prescription drugs for mental health conditions have revolutionized the treatment landscape, the prolonged exposure to these drugs can lead to a range of adverse effects. For instance, the central nervous system (CNS) is speculated to be the primary target of most mental health medications, making it particularly vulnerable to side effects such as cognitive impairment, movement disorders, and withdrawal syndromes [13]. The long-term use of antipsychotics is associated with tardive dyskinesia and metabolic syndrome [14], while mood stabilizers like lithium can cause nephrotoxicity and thyroid dysfunction [15]. Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are linked to gastrointestinal disturbances, sexual dysfunction, and increased risk of bleeding [16]. The endocrine system has been reported to be disrupted by antidepressants like clomipramine and fluoxetine, leading to conditions like hyperprolactinemia and thyroid dysfunction [17].

Methodology

This paper followed a systematic review methodology to extract relevant data from studies published in peer-reviewed journals over the past two decades. Different databases including PubMed, MEDLINE, Scopus, Google Scholar, Clinical Studies, Cochrane, ScienceDirect, PsycINFO, and all other evidence-based medicinal journals were used to get a detailed organ-specific analysis of the long-term side effects of commonly prescribed mental health medications, exploring both the underlying physiological mechanisms and the clinical implications. Additionally, the safety and efficacy of non-pharmacological interventions for mental health management were studied.

Organ-Specific Analysis of Long-Term Side Effects of Mental Health Medications

Central Nervous System (CNS)

Long-term use of antipsychotics has been linked to cognitive decline, including memory loss and decreased executive functioning. Ho et al., [18] studied the impacts of the use of antipsychotic drugs on the loss of brain tissues in schizophrenia patients. The changes in brain volume were prospectively measured in 211 patients with the help of neuroimaging after the onset of the disease. In this study, a total of 674 scans of the enrolled patients were taken in high resolution. During the follow-up study, there were significant reports of a decrease in the brain tissue volume and an increase in the cerebrospinal fluid after the use of antipsychotic drugs. After combining the results from animal studies, it was found that the antipsychotic drugs have a measurable negative impact on the brain volume over time.

Tardive dyskinesia (TD) is a persistent and irreversible condition characterized by involuntary movements [19]. The prolonged use of antipsychotic drugs which act as dopamine receptor blocking agents (DRBAs) has been well-documented to cause movement disorders including tardive dyskinesia. These drugs induce hypersensitivity and dysregulation of dopamine receptors resulting in insufficient movements with either high or reduced speed [20]. Benzodiazepines (BZDs) (e.g., Alprazolam, Lorazepam, Diazepam) are antipsychotic drugs that are widely used for treating the symptoms of insomnia, acute agitation, anxiety, epilepsy, mania, and muscle relaxation. They are known for their anxiolytic and amnesic properties. These medications act as an allosteric modulator of the GABA receptor, which is one of the commonly found neurotransmitters of the brain. These drugs increase the efficacy of this receptor, thereby producing a calming effect in the body. Despite their efficacy, they have numerous side effects including cognitive impairment, lethargy, ataxia, dizziness, fatigue, vertigo, motor impairment [21], blurry vision, euphoria, and erratic behavior [22]. They are known for their potential to cause dependence, with withdrawal symptoms that can be severe and prolonged [23]. Antipsychotics and antidepressants are known to cause drug-induced parkinsonism, a syndrome similar to Parkinson's disease, with symptoms like tremors, bradykinesia (slowness of movement), and rigidity. This is the second most common type of parkinsonism with idiopathic Parkinson's disease on the top. By limiting the use of drugs, the effect of this disease can become reversible [24].

Cardiovascular System

Cardiovascular diseases are one of the major causes of death among individuals suffering from several mental disorders. There have been several reports of sudden deaths in individuals who were using a certain kind of antipsychotic treatment. This has largely raised several concerns regarding the safety of these drugs. Apart from this, these drugs are postulated to produce many metabolic problems including insulin resistance, hyperlipidemia, and weight gain that are indirectly associated with many heart complications [25].

Antidepressants have also been reported to cause several cardiac issues including electrocardiogram changes, hypertension, electrolyte dysregulation, tachycardia, arrhythmias, a decrease in cardiac conduction, and sudden cardiac arrest [8]. Antidepressants like monoamine oxidase inhibitors (MAOIs) (e.g., Phenelzine) have been reported to cause several symptoms including agitation, hypotension, seizure, tachycardia, acute myocarditis, and hypertension [26]. Medications like venlafaxine and duloxetine

can elevate blood pressure and heart rate, particularly at higher doses, leading to an increased risk of hypertension and related complications [27]. Tricyclic antidepressants are particularly notorious for causing heart rhythm disturbances, which can be life-threatening [28].

When antipsychotic drugs like benzodiazepines are administrated with other mental health medications like opioids, they cause hemodynamic and cardiovascular perturbations [29]. Atypical antipsychotics, such as olanzapine and clozapine, often lead to significant weight gain [30], which increases the risk of developing metabolic syndrome, a cluster of conditions that heightens cardiovascular risk [31].

Liver

Drug-induced liver injury is considered the 4th major cause of liver toxicity in Western countries. The use of mental health medications including antipsychotic and antidepressant drugs has been reported to cause either hepatocellular toxicity and cholestatic or a combination of both considering the underlying injury [32]. One of the commonly used antipsychotic drugs, Chlorpromazine induces a negative effect on normal bile secretion and causes cholestasis [33]. Other antipsychotic drugs like valproate have been associated with liver toxicity, particularly with long-term use, leading to conditions such as hepatic steatosis or even liver failure in severe cases [33,34].

Antidepressant drugs induce hepatocellular injury by causing an abnormally high level of serum alanine aminotransferase and bilirubin with little or no change in the level of alkaline phosphatase [35]. The hepatocellular injury causes loss of hepatocellular cells, progressive liver failure, hepatic encephalopathy, and jaundice. While in case of Cholestasis, a high level of alkaline phosphatase has been reported. In this condition, the bile flow from the liver is reduced, leading to jaundice, cirrhosis, liver failure, and other complications [36].

Kidneys

The kidneys, responsible for filtering waste from the blood and maintaining fluid balance, are vulnerable to the adverse effects of these drugs due to their role in excreting them [37]. The term, nephrotoxicity is postulated to manifest as acute kidney injury (AKI), chronic kidney disease (CKD), or electrolyte imbalances [38].

SSRIs such as paroxetine contributing to hyponatremia (electrolyte imbalance caused by low sodium levels) and, in turn, kidney dysfunction have been reported in previous literature [39-41]. Seifert et al., [41] studied the association of antipsychotic drugs like SSRI and SSNRIs and the occurrence of hyponatremia in patients treated in a hospital. After 7 days dose period, incidence of HN was observed in patients treated with SSRI (0.071%) and SSNRIs (0.081%). These drugs were found to reduce renal blood flow and predispose patients to AKI. TCAs, like amitriptyline and nortriptyline, have been associated with anticholinergic effects, which can cause urinary retention and increase the risk of urinary tract infections (UTIs), a potential source of kidney injury [42]. Clozapine is particularly notable for its potential to cause nephrotoxicity due to its effect on renal function. It has been linked to interstitial nephritis and acute renal failure, particularly in patients with pre-existing kidney issues [43].

Lithium is also infamous for its nephrotoxic potential. Long-term lithium use is associated with CKD, nephrogenic diabetes insipidus (NDI), and glomerular dysfunction [44]. NDI is a condition where the kidneys lose their ability to concentrate urine, leading to excessive urination and thirst. Lithium-induced nephropathy manifests as chronic tubulointerstitial nephritis, which may progress to end-stage renal disease (ESRD) in severe cases. Lithium toxicity, marked by elevated serum lithium levels, may also result in acute renal failure [45]. Valproic acid, another mood stabilizer, has been linked to reversible kidney damage, though its nephrotoxic potential is less severe than lithium [15].

Endocrine System

The endocrine system of the body is responsible for making all the hormones in the body. Benzodiazepines can impair glucose metabolism, contributing to insulin resistance and increasing the risk of diabetes. Bobo et al., [46] reported a three-fold increase chance of diabetes mellitus in individuals who were earlier diagnosed with mental disorders and had been using antipsychotic drugs. Antipsychotic drugs also induce adiposity and weight gain in patients suffering from diabetes mellitus [47,48].

Lithium, a gold-standard treatment for bipolar disorder, is associated with several endocrine side effects. One of the most common complications of long-term lithium use is hypothyroidism. Lithium interferes with thyroid hormone synthesis by inhibiting the release of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland. This may result in elevated thyroid-stimulating hormone (TSH) levels, leading to goiter and clinical hypothyroidism [49]. McKnight et al. [50] conducted a systematic review and found that lithium causes an increase in the production of thyroid-stimulating hormone (TSH) levels. Moreover, lithium has been found to induce negative effects on the parathyroid gland by causing an increase in the production of blood calcium and the parathyroid gland, often resulting in bone density loss [51]. Antipsychotics, particularly first-generation types, can elevate prolactin levels, leading to hyperprolactinemia. The increase in prolactin levels is caused by the binding of these drugs with the dopamine D_2 receptor and blocking the activity of hypothalamic dopamine. These drugs also cause sexual dysfunction and galactorrhea [52]. Valproic acid, another widely used mood stabilizer, has been linked to polycystic ovary syndrome (PCOS) in women. Valproate increases androgen levels, leading to menstrual irregularities, hirsutism, and weight gain [53].

Gastrointestinal System

SSRIs drugs can increase the risk of gastrointestinal bleeding, especially when combined with nonsteroidal anti-inflammatory drugs (NSAIDs). The use of NSAIDs is mainly reported to cause upper gastrointestinal bleeding. The risk is linked to the serotonin's role in platelet aggregation, which SSRIs inhibit, leading to a higher likelihood of bleeding [54]. Serotonin is not produced by platelets,

rather they uptake serotonin from the serotonin transporter. SSRIs inhibit the activity of the transporter protein. This causes the platelets to become deficient of serotonin, which is required to form clots. Thus, the chances of an increase in the bleeding become high. Antidepressants like SSRIs and SNRIs also commonly cause gastrointestinal symptoms such as nausea, vomiting, and diarrhea, particularly during the initial weeks of treatment. For some patients, these side effects may persist long-term [55]. Gartlehner et al. [56] reported an association between the high chances of vomiting and nausea cases in patients who were using venlafaxine. More than 50% of the individuals using antipsychotic drugs suffer from constipation. Xu et al., [57] reported the damaging impacts of antipsychotics on the gastrointestinal tract of schizophrenia patients. Clozapine, a second-generation antipsychotic is known for causing severe constipation, which can lead to serious complications like colon perforation, bowel obstruction, ischemic bowel disease, paralytic ileus, and bacterial septicemia. It requires proactive management with laxatives or other interventions. If left untreated, these symptoms can be life-threatening.

Exploration of Healthy Alternatives

Mental health medications, such as antidepressants, antipsychotics, and anxiolytics, have been the cornerstone of treatment for conditions like depression, anxiety disorders, schizophrenia, and bipolar disorder. While these medications can offer symptom relief, they often come with numerous side effects [58]. Long-term reliance on these medications can also lead to dependency and a diminished sense of control over one's mental health [59]. For chronic mental health conditions, however, relying solely on pharmacological treatments can mask underlying psychological issues that may be better addressed through other healthy alternatives.

Psychotherapy

Psychotherapy, often referred to as “talk therapy,” involves various techniques aimed at understanding and odifying emotional, cognitive, and behavioral patterns. Cognitive-behavioral therapy (CBT), dialectical behavior therapy (DBT), psychodynamic therapy, and other forms of psychotherapy can be highly effective, particularly for anxiety, depression, and borderline personality disorder [60,61].

Psychotherapy works by promoting psychological healing through a process of exploration, reflection, and change. The therapeutic relationship, where the patient builds trust and a connection with their therapist, is crucial to this process [62]. Rather than simply alleviating symptoms as in the case of mental health medications, these therapies foster deeper self-awareness and equip patients with coping strategies for long-term management of their underlying conditions [62].

DeRubeis et al., [63] compared CBT to antidepressant medications and found that both were equally effective in the short term, but CBT had the added benefit of reducing the likelihood of relapse after treatment ended. Other therapies like DBT focus on teaching patients how to manage intense emotions and develop emotional resilience. This can be particularly helpful for individuals with borderline personality disorder or mood disorders, where emotional dysregulation is a core feature.

Lifestyle Modifications

Physical activity

Physical activity is one of the most well-studied lifestyle interventions for mental health. Exercise, whether aerobic or resistance-based, has been shown to reduce symptoms of depression, anxiety, and stress. Exercise increases the production of neurotransmitters such as serotonin, dopamine, and norepinephrine, which are critical for mood regulation. These neurochemical changes mimic the effects of antidepressants, making exercise a natural alternative to medication [64].

Jain et al., [65] reported the production of endorphins in response to exercise. Exercise stimulates the release of beta-endorphins which are also often referred to as "feel-good" hormones. These hormones create a sense of well-being and reduce perceptions of pain or discomfort [66,67].

A meta-analysis by Schuch et al., [68] found that exercise was associated with a significant reduction in depressive symptoms. He found that people who are not involved in any kind of physical activity have high rates of depression. He concluded that exercise is not only effective for reducing symptoms but may also prevent the onset of depression in at-risk individuals.

Yau et al., [69] reported that exercise promotes neurogenesis (the formation of new neurons) in areas of the brain associated with memory and learning, such as the hippocampus. This may help counteract the cognitive impairments often associated with depression and anxiety. Other mindfulness activities like yoga have been used for centuries as a holistic approach to manage stress and mental health issues. Yoga combines physical movement, breath control, and meditation to promote mental and physical well-being [70]. Regular yoga practice has been shown to increase neuroplasticity, or the brain’s ability to reorganize itself by forming new neural connections. This can improve resilience to stress and anxiety over time [71]. Strøm-Pedersen, [72] studied the impact of yoga and found that yoga can significantly reduce the symptoms of depression, anxiety, and post-traumatic stress disorder (PTSD). He suggested that yoga could be an effective complementary therapy for individuals with mood disorders.

Diet and Mental Health

The unique association between diet and mental health has been a topic of interest for ages. Diet plays a critical role in mental health as it influences mood, energy levels, and cognitive functioning. The gut-brain axis refers to the complex communication system between the gastrointestinal system and the brain. Gut health, influenced by diet, has been shown to impact mental health, and normal cognitive functions of the brain [73,74]. Stable blood sugar levels are crucial for maintaining energy levels and mood stability. Diets high in processed foods and sugars can negatively affect gut microbiota, contributing to mood disorders [75]. Conversely, a diet rich in fruits, vegetables, whole grains, and omega-3 fatty acids has a modulatory effect and supports a healthy gut microbiome,

which in turn promotes mental health. A healthy diet is not only responsible for shaping the growth of healthy bacteria in the gut, but it also influences the structure and function of the brain [76].

Chronic inflammation is associated with mental health disorders, particularly depression. Diets high in processed foods and trans fats can exacerbate inflammation, [77] while anti-inflammatory foods such as fatty fish, nuts, and leafy greens can help reduce it [78]. Ensuring adequate intake of healthy foods rich in nutrients can help support brain function and mood regulation [79]. Jacka et al., [80] found that individuals who followed a Mediterranean-style diet that is usually rich in whole grains, fruits, vegetables, nuts, and fish, experienced a significant reduction in depressive symptoms compared to those on a typical Western diet. He suggested that dietary interventions can serve as an adjunct to, or even replace, pharmacological treatments for certain mental health conditions.

Herbal Remedies

Herbal supplements have been used for centuries in traditional medicine to treat a variety of ailments, including mental health conditions with little or no side effects. Different herbal remedies including St. John's Wort (treat mild to moderate depression) [81], Valerian Root (Often used to treat anxiety and insomnia) [82], Ginkgo Biloba (improve cognitive function) [83], ashwagandha (reduce stress and anxiety) [84] and chamomile (produce calming effect) [85] have been reported in previous literature for treating many mental health problems. These herbal remedies can be used as a substitute for modern drugs that come with many side effects.

Herbal remedies usually mimic the activity of the chemical drug for treating several mental health complications. For example, St. John's Wort is one of the most extensively studied herbs for depression and has been shown to mimic the action of SSRIs by inhibiting the reuptake of serotonin. This increases serotonin availability in the brain, leading to mood enhancement [86]. Other herbal remedies like valerian root have a mood of action similar to benzodiazepines. It increases the activity of GABA, an inhibitory neurotransmitter that has a calming effect on the nervous system [87]. Ashwagandha mimics the action of antidepressants by modulating the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the body's stress response [88]. Although research on herbal remedies has grown, it remains limited compared to the extensive clinical trials conducted for pharmaceuticals. More rigorous studies are needed to fully understand the long-term effects and safety of these remedies.

Social Support System

Social support systems, including family, friends, community groups, and support networks, play a critical role in mental health. Strong social connections are associated with better mental health outcomes and increased resilience to stress. Having someone to talk to during times of stress or distress provides emotional relief and helps individuals process their feelings [89]. This can reduce the risk of developing anxiety or depression. Being part of a community or group fosters a sense of belonging and purpose. This is particularly important for individuals who may feel isolated or disconnected, as it provides a buffer against loneliness and depression [90].

Conclusion

Although psychiatric medications have an essential role in managing mental health conditions, the long-term side effects on various organs cannot be overlooked. Given these risks, there is an urgent need for a deeper understanding of the long-term organ-specific side effects of mental health medications. All the healthy alternatives described in this paper have unique benefits, and when tailored to an individual's needs, they can significantly enhance mental well-being, reduce symptoms, and promote long-term health. This paper emphasized on creating a balanced approach that combines the strengths of pharmacological and non-pharmacological treatments to potentially mitigate adverse effects associated with chemically formulated drugs. Future research should continue to explore these alternatives, aiming to reduce the reliance on long-term pharmacotherapy and promote maximum mental health care.

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