The Relationship between β-blockers and Mental Health

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ABSTRACT

Beta-blockers (β-blockers) are pharmacotherapeutics used to treat patients with cardiovascular symptoms since their discovery in the 1960s. They target B1 and B2 receptors which are involved in the stress response, leading to reduced activation of the "flight-or-fight mechanism." β-blockers have also been beneficial in treating anxiety disorders and other mental health complications. Currently, the only approved drugs for anxiety and other mental health conditions are benzodiazepines and selective serotonin reuptake inhibitors. Historically, there has been strong resistance to the use of β-blockers in mental health treatment because of the prevalence of depressive symptoms during treatment. Recently, multiple studies have not seen a strong correlation between β-blockers and depression in patients. Although there are still other adverse effects related to the usage of β-blockers, investigating the relationship between depressive symptoms and β-blockers may suggest a potential therapeutic option in mental health treatments. This review explores the history of β-blockers, their mechanism of action, developments in their use as a mental health treatment, and currently approved pharmacotherapeutics for mental health.

Keywords: Beta-blockers, anxiety, depression, mental health, cardiovascular

1.0 INTRODUCTION

Beta-blockers (β-blockers) are a class of pharmacotherapeutics used to manage cardiovascular symptoms such as angina, hypertension, and arrhythmia.[1] propranolol, a nonselective beta-blocker for epinephrine, and norepinephrine for angina pectoris treatment for more than fifty years.[2] These medications work by blocking the action of specific hormones, such as adrenaline in the central nervous system to prevent the stress-inducing "fight-or-flight" reaction. The activation of the "fight-or-flight" stress response leads to increased blood pressure, heart palpitations, and anxiety, making β-blockers very advantageous for those with cardiovascular symptoms.[3] β-Blockers also often help with mental health disorders such as anxiety and post-traumatic stress disorder (PTSD). For a while, there was resistance to using these agents in treatment because the scientific community believed that β-blockers usage leads to side effects such as tiredness and fatigue, as well as cases of severe depression.[4] However, more recent developments have shown that depressive behaviour may not be as strongly related to β-blockers usage as previously believed.[5] This would drastically change β-blockers usage in mental health management and treatment.

2.0 β-BLOCKERS MECHANISM OF ACTION

β-blockers, also known as beta-adrenergic antagonists, are a class of medications most prescribed to lower blood pressure.[1] Their mechanism of action is facilitated by their ability to block the endogenous effects of epinephrine (adrenaline). Since the 1970s, β-blockers have been used to alleviate symptoms of social anxiety disorder, generalized anxiety disorder, and PTSD because of their mechanism of action.[6] Propranolol and atenolol are two of the most popular β-blockers. Propranolol is lipophilic, meaning it can cross the blood-brain barrier to potentially affect both somatic and central nervous system target tissues.[6] These molecules are adrenoreceptor antagonists, which compete with catecholamines, hence stopping their effects on the autonomic nervous system.[7] Catecholamines molecules are neurotransmitters and hormones essential for the homeostasis of the autonomic nervous system.[8] Dopamine, norepinephrine, and epinephrine are examples of catecholamines, but β-blockers target norepinephrine and epinephrine. By targeting the B1 and B2 receptors, the β-blockers attach to receptors specific to norepinephrine and epinephrine, preventing

them from binding, thus mitigating their impact. For example, under a 'trigger' situation for anxiety, epinephrine, cortisol, and norepinephrine are released, causing various effects associated with the 'flight-or-fight' response. Some effects include tachycardia, palpitations, hypertension, hyperventilation, nausea, vomiting, and sweating.[6] By targeting norepinephrine and epinephrine, β-blockers reduce the overall symptomatic response, reducing the severity of the attack. Despite this, β-blockers have not been approved by the U.S. Food and Drug Administration (FDA) and are prescribed out of scope for anxiety disorders.[6]

3.0 DEVELOPMENTS AROUND β-BLOCKERS

One of the earliest indications that β-blocker usage may cause depressive symptoms came from a study conducted in 1967 by Waal. The study observed that 50% of patients prescribed more than 120 mg/day of propranolol for hypertension reported signs of depression.[9] β-blockers inhibit serotonin receptors in the central nervous system, which are responsible for feelings of happiness and pleasure. After that initial report, numerous studies have refuted and supported the argument, making this a frequently discussed topic. One of these reports stated how the research team found no significant difference in depressive symptom assessment between non-β-blocker users and β-blocker users.[10] Those findings would suggest that β-blockers might not be able to affect serotonin inhibitors as strongly as previously believed. A multitude of contrasting opinions can potentially explain the resistance that many overlooking bodies, such as the FDA, feel about using β-blockers in a role for mental health treatment.

While many previous studies state this causal relationship, recent papers also conclude similar findings. In a 2022 study by Lengton et al.,[11] the association between depression and β-blockers was investigated in chronic dialysis patients with and without diabetes. The investigation of 684 chronic dialysis patients revealed a possible association between lipophilic β-blockers and an increased risk of depressive symptoms in dialysis patients, specifically those with diabetes.[11] Similar to other studies, the correlation was observed with no specific biological factors examined to justify the findings.

On the contrary, in March 2021, a report investigating the link between β-blockers and depression was shared in the American Heart Association Journal and presented some significant findings. In the systemic review, the team looked at psychiatric adverse events (PAEs) in over 50,000 individuals exposed to β-blockers, specifically during treatment.[5] During the study, symptoms observed during β-blocker therapy were like those observed in previous findings where depression and β-blockers were not linked. Their findings provided substantial evidence against a relationship between β-blocker use and increased PAEs in depression. Sleep-related disorders such as insomnia and unusual dreams, however, there are possible exceptions.[5] The report shares how PAEs are common during β-blocker treatment, but there is no direct association between β-blocker use and most PAEs. The study focused on patients prescribed β-blockers for hypertension and patients with cardiovascular ailments that tend to develop mental health disorders. Hence, there is no association between β-blockers and depression, which is why concerns about an increased risk of PAEs are unjustifiable and should not affect β-blocker use.[5]

Other recent work builds on this idea that there is no causal relationship between depression and β-blockers. For example, in a study by Bornand et al.,[12] the researchers used a case-control study to see if β-blockers led to an increased risk of new-onset depression. After investigating data from 118,705 patients, researchers observed limited elevated risk of depression among short-term propranolol users compared to patients with neuropsychiatric disorders.[12] Instead, this relationship is due to a protopathic bias. Protopathic bias occurs when treatment is initiated as a response to a symptom being observed because of the disease which is under surveillance.

4.0 MENTAL HEALTH TREATMENTS

Currently, the only approved medications for anxiety, PTSD, and other mental health disorders are benzodiazepines (BZDs), sedatives, and antidepressants such as selective serotonin reuptake inhibitors (SSRIs). BZDs side effects include drowsiness, lethargy, and fatigue.[13] At higher concentrations, BZD causes motor impairment, vertigo, and mood swings. Along with those side effects, BZDs are metabolized in the liver, meaning that certain drugs can increase or decrease the elimination half-life of BZDs.[13] Overall, it shows that it may not be ideal to treat patients with BZDs as several factors can drastically impact treatment. As for SSRIs, some common side effects are sexual dysfunction, weight changes, dizziness, headaches, and gastrointestinal distress.[14] SSRIs also have the potential to prolong the QT interval, a measurement that represents the duration of ventricular depolarization to complete repolarization, which can lead to fatal arrhythmia and torsade de pointes.[14] Although SSRIs are beneficial, there are significant adverse effects associated with them. The effectiveness overweighs the side effects to an extent, which is why SSRIs are still commonly used.

5.0 CONCLUSION

That is not to say that β-blockers do not have adverse effects; adverse effects range from insomnia, fatigue to cardiac problems.[1] However, there have been limited studies regarding β-blockers and mental health treatments due to the perceived notion that these molecules lead to depression and would offset any progression made during treatment for mental health disorders. The recent developments in the field are a promising sign towards further usage of β-blockers in the treatment of mental health disorders. With increasing confidence that β-blockers treatment and depression are not directly correlated, there is a strong possibility that significant research will be conducted to solidify β -blockers as a treatment modality for anxiety disorders and PTSD. Additional evidence might even lead to FDA approval for anxiety disorders, meaning that the way healthcare providers approach mental health disorders may change along with developments in the field of β-blockers.

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