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Impact of antidepressant therapy on cardiac function and cardiovascular risk: Review

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Abstract
Common comorbid conditions that worsen the intensity and duration of chronic pain are emotional disorders. In particular, increased pain length and intensity might result from depressive symptoms. The underlying mechanisms of chronic pain and depression comorbidity, as well as the use of antidepressants to alleviate pain, have been the subject of clinical and preclinical research. Additionally, platelets play a crucial role in the haemostatic process that is started when pathologic thrombus forms in cardiovascular diseases. Congenital disorders involving serotonin-deficient platelets, which can result in potentially fatal bleeding issues, demonstrate the importance of serotonin release from platelets for functional haemostasis. In individuals with post-MI depression, SSRIs lower the risk of recurrent myocardial infarction (MI). Furthermore, SSRIs prevent platelets from forming tight clots in vitro, suggesting that they have a direct anti-thrombotic or pro-fibrinolytic effect. As with many medications, this means that administering SSRIs requires medical judgment to ensure that the advantages outweigh the hazards for each patient.

Keywords: Anti-Depressant drugs, Heart, liver, cholesterol, Serotonin

Introduction
Depression is one of the most prevalent mental diseases. Although depression typically manifests in adults between the ages of 35 and 40, the percentage of younger individuals including adolescents who experience sadness has increased recently [1]. Depression can be effectively treated with antidepressant medications. Within a few weeks of beginning treatment, almost half of those with moderate to severe depression report feeling better. Other ailments like persistent headaches and some types of discomfort are also treated with them [2].

What are anti-depressant drugs?
Antidepressants are a class of medications that repair chemical imbalances of neurotransmitters in the brain to treat the symptoms of depressive illnesses. Mood and behavioural abnormalities may be caused by chemical imbalances. Since they serve as the conduit for communication between the brain's nerve cells, neurotransmitters are essential. After symptoms have subsided, a course of antidepressants (used for depression) will be taken for at least six months [1]. Although they can happen, side effects are usually mild. Neurotransmitters are chemical messengers that carry messages from one neuron to another. Information on emotions, behaviour, body temperature, appetite, and several other functions can be transmitted through the signals. Which neurons are triggered and which area of the brain is stimulated determine the kind of information transmitted [2].

Classification of anti-depressant drugs
They are several antidepressants that are used to treat
specific conditions; they are:
1. Selective serotonin re-uptake inhibitors (SSRIs) De-pressants
2. Serotonin-noradrenaline re-uptake inhibitors (SNRIs).
3. Noradrenaline and specific serotonergic antidepressants (NASSAs).
4. Serotonin antagonists and reuptake inhibitors (SARIs).

5. Tricyclic antidepressants.
6. Monoamine-oxidase inhibitor (MAOI) antidepressants

Mechanism Of Action

Brain

Each antidepressant modulates mood and behaviour by targeting certain neurotransmitters in a slightly different way. It is thought that all currently approved antidepressants raise serotonin, norepinephrine, or both in the synapse. Antidepressant medications target reuptake by the nerve terminals, however there are several ways to boost these neurotransmitters [7].

The Communication Gap in Biology

The intricate network of billions of neurons in the human brain communicates with one another through chemical messengers known as neurotransmitters. Chemicals like serotonin are released by one neuron into a minuscule area known as the synapse, where they must "click" into the receptors of the subsequent cell in order for a message to be transmitted. This connection frequently breaks down in a depressed brain because the transmitting cell reabsorbed these chemicals too quickly, a process called as reuptake. Selective Serotonin Reuptake Inhibitors (SSRIs), a class of antidepressants, physically block this "vacuuming" mechanism. Important molecules are able to remain in the synaptic gap for a longer period of time when the reuptake pumps are blocked, which increases the likelihood that the message will be effectively conveyed [12].

SSRIs

The enzyme 5HT (5-hydroxytryptamine/serotonin) is reabsorbed into presynaptic terminals by the serotonin transporter; neuronal uptake is the primary mechanism that inhibits 5HT-mediated neurotransmission. While preventing reuptake, SSRIs enhance and prolong serotonergic neurotransmission. Continuous administration of SSRIs results in sustained increases in cyclic AMP signalling, phosphorylation of nuclear transcription factors, expression of trophic factors like BDNF, and enhanced neurogenesis. Nowadays, the first-line drugs for treating depression are SSRIs [11].

SNRIs

By blocking serotonin and norepinephrine reuptake in the synapse, serotonin and norepinephrine reuptake inhibitors (SNRIs) increase the stimulation of postsynaptic receptors. The affinity of SNRIs for the serotonin and norepinephrine transporters varies. Milnacipran and levomilnacipran are more selective at blocking norepinephrine reuptake than serotonin reuptake, in contrast to other selective serotonin-norepinephrine reuptake inhibitors such as duloxetine, venlafaxine, and desvenlafaxine [11].

HEART

Although SSRIs are mainly intended to address the chemical imbalances in the brain, they also have a minor but noteworthy impact on the cardiovascular system. Antidepressants can function as minor "blood thinners" by changing the way blood platelets clump together since serotonin receptors are not only prevalent in the brain but are also present in high quantities on blood platelets and in heart muscle. Since it may lower the chance of clots, this can be advantageous for many people, especially those who already have heart problems. However, by prolonging the "repolarization" phase—the period of time the heart takes to reset between beats—some antidepressants can also alter the electrical timing of the heart. However, some antidepressants can also change the electrical timing of the heart by extending the "repolarization" phase, which is the time it takes for the heart to reset between beats [13].

MAOIs

(Tranylcypromine, Phenelzine, Moclobemide, Selegiline, etc.) were the first antidepressants to be used. They are helpful in lessening the symptoms of depression, but a number of adverse side effects and drug interactions severely limit their therapeutic use. These drugs may affect a number of neurotransmitter systems. Because it takes time to establish such neurotransmitter disruptions, cardiovascular adverse effects usually manifest 12–24 hours after MAOIs reach their dangerous levels. Tachycardia and hypotension are frequent adverse effects of MAOIs [9].

TCAs

However, because of cardiovascular adverse events, their use has been limited in recent decades. TCAs are still frequently used even though they are not prescribed as much these days, especially when patients do not respond to SSRI therapy. TCAs have been linked to cardiovascular problems in both individuals without a history of heart disease and those with CVD. TCAs can slow conduction velocity, which is shown on the ECG by prolonged PR, QRS, and QT intervals, by delaying phase 0 of depolarization and impairing electrical conduction in His-Purkinje fibres as well as in atrial and ventricular myocytes. This delay is brought on by TCAs' inhibition of fast sodium channels, which can be hazardous, particularly in patients with a history of conduction defects, those taking class 1 antiarrhythmic medications, or those taking large doses of TCAs [10].

SSRIs

SSRIs at therapeutic levels are unlikely to cause cardiovascular adverse effects, which are often minor. However, using SSRIs has been linked to conduction anomalies like QT interval prolongation, orthostatic hypotension, and moderate bradycardia. Patients with underlying vulnerabilities, such as congenital long QT syndrome, recent myocardial infarction, hypokalemia, hypomagnesemia, or drug overdose, are more likely to experience SSRI-induced QT interval prolongation and subsequent TdP [9]. By preventing serotonin from entering platelets, SSRIs disrupt platelet activation and aggregation, which lowers the incidence of ischemic cardiac events. Research indicates that certain anomalies of platelet function indices in individuals with ischemic heart disorders can be normalized or at least improved by this class of antidepressants. However, it is possible that SSRIs' inhibitory effects on platelet activation and aggregation could result in irregular bleeding and poor haemostasis. When providing these medications to patients who have underlying haemostatic problems or are on anticoagulation treatments, it is important to take this into consideration [10].

SNRIs

SNRIs boost neurotransmission by blocking the reuptake of norepinephrine from the synaptic cleft in addition to

serotonin. Elevated levels of serotonin and norepinephrine can quicken cardiac sympathetic activity, which can cause a little rise in systemic blood pressure and heart rate. It appears that hazardous tachyarrhythmias and/or hypertensive crises can result from excessive sympathetic activation. Patients on SNRIs, especially Venlafaxine, should have their blood pressure checked because epidemiological studies have shown elevated blood pressure. Because venlafaxine blocks sodium channels, it is also thought to cause QTc prolongation at hazardous levels [10].

How Does Antidepressnats Increase Cholestrol Effects Cardiovascular Disease

In humans, platelets carry nearly all of the serotonin in circulation in thick granules. Although serotonin is a mild platelet agonist, its effects are amplified by adrenaline and ADP. Both its function as a neurotransmitter and its function as a neurohormone determine how serotonin affects the cardiovascular system. Increased serotonin availabilty in the heart has been demonstrated to cause arrhythmia, which can result in valvular fibroplasias or heart Block. As of overtaking of the anti-depressant drugs, it blocks the serotonin signaling and histamine H1 receptors. By, blocking these receptors we can observe the increase of appetite and weight gain. Due to overtake of the food the weight of the person gets increase and fat in the body increases where the LDL, Triglycerides, and total cholesterol levels increases and decreases the levels of the HDL(good cholestrol).Increase of the lipids in our body, these gets accumulated in the blood vessels and deposit as fat in the arteries which narrows the blood vessel and stops the sufficient blood supply to the heart and causes atherosclerosis, ischemic heart disease, and hypoxia conditions where the patient may get heart stroke, heart attack, myocardial infarction.

Liver

Certain antidepressant medications raise the levels of the liver enzymes AST and ALT, which carry out the metabolism of amino acids. As a result, these medications enter the bloodstream and cause harm to the liver cells as well as activate the liver's immune system.By over taking of the drugs the fat stored in the liver as cholesterol and we can find that bad cholesterol in our body gets increased and it reduced the glucose intake and the cholesterol formed gets accumulated in the blood vessel and gets narrowed and it stops the sufficient blood supply and causes heart disease. Antidepressants can affect cholesterol levels by a combination of direct cellular actions and metabolic alterations, even though their primary target is the brain. Increases in total cholesterol and LDL (the "bad") cholesterol have been associated with particular drugs, including SNRIs (like Venlafaxine) and some atypical antidepressants (like Mirtazapine). This occurs because these medications have the potential to change the way the body metabolizes fats and may also promote weight gain or an increase in hunger, both of which can subtly raise cholesterol levels. But the association is complicated and "drug-specific"; for example, some research indicates that SSRIs like sertraline may cause a slight rise in cholesterol, while other studies indicate that medications like fluoxetine may actually help lower it. Doctors frequently check "lipid profiles" to make sure that the chemical bridge to mental wellness doesn't unintentionally create a metabolic detour for your heart health because your liver is in charge of both processing these medications and controlling your cholesterol [14].

Side Effects

TCAs

The anticholinergic effects of tricyclic antidepressants may potentially make falls more likely. Additionally, they have dose-dependent effects on blood pressure and heart rate that impact cardiovascular function. Research has indicated that TCAs cause more body wobble and, consequently, less postural balance. When using TCAs instead of selective serotonin reuptake inhibitors (SSRIs), blood pressure often decreases more. With the exception of clomipramine, which had a small user base, the drop in blood pressure with TCAs appeared to be dose dependent. Nevertheless, a separate study found that clomipramine caused a dose-dependent drop in blood pressure. An antidepressant class linked to drowsiness, dry mouth, constipation, impaired vision, urine retention, and elevated intraocular pressure. Hypertension, irregular heartbeats, anxiety, sleeplessness, seizures, headaches, rash, nausea, vomiting, cramping in the abdomen, weight loss, and sexual dysfunction are also linked to them. Rarely do tricyclic antidepressants result in liver failure [4].

SSRIs

Orthostatic hypotension has also been linked to SSRIs. But compared to TCAs, the drop in blood pressure was significantly less. In this study, fluvoxamine was linked to a drop in blood pressure, whereas paroxetine was not. Citalopram did not cause orthostatic hypotension, according to another study. Compared to SSRIs, TCAs tended to cause a greater heart rate and a longer QTc interval. While paroxetine had no effect, other trials showed that sertraline increased body sway and, thus, reduced postural balance during the first week of treatment but not after longer. Two classes of antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs), are linked to abnormal thinking, agitation, anxiety, headaches, dizziness, insomnia, sexual dysfunction, sedation, tremor, sweating, weight loss, diarrhea, constipation, dry mouth, rash, and nausea. SSRIs have infrequently been linked to hypoglycemia (low blood glucose), hyponatremia (low salt), and seizures [4].

MAIOs

A category of antidepressants linked to constipation, nausea, diarrhea, sexual dysfunction, weight gain or loss, edema, high blood pressure, fainting, abnormal heart rhythm, dizziness, headache, drowsiness, insomnia, anxiety, and postural hypotension (feeling faint upon standing due to decreased blood flow to the brain). Seizures, rash, impaired vision, and hepatitis are not commonly associated with MAOIs [4].

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