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Adverse effects of antidepressant medications: A comparative analysis of different classes

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Abstract

This review offers a comparative analysis of the adverse effects associated with various classes of antidepressants, and effective strategies to manage their effects in clinical practices. Antidepressant medications, essential for treating depression, display diverse side effect profiles that significantly influence patient adherence and the success of treatment regimens. Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are generally well-tolerated, yet they are frequently associated with sexual dysfunction and weight gain, which can hinder patient compliance. Tricyclic antidepressants (TCAs), known for their efficacy, have a higher incidence of cardio toxic effects and anticholinergic side effects, making them less suitable for certain populations. Monoamine oxidase inhibitors (MAOIs), though effective for treatment-resistant cases, are used less frequently due to the need for dietary restrictions and the risk of severe drug interactions. This review describes mechanism of action of commonly used antidepressants from various classes and stresses on the specific adverse effect profiles of each drug class. Further, we discuss the strategies for managing adverse effects, such as dosage adjustments and switching medications, which play a crucial role in enhancing medication adherence and improving treatment outcomes. This review article aims to equip clinicians with the necessary knowledge to optimize antidepressant therapy by balancing efficacy against potential adverse effects, thereby improving patient well-being and therapeutic success.

Keywords: Antidepressants, adverse effects, strategies to manage side effects, clinical practice

1. Introduction

Depression is a major global health challenge that adversely affects an individual's mood, physical health, and quality of life. According to the World Health Organization (WHO), depression is a leading cause of disability worldwide and is a major contributor to the overall global burden of disease. The management of depression typically involves pharmacological treatments alongside psychotherapy and lifestyle modifications [1-4]. Among these, antidepressant medications play a critical role. However, the efficacy of these drugs is often compromised by their adverse effects, which can vary widely between different classes of antidepressants. This variability significantly impacts patient adherence to the treatment, posing a challenge to achieving optimal therapeutic outcomes. Antidepressants are classified into several categories, each with distinct mechanisms of action and associated side effect profiles. The major classes include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs), Atypical antidepressants, and Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs) [5-7].

SSRIs and SNRIs are generally preferred in clinical practice due to their favourable safety profiles, but they are often associated with side effects such as sexual dysfunction, weight gain, and emotional blunting, which can significantly affect a patient's willingness to continue the treatment. TCAs, while effective for major depression, are burdened with more severe side effects like cardiotoxicity, anticholinergic effects, and sedation, making them less suitable for elderly patients or those with certain medical comorbidities. MAOIs, effective in cases of treatment-resistant depression, require strict dietary restrictions to prevent hypertensive crises, a requirement that complicates adherence and limits their use [8-10]. The introduction of SSRIs in the late 1980s marked a significant advancement in the treatment of depression due to their improved safety profile over older antidepressants like

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TCAs and MAOIs. SSRIs primarily affect serotonin levels in the brain and are less likely to cause severe adverse effects. However, the issue of side effects remains a significant concern, as even mild but chronic side effects can lead to non-adherence, which is a substantial barrier to the effective management of depression. Studies have shown that adherence to antidepressant therapy can be as low as 50%, with discontinuation often occurring within the first few months of treatment [11-14].

Non-adherence not only hampers recovery from the current depressive episode but also increases the risk of relapse and recurrence. It is crucial, therefore, for healthcare providers to consider the side effect profiles of antidepressants when prescribing these medications. This involves not only selecting the right drug for the right patient but also managing side effects effectively when they occur. For instance, patients who are particularly sensitive to weight changes or sexual dysfunction might better tolerate certain SSRIs or SNRIs or may require a tailored approach that includes periodic adjustments in the medication regimen. The impact of antidepressant side effects on quality of life cannot be overstated. Sexual dysfunction, for instance, affects approximately 30-70% of patients taking SSRIs and SNRIs and can severely affect an individual's relationships and self-esteem. Similarly, weight gain associated with long-term use of some antidepressants can increase the risk of metabolic syndrome and cardiovascular disease, adding to the health burden of the patient. Moreover, the emotional blunting reported by some patients on SSRIs can lead to a diminishment in life satisfaction and may paradoxically worsen some depressive symptoms [15-18].

Elderly patients present a unique challenge in the management of depression, as they are more susceptible to the side effects of antidepressants. TCAs, for example, can intensify or lead to cardiac arrhythmias, postural

hypotension. SSRIs, though safer, can increase the risk of gastrointestinal bleeding, especially when combined with nonsteroidal anti-inflammatory drugs. Such interactions and side effects must be carefully managed through close monitoring and regular follow-ups. In addition to the physiological side effects, psychological side effects such as increased anxiety, agitation, and sleep disturbances can also occur, particularly during the initial stages of treatment with antidepressants. These effects can be distressing and may lead some patients to discontinue treatment prematurely if not adequately addressed by healthcare providers [19, 20].

Although antidepressants are a cornerstone in the treatment of depression, their associated adverse effects are a significant barrier to adherence and successful outcomes. It is imperative for clinicians to navigate these challenges through careful medication selection, proactive management of side effects, and patient education. Engaging patients in discussions about the potential side effects and benefits of therapy can foster better adherence practices and enhance the overall effectiveness of treatment. As research continues to evolve, it is hoped that newer antidepressants with more favourable safety and tolerability profiles will be developed, further improving the management of depression.

2. Classification of antidepressants

Antidepressants can be classified into several major groups based on their chemical structure and mechanism of action. The major classes include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs), Atypical antidepressants, and Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs). This classification is represented in Figure 1.

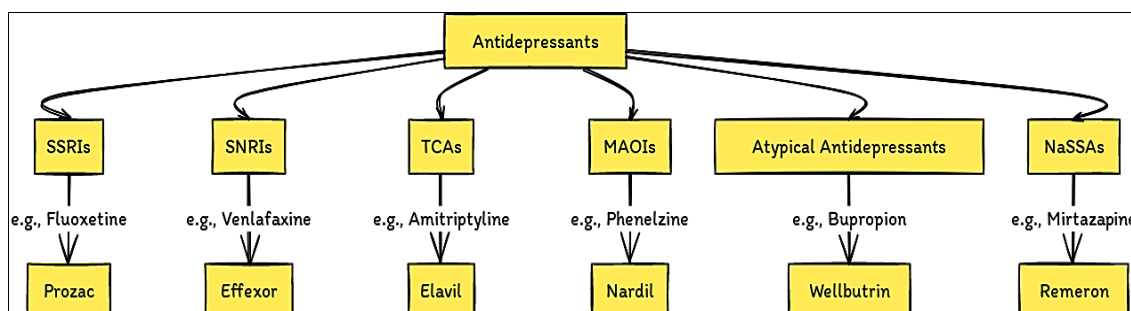


Fig 1: Classification of antidepressants

Each class varies in its therapeutic effects and side effect profiles due to differing mechanisms of action, which are critical in selecting the appropriate treatment. The commonly used drugs for each class are described in Table 1.

2.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

These drugs were introduced in the mid-1980s, with the approval of fluoxetine (Prozac) as a ground breaking event in psychiatric medication. Before the advent of SSRIs, the treatment of depression and related disorders was dominated by older classes of drugs such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which, although effective, posed significant risks and were associated with severe side effects. The development of SSRIs provided a safer, more tolerable alternative that was

easier to manage clinically. SSRIs are among the most commonly prescribed antidepressants in contemporary psychiatric practice [21-24]. They are heralded as the first line of treatment for depression and numerous other psychiatric disorders due to their efficacy, safety profile, and relatively mild side effects. The advent of SSRIs marked a significant milestone in the pharmacological treatment of depression, revolutionizing the therapeutic approach to this pervasive mental health condition.

Mechanism of Action

SSRIs function primarily by increasing the levels of serotonin in the brain, a neurotransmitter associated with feelings of well-being and happiness. They achieve this by inhibiting the reuptake of serotonin at the synaptic cleft, which means they prevent the reabsorption of serotonin

back into the nerve cells that released it. As a result, more serotonin is available to pass further messages between nearby nerve cells. This mechanism of action is significant because it is believed that an imbalance in serotonin levels can lead to depression and other mood disorders.

2.2 Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

These drugs were developed following the discovery of SSRIs. While SSRIs were revolutionary in treating depression by selectively inhibiting the reuptake of serotonin, it became apparent that some patients did not fully respond to SSRIs alone. This observation led to the development of SNRIs, which target both serotonin and norepinephrine neurotransmitters. They provided an alternative for patients who did not respond adequately to SSRIs. Some of them are notable for their use not only in psychiatric conditions but also in the treatment of pain syndromes such as diabetic neuropathy and fibromyalgia [25-27].

Mechanism of Action

SNRIs function by inhibiting the reuptake of both serotonin and norepinephrine in the brain. This dual reuptake inhibition is thought to contribute to more balanced neurotransmitter levels in the central nervous system, which can help alleviate symptoms of depression and anxiety more effectively than the modulation of serotonin alone.

2.3 Tricyclic Antidepressants (TCAs)

TCAs were among the first classes of antidepressants used clinically, introduced in the late 1950s. Prior to the development of SSRIs, TCAs were the primary treatment option for depression and other mood disorders. Despite their efficacy, the use of TCAs has declined due to the introduction of SSRIs, which offer a safer profile and fewer side effects. However, TCAs are still used today, particularly in cases where modern antidepressants are ineffective. TCAs are known for their effectiveness in treating major depressive disorder, especially in more severe cases that do not respond to other treatments [28-31]. They are also utilized for their benefits in treating chronic pain, neuropathic pain, and certain anxiety disorders. TCAs work by blocking the reuptake of neurotransmitters, primarily serotonin and norepinephrine, at the synaptic cleft. This blockade results in increased concentrations of these neurotransmitters in the central nervous system. TCAs also affect other neurotransmitter systems, which contributes to their broad pharmacological profile and the basis for many of their side effects.

2.4 Monoamine Oxidase Inhibitors (MAOIs)

MAOIs are among the oldest classes of antidepressants, first

introduced in the 1950s. Despite their clinical efficacy, MAOIs are typically used as a last resort due to the stringent dietary restrictions required and potential for severe side effects. They are primarily prescribed for patients who do not respond to other antidepressants like SSRIs and TCAs [32-35]. They are effective in treating various types of depression, particularly atypical depression, which often resists treatment with other antidepressant drugs. They are also used for treating Parkinson's disease due to their effects on dopamine levels, as well as for social anxiety and certain phobias.

MAOIs work by inhibiting the activity of monoamine oxidase, an enzyme that breaks down neurotransmitters such as serotonin, norepinephrine, and dopamine in the brain. By blocking this enzyme, MAOIs increase the levels of these neurotransmitters, enhancing mood and emotional balance. This mechanism is distinct as it not only increases neurotransmitter levels but also affects neurotransmitter metabolism globally within the nervous systems.

2.5 Atypical antidepressants

These are a diverse group of medications that do not fit neatly into the more established categories like SSRIs, TCAs, or MAOIs. They are called 'atypical' because their mechanisms of action differ from those of the typical antidepressants, or they target additional neurotransmitter systems beyond just serotonin and norepinephrine. These medications are often used when patients do not respond to traditional antidepressants or when they experience intolerable side effects. They are mainly used for treating major depressive disorder, anxiety disorders, and other mental health conditions [36-39]. They can offer advantages over other antidepressants, such as fewer sexual side effects or a different side effect profile, which may be preferable for certain patients.

2.6 Noradrenergic and specific serotonergic antidepressants (NaSSAs)

These are a class of atypical antidepressants that are specifically designed to target and modulate both the noradrenergic and serotonergic systems in the brain, but in a manner distinct from other antidepressants [37-41]. NaSSAs are primarily used in the treatment especially when symptoms include anxiety or insomnia.

NaSSAs work by blocking alpha-2 adrenergic receptors, which typically inhibit the release of norepinephrine and serotonin. By blocking these receptors, NaSSAs increase the release of these neurotransmitters in the brain. Additionally, by antagonizing certain serotonin receptors, NaSSAs prevent the usual negative feedback mechanism, thereby increasing serotonergic neurotransmission in other pathways. This unique action helps in alleviating depression and associated symptoms.

Table 1: Commonly used drugs for various antidepressant classes

Class	Commonly used drugs			
	Fluoxetine	Sertraline	Citalopram	
SSRIs	<ul style="list-style-type: none"> - One of the most prescribed SSRIs. - First of its kind to be used and is approved for the treatment of major depressive disorder, obsessive-compulsive disorder, bulimia nervosa, and 	<ul style="list-style-type: none"> - Marketed under the brand name Zoloft - Used to treat major depressive disorder, anxiety disorders, post-traumatic stress disorder, premenstrual dysphoric disorder, and obsessive-compulsive 	<ul style="list-style-type: none"> - Sold as Celexa, it is used primarily to treat depression. - Also effective for treating certain anxiety disorders. - Noteworthy for its selective action, which typically results in fewer side effects related to 	

	panic disorder.	disorder. - Known for its relatively mild side-effect profile and good efficacy.	non-serotonin receptors.	
SNRIs	Venlafaxine - Primarily used to treat major depressive disorder, generalized anxiety disorder, panic disorder, and social phobia. - Also effective in treating vasomotor symptoms associated with menopause.	Duloxetine - Used for the treatment of major depressive disorder, generalized anxiety disorder, fibromyalgia, diabetic neuropathy, and chronic musculoskeletal pain.	Desvenlafaxine - Synthetic form of the major active metabolite of venlafaxine.	Levomilnacipran - Known for its higher selectivity for norepinephrine reuptake inhibition compared to serotonin.
	Amitriptyline - Widely prescribed for its efficacy in treating major depression, neuropathic pain, and migraine prophylaxis. - Its utility in a range of pain syndromes underscores its importance in clinical practice.	Imipramine - One of the earliest TCAs to be used, imipramine is effective in treating major depression, panic disorder, and nocturnal enuresis in children. - Its diverse indications make it a versatile but potent medication.	Nortriptyline - Often preferred over other TCAs due to its somewhat more favorable side effect profile and therapeutic window. - Primarily used for depression but is also effective in treating chronic pain conditions.	
MAOIs	Phenelzine - Often used for treating depression and certain anxiety disorders. - Known for its effectiveness in patients who do not respond to other treatments.	Tranlycypromine - One of the more stimulating MAOIs, often preferred when increased energy and motivation are desired therapeutic effects.	Isocarboxazid - Known for its efficacy in patients with atypical symptoms who have failed other antidepressant therapies.	
	Bupropion - Primarily affects dopamine and norepinephrine reuptake, making it unique among antidepressants. - Often used for patients who experience sexual side effects from other antidepressants or those who require a mood lift with less risk of weight gain.	Mirtazapine - Works by antagonizing central alpha-2 adrenergic inhibitors and serotonin receptors. - This dual action results in increased release of norepinephrine and serotonin. - Often used to help with sleep and appetite increase in patients who need such effects.	Trazodone - Primarily used for its sedative properties, especially in patients with insomnia. - Works as a serotonin receptor antagonist and reuptake inhibitor, which helps to modulate mood and anxiety.	Vortioxetine - Known for its action as a serotonin modulator and stimulator. - Binds to several different serotonin receptors and inhibits the serotonin transporter, leading to antidepressant and anxiolytic effects.
Atypical antidepressants	Mirtazapine - Known for its efficacy in treating major depressive disorder with significant improvements in sleep and appetite. - Particularly beneficial for patients who have depression with insomnia or who need to gain weight.			

3. Adverse effects of antidepressants

3.1 SSRIs: While SSRIs are generally considered safe and effective for treating depression and other psychiatric

disorders, they can have various adverse effects, ranging from mild to severe. Here are some of the common adverse effects associated with SSRIs:

Table 2: Common adverse effects associated with SSRIs-

Adverse Effect Category	Specific Adverse Effects
Gastrointestinal Symptoms	Nausea: Common during initial treatment; often subsides after a few weeks. Diarrhea or Constipation: Changes in bowel habits may occur. Indigestion: Symptoms of heartburn or indigestion.
Sexual Dysfunction	Decreased Libido: Reduced sexual desire in men and women. Erectile Dysfunction: Difficulty achieving or maintaining an erection (in men). Delayed Ejaculation and Orgasm Difficulty: Inhibited ejaculation in men; difficulty achieving orgasm in both sexes.
Insomnia or Sleep Disturbances	Difficulty falling or staying asleep, vivid dreams, or nightmares.
Weight Changes	Weight Gain: Common over long-term use; can impact treatment adherence. Weight Loss: Less common than weight gain.
Increased Anxiety or Agitation	May increase anxiety or agitation, especially initially.
Suicidal Thoughts or Behavior	Increased risk in young adults and adolescents, especially during initial weeks.
Serotonin Syndrome	Rare but serious condition with symptoms like confusion, rapid heart rate, and muscle rigidity; requires prompt medical attention.

3.2 SNRIs

While SNRIs are generally effective in managing these

conditions, they can also produce a range of adverse effects, which can vary in severity from person to person.

Table 3: Common adverse effects associated with SNRIs

Adverse Effect Category	Specific Adverse Effects
Insomnia or Sleep Disturbances	Difficulty falling asleep or staying asleep (Insomnia): It is a common side effect of SNRIs, particularly during the early stages of treatment. Some individuals may also experience vivid dreams or nightmares, which can disrupt sleep patterns and contribute to daytime fatigue. Daytime sleepiness: In contrast to insomnia, some individuals may experience excessive daytime sleepiness or drowsiness while taking SNRIs, which can impair concentration and productivity.
Increased Blood Pressure	SNRIs have the potential to elevate blood pressure, particularly at higher doses. This effect may be of concern for individuals with pre-existing hypertension or cardiovascular risk factors, and regular monitoring of blood pressure may be necessary during treatment.
Sweating	Excessive sweating, particularly at night, is a common side effect of SNRIs. This can be bothersome and may contribute to discomfort, especially during warmer weather or physical activity.
Anxiety or Nervousness	Some individuals may experience increased anxiety or nervousness while taking SNRIs, especially during the initial stages of treatment. This effect may subside over time as the body adjusts to the medication, but it can be distressing for some individuals.
Headache	Headaches are a relatively common side effect of SNRIs, particularly during the early stages of treatment. These headaches are typically mild to moderate in severity and may improve as the body acclimates to the medication.
Dizziness or Light-headedness	Dizziness or light-headedness may occur, particularly when standing up quickly, while taking SNRIs. This effect is more common during the initial weeks of treatment and may be transient as the body adjusts to the medication.

3.3 TCAs

These are effective medications for treating depression and other psychiatric disorders, but they are also associated with a range of adverse effects, some of which can be significant.

Understanding these adverse effects is important for both patients and healthcare providers to make informed treatment decisions and manage any potential risks.

Table 4: Common adverse effects associated with TCAs

Adverse Effect Category	Specific Adverse Effects
Anticholinergic Effects	TCAs have significant anticholinergic activity, meaning they block the action of acetylcholine, a neurotransmitter involved in various bodily functions. This can lead to several adverse effects, including: Dry mouth: TCAs can reduce salivary gland secretion, leading to dryness and discomfort in the mouth. Blurred vision: Anticholinergic effects can affect the muscles in the eyes, leading to blurred vision and difficulty focusing. Constipation: TCAs can slow down intestinal motility, leading to constipation and difficulty passing stool. Urinary retention: Anticholinergic activity can interfere with bladder function, leading to difficulty urinating and urinary retention. Cognitive impairment: Anticholinergic effects may cause cognitive impairment, including confusion, memory problems, and difficulty concentrating, especially in older adults.
Orthostatic Hypotension	TCAs can cause a drop in blood pressure upon standing up, known as orthostatic hypotension. This can lead to symptoms such as dizziness, light-headedness, and even fainting. Orthostatic hypotension is more common with higher doses of TCAs and can increase the risk of falls, particularly in older adults.
Sedation	Many TCAs have sedating properties, which can cause daytime drowsiness and impair cognitive and motor functions. Sedation may improve over time as the body adjusts to the medication, but it can be bothersome, especially for individuals who need to remain alert and focused during the day.
Weight Gain	TCAs are associated with weight gain in some individuals, which may be due to their effects on appetite and metabolism. Weight gain can contribute to dissatisfaction with treatment and may impact adherence to medication.
Cardiac Effects	TCAs can have effects on the cardiovascular system, including prolongation of the QT interval on electrocardiogram (ECG). Prolongation of the QT interval can increase the risk of cardiac arrhythmias, particularly in individuals with pre-existing heart conditions or those taking other medications that also prolong the QT interval.
Sexual Dysfunction	TCAs can cause sexual side effects, including decreased libido, erectile dysfunction (in men), and difficulty achieving orgasm. These effects may contribute to sexual dissatisfaction and impact overall quality of life.
Serotonin Syndrome	While less common than with other classes of antidepressants like SSRIs and SNRIs, TCAs can still cause serotonin syndrome when taken in combination with other medications that increase serotonin levels. Serotonin syndrome is a potentially life-threatening condition characterized by symptoms such as confusion, agitation, rapid heart rate, high blood pressure, dilated pupils, muscle rigidity, sweating, and tremors.
Overdose Risk	Overdose with TCAs can lead to life-threatening cardiac arrhythmias, seizures, and coma. Therefore, prescribing physicians should carefully consider the risk of overdose, especially in individuals with a history of suicide attempts or substance abuse.

3.4 MAOIs

While MAOIs can be effective in managing depression, they

are also associated with a range of adverse effects, some of which can be serious.

Table 5: Common adverse effects associated with MAOIs

Adverse Effect Category	Specific Adverse Effects
Hypertensive Crisis	One of the most significant risks associated with MAOIs is the potential for a hypertensive crisis, also known as a hypertensive reaction or hypertensive crisis. This occurs when MAOIs interact with certain foods or medications that contain tyramine, a compound found in aged, fermented, or spoiled foods. Tyramine can cause a sudden and dangerous increase in blood pressure, leading to symptoms such as severe headache, palpitations, chest pain, nausea, vomiting, sweating, and even stroke or death in severe cases. Foods to avoid include aged cheeses, cured meats, fermented, or pickled foods, and certain alcoholic beverages. Certain medications, including some over-the-counter cold and cough medications, decongestants, and diet pills, can also interact with MAOIs to cause a hypertensive crisis.
Seonin Syndrome	Like other classes of antidepressants, MAOIs can also cause serotonin syndrome when taken in combination with other medications that increase serotonin levels. Serotonin syndrome is a potentially life-threatening condition characterized by symptoms such as confusion, agitation, hallucinations, rapid heart rate, high blood pressure, dilated pupils, muscle rigidity, sweating, tremors, and in severe cases, seizures, and coma. Therefore, it's essential to avoid combining MAOIs with other serotonergic medications, including SSRIs, SNRIs, tricyclic antidepressants, and certain pain medications.
Orthostatic Hypotension	MAOIs can cause a drop in blood pressure upon standing up, known as orthostatic hypotension. This can lead to symptoms such as dizziness, light-headedness, and fainting, particularly when transitioning from lying down or sitting to standing. Orthostatic hypotension can increase the risk of falls, especially in older adults.
Weight Gain	Some individuals may experience weight gain while taking MAOIs, although this adverse effect is generally less common compared to some other classes of antidepressants.
Sexual Dysfunction	MAOIs can cause sexual side effects, including decreased libido, erectile dysfunction (in men), and difficulty achieving orgasm. These effects may contribute to sexual dissatisfaction and impact overall quality of life.
Insomnia or Sleep Disturbances	While less common than with some other antidepressants, MAOIs can also cause insomnia or other sleep disturbances in some individuals.
Gastrointestinal Symptoms	Nausea, vomiting, and Diarrhea may occur as side effects of MAOIs, especially when initiating treatment. These symptoms may improve over time as the body adjusts to the medication.
Edema	Peripheral edema, or swelling of the extremities, has been reported as a rare side effect of MAOI therapy.
Liver Toxicity	In rare cases, MAOIs may cause liver toxicity, leading to elevated liver enzymes and liver damage. Regular monitoring of liver function may be recommended in individuals taking MAOIs, especially those with pre-existing liver conditions or those taking other medications that can affect liver function.

3.5 Atypical antidepressants

These drugs work through various mechanisms to alleviate depressive symptoms and may be prescribed when other

antidepressants haven't been effective or have caused intolerable side effects. Despite their name, atypical antidepressants can still produce a range of adverse effects.

Table 6: Common adverse effects associated with atypical antidepressants.

Adverse Effect Category	Specific Adverse Effects
Sedation/Sleep Disturbances	Atypical antidepressants can cause sedation or sleep disturbances, leading to daytime drowsiness or insomnia.
Gastrointestinal Symptoms	Nausea and Vomiting, particularly during the initiation of treatment. These symptoms usually improve over time but can be bothersome for some individuals.
Weight Changes	They are notorious for increasing appetite and causing weight gain in some individuals. This effect can be particularly problematic for those who are already overweight or obese.
Sexual Dysfunction	They can cause sexual side effects, including decreased libido, erectile dysfunction (in men), and difficulty achieving orgasm. These effects can have a significant impact on quality of life and may contribute to treatment discontinuation.
Seizures	They carry a risk of lowering the seizure threshold, especially at higher doses or in individuals with a history of seizures. Seizures are more likely to occur when bupropion is used off-label for smoking cessation.
Priapism	A prolonged and painful erection unrelated to sexual stimulation, is a rare but serious side effect associated with Trazodone. It requires immediate medical attention to prevent complications.
Dry Mouth	These medications can cause dry mouth, leading to discomfort. While generally not considered a serious adverse effect, it can be bothersome for some individuals.
Headache	Headaches are relatively common, particularly during the early stages of treatment. These headaches are typically mild to moderate in severity and may improve with continued use.
Liver Toxicity	They pose a risk of liver damage in some individuals. Liver function should be monitored regularly during treatment with Nefazodone.

3.6 Noradrenergic and specific serotonergic antidepressants (NaSSAs)

NaSSAs like mirtazapine are generally well-tolerated, they can still produce a range of adverse effects.

Table 8: Common adverse effects associated with atypical antidepressants.

Adverse Effect Category	Specific Adverse Effects
Sedation	Sedation is one of the most common side effects of mirtazapine. Due to its histamine-blocking properties, mirtazapine often causes drowsiness, especially at lower doses. This sedative effect can be beneficial for individuals with insomnia but may also lead to daytime drowsiness and impair cognitive function.
Increased Appetite and Weight Gain	Mirtazapine is known for its ability to increase appetite and promote weight gain. This effect is primarily due to its antagonism of certain serotonin receptors (5-HT _{2C} receptors), which leads to an increase in appetite and food

	intake. Weight gain is a common concern for individuals taking mirtazapine, particularly in the initial months of treatment.
Orthostatic Hypotension	Like many other antidepressants, mirtazapine can cause orthostatic hypotension, a drop in blood pressure upon standing up. Symptoms may include dizziness, light-headedness, and fainting. This effect is more common at higher doses and during the initial stages of treatment.
Dry Mouth	Dry mouth is a relatively common side effect of mirtazapine. It occurs due to its anticholinergic properties, which reduce saliva production. While dry mouth is usually mild and transient, it can be bothersome for some individuals.
Constipation	Mirtazapine can slow down intestinal motility, leading to constipation in some individuals. This effect is more common in older adults and may require dietary adjustments or the use of laxatives to manage.
Increased Serum Cholesterol and Triglycerides	Mirtazapine has been associated with increases in serum cholesterol and triglyceride levels, which may contribute to cardiovascular risk factors. Regular monitoring of lipid levels may be recommended, especially in individuals with pre-existing cardiovascular conditions.
Agitation or Restlessness	While less common than sedation, some individuals may experience agitation or restlessness while taking mirtazapine. This effect may be more pronounced during the initial stages of treatment and typically resolves over time as the body adjusts to the medication.
Dizziness	Dizziness is a common side effect of mirtazapine, particularly when standing up quickly or moving from a lying to a sitting position. It is usually mild and transient but can be concerning, especially if it leads to falls or injuries.
Nausea and Vomiting	Nausea and vomiting are relatively uncommon side effects of mirtazapine but can occur, especially when initiating treatment or at higher doses. These symptoms may improve over time as the body adjusts to the medication.
Serotonin Syndrome (Rare)	While rare, mirtazapine can potentially cause serotonin syndrome when used in combination with other serotonergic medications. Symptoms of serotonin syndrome include confusion, agitation, hallucinations, rapid heart rate, high blood pressure, dilated pupils, muscle rigidity, sweating, tremors, and in severe cases, seizures, and coma. Therefore, it's crucial to avoid combining mirtazapine with other medications that increase serotonin levels without medical supervision.

3.7 Effects of discontinuing antidepressants

Stopping the use of antidepressants can pose significant challenges due to the high incidence of discontinuation symptoms associated with antidepressant discontinuation syndrome (ADS). Common symptoms of ADS include insomnia, flu-like symptoms, mood disturbances, dizziness, and paraesthesia's, which can vary in duration from days to months. Effective management of ADS involves educating patients about these potential symptoms, identifying those at

greater risk, and implementing a slow tapering or cross-tapering strategy to minimize symptoms. Tapering schedules should extend over weeks to months. If discontinuation symptoms occur, it's advisable to restart the previous dose and taper off even more gradually, while providing additional treatment for any symptomatic relief needed [40-42]. Discontinuation symptoms of antidepressants are listed in Table 9.

Table 9: Discontinuation symptoms of antidepressant drugs

System	SSRIs	SNRIs	TCAs	MAOIs	Atypical
General	Flu-like symptoms, Fatigue	Flu-like symptoms, Fatigue, Diaphoresis	Flu-like symptoms, Fatigue	Flu-like symptoms, Fatigue	Flu-like symptoms, Fatigue
Cardiovascular	Tachycardia, Flushing	Tachycardia, Hypertension, hypotension, Syncope	Tachycardia, Arrhythmia, Syncope	Tachycardia, Arrhythmia	
Gastrointestinal	Nausea, vomiting, Diarrhea, Anorexia	Nausea, vomiting, Diarrhea, Anorexia	Nausea, vomiting, Diarrhea, Anorexia	Nausea, vomiting, Diarrhea, Anorexia	Nausea, vomiting, Diarrhea, Anorexia (mirtazapine)
Neurologic	Headache, Gait instability, Dizziness, Paresthesias, brain zaps, Tremor, ataxia, Myoclonus, muscle jerking, Parkinsonism	Headache, Gait instability, Dizziness, Paresthesias, brain zaps, Tremor, ataxia, Stroke-like symptoms, Seizure, myoclonus, muscle jerking	Headache, Paresthesias, Tremor, ataxia, Seizure, Parkinsonism	Headache, Paresthesias, Tremor, ataxia, Seizure, myoclonus, muscle jerking, Parkinsonism, Dystonia, Catatonia	Headache, Dizziness, Paresthesias, Tremor, Dystonia (bupropion)
Psychiatric	Anxiety, panic, Depression, mania, Suicidal ideation, Anger, irritability, Mood swings, Depersonalization, derealization, Hallucinations	Anxiety, panic, Depression, mania, Suicidal ideation, Anger, irritability, Mood swings, Depersonalization, derealization, Hallucinations	Anxiety, panic, Depression, mania, Suicidal ideation, Anger, irritability, Mood swings, Depersonalization, derealization, Hallucinations	Depression, lability, Suicidal ideation, Anger, irritability, Aggression, agitation, Hallucinations, Delusions	Anxiety, panic, Depression, mania, Suicidal ideation, Anger, irritability, Mood swings, ation, derealization
Cognitive	Confusion, delirium, Inattention	Confusion, delirium, Inattention	Confusion, delirium, Inattention	Confusion, delirium, Inattention	
Sleep	Sleep disturbances, Nightmares, vivid dreams	Sleep disturbances, Nightmares, vivid dreams	Sleep disturbances, Nightmares, vivid dreams	Sleep disturbances, Nightmares, vivid dreams	Sleep disturbances, Nightmares, vivid dreams
Visual	Vision changes	Vision changes	Vision changes	Vision changes	
Sexual	Dysfunction	Dysfunction	Dysfunction	Dysfunction	Dysfunction

4. Strategies to manage adverse effects of antidepressants

4.1 Start Low, Go Slow

a. SSRIs

These are initiated at low doses to minimize the risk of side effects such as nausea, agitation, and headache. Starting at a low dose, like 10-20 mg/day for fluoxetine or 25-50 mg/day for sertraline, allows patients to adapt to the medication gradually. Slow titration, typically over several weeks, helps improve tolerability and reduce the likelihood of adverse reactions.

b. SNRIs

SNRIs follow a similar approach, with medications like venlafaxine starting at 37.5-75 mg/day. This cautious dosing strategy is essential to mitigate side effects such as gastrointestinal disturbances, insomnia, and increased blood pressure, which can occur with SNRI therapy.

c. TCAs

TCAs are initiated at low doses, such as 10-25 mg/day for amitriptyline, due to their narrow therapeutic index and potential for serious adverse effects like anticholinergic effects, sedation, and cardiac toxicity. Slow titration is crucial to minimize the risk of toxicity and improve tolerability.

d. MAOIs

MAOIs like phenelzine are started at low doses, such as 15 mg/day, to avoid the risk of hypertensive crisis associated with rapid dose escalation. Close monitoring of blood pressure and dietary restrictions is necessary during dose titration.

e. Atypical Antidepressants

Drugs like bupropion and mirtazapine are also initiated at low doses to minimize side effects. For example, bupropion may start at 75 mg/day. Slow titration helps reduce the risk of adverse reactions such as insomnia, agitation, and dry mouth.

4.2 Regular Monitoring

Regular monitoring is a cornerstone of effective antidepressant therapy, ensuring that patients receive timely assessment of treatment response and detection of adverse effects. For SSRIs, monitoring typically involves frequent follow-up appointments, especially during the initial weeks of treatment, with visits scheduled every 1-2 weeks. Clinicians utilize standardized rating scales such as the Patient Health Questionnaire-9 (PHQ-9) or the Quick Inventory of Depressive Symptomatology (QIDS) to assess symptom severity and treatment response. Concurrently, they monitor for emerging side effects, changes in depressive symptoms, and suicidal ideation, while also assessing vital signs like blood pressure and heart rate. Similarly, patients initiating SNRIs require close monitoring, with follow-up appointments and assessment tools mirroring those used for SSRIs. TCAs, with their higher risk of adverse effects and toxicity, necessitate even more vigilant monitoring, often requiring weekly follow-up appointments during the initial treatment phase^[43-45]. Here, structured interviews or rating scales such as the Inventory of Depressive Symptomatology (IDS) help evaluate symptom severity, while clinicians closely monitor for

common side effects like dry mouth, constipation, and orthostatic hypotension. Additionally, MAOIs, due to dietary restrictions and potential drug interactions, mandate frequent monitoring, with appointments every 1-2 weeks. In these cases, clinicians educate patients about dietary restrictions and monitor blood pressure regularly to detect signs of hypertensive crises or serotonin syndrome. Finally, patients starting atypical antidepressants receive regular follow-up appointments, typically every 1-2 weeks, with monitoring tailored to the specific side effect profiles of each medication. Through meticulous and systematic regular monitoring, clinicians ensure the safety, efficacy, and overall well-being of patients undergoing antidepressant therapy.

4.3 Psychoeducation and Psychotherapy

Psychoeducation aims to provide patients with information about depression, treatment options, and coping strategies. It helps improve treatment adherence, reduce stigma, and empower patients to play an active role in managing their condition. Psychotherapeutic interventions like Cognitive-Behavioural Therapy (CBT), Interpersonal Therapy (IPT), and Mindfulness-Based Cognitive Therapy (MBCT) complement pharmacotherapy by addressing underlying psychological factors contributing to depression and teaching patients skills to cope with stressors and symptoms^[40]. Integrated treatment models that combine pharmacotherapy with psychotherapy have shown efficacy in improving treatment outcomes and preventing relapse. These models emphasize collaboration between psychiatrists, psychologists, and other mental health professionals to provide comprehensive care tailored to the individual needs of each patient.

4.4 Side Effect Management

In managing side effects associated with antidepressant therapy, a multifaceted approach is essential to optimize treatment tolerability and adherence. Clinicians must proactively identify and address side effects to ensure patients receive the maximum benefit from their medication regimen. Strategies for side effect management encompass several key elements. First, patient education plays a crucial role in empowering individuals to recognize and report adverse reactions promptly. By providing comprehensive information about potential side effects, their expected duration, and strategies for coping with them, clinicians empower patients to actively participate in their treatment. Additionally, close monitoring of patients during follow-up appointments allows clinicians to assess the emergence of side effects and tailor management strategies accordingly^[44]. Depending on the nature and severity of the side effect, interventions may include dose adjustments, switching to an alternative medication, or adjunctive therapies to alleviate specific symptoms. For example, patients experiencing gastrointestinal disturbances with SSRIs may benefit from taking their medication with food or switching to a different SSRI with a more favourable side effect profile. Similarly, patients experiencing sexual dysfunction may benefit from adjunctive treatments such as phosphodiesterase inhibitors or alternative antidepressants with a lower risk of sexual side effects. Throughout the management process, patient-centred care and shared decision-making are paramount, allowing clinicians and patients to collaboratively navigate treatment options and optimize outcomes while minimizing

the burden of side effects.

4.5 Switching or Augmenting Strategies

Switching or augmenting strategies are important considerations in the management of depression when patients experience inadequate response or intolerable side effects to their current antidepressant regimen. Switching involves changing to a different antidepressant, either within the same class or to a different class, to address treatment resistance or side effect intolerance. Augmentation, on the other hand, involves adding adjunctive medications or non-pharmacological interventions to enhance the efficacy of existing antidepressant therapy. These strategies are often employed when initial treatments fail to achieve remission or when patients experience persistent symptoms despite adequate trials of antidepressants. Switching antidepressants may be guided by factors such as previous treatment response, side effect profiles, and patient preferences. For example, patients who do not respond to SSRIs may benefit from switching to SNRIs or other classes of antidepressants such as bupropion or mirtazapine. Augmentation strategies may involve adding medications such as atypical

antipsychotics, mood stabilizers, or thyroid hormones to enhance antidepressant efficacy. Non-pharmacological interventions like cognitive-behavioural therapy (CBT), electroconvulsive therapy (ECT), or transcranial magnetic stimulation (TMS) may also be considered as augmentation strategies. The decision to switch or augment antidepressant therapy should be individualized based on patient-specific factors, including treatment history, comorbidities, and patient preferences. Close monitoring is essential during the transition period to assess treatment response and tolerability, and adjustments may be made as needed to optimize outcomes [43, 45]. Through a collaborative and patient-centred approach, clinicians can effectively navigate switching or augmentation strategies to achieve remission and improve the overall well-being of patients with depression.

The flowchart represented in Figure 2 outlines the decision-making steps a healthcare provider might follow when selecting an antidepressant, starting from symptom assessment to monitoring the effectiveness of the chosen medication.

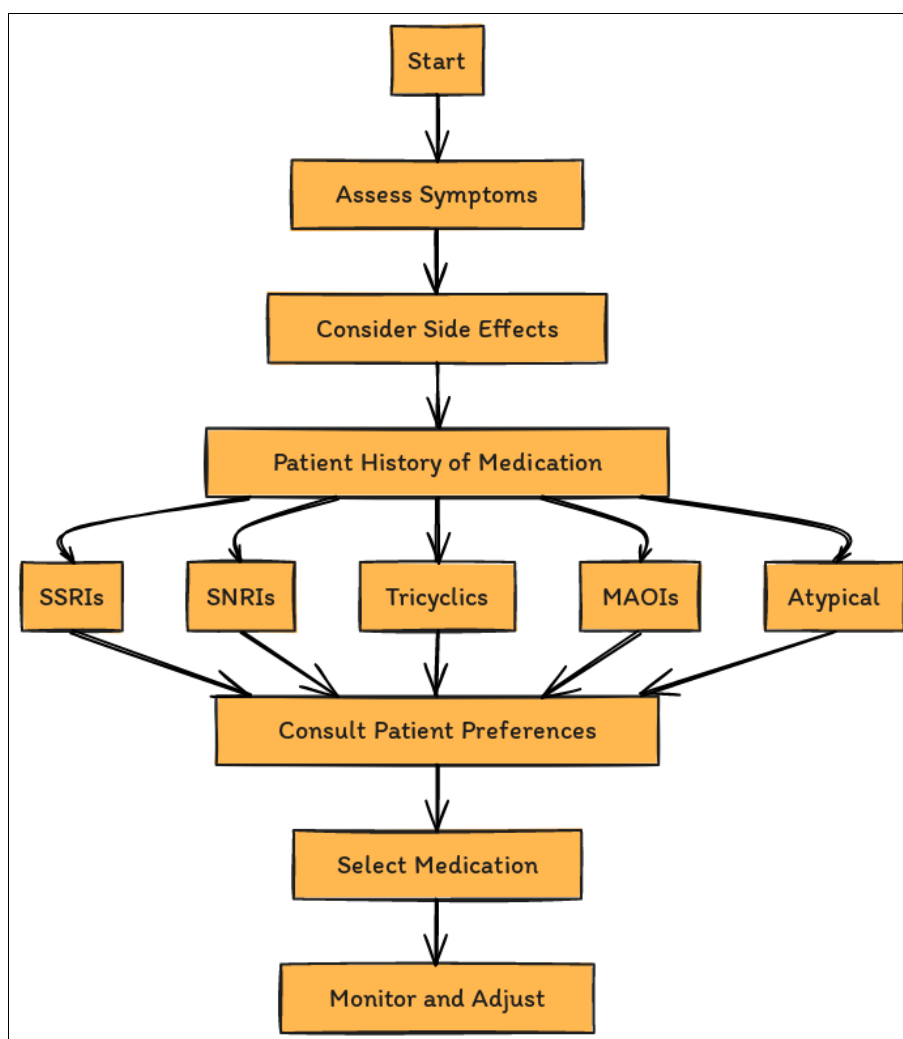


Fig 2: Flow chart representing decision-making steps to be followed when selecting an antidepressant

Case Study: Strategies to Manage Adverse Effects of Antidepressants

Patient Profile

- **Name:** Sarah Thompson
- **Age:** 45

- **Diagnosis:** Major Depressive Disorder (MDD)
- **Current Medication:** Sertraline (SSRI) 100 mg/day

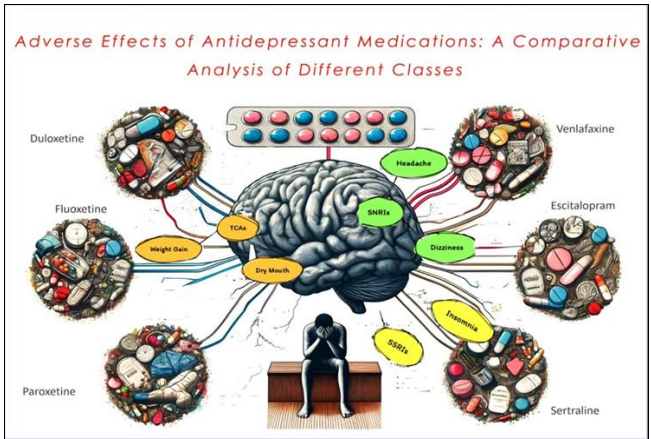
Background: Sarah Thompson, a 45-year-old woman, was diagnosed with Major Depressive Disorder (MDD) and

started on sertraline, a selective serotonin reuptake inhibitor (SSRI), at a dose of 100 mg/day. Although the medication significantly improved her depressive symptoms, Sarah experienced several adverse effects, including sexual

dysfunction, weight gain, and insomnia, which were affecting her quality of life and adherence to the treatment [45].

Table 10: Strategies to Manage Adverse Effects of Antidepressants

Sr. No	Strategy	Description	Example/Outcome
1	Start Low, Go Slow	Begin with a low dose and gradually increase to minimize initial side effects.	Sarah started sertraline at 25 mg/day and titrated up to 100 mg/day. Initial side effects were minimized.
2	Regular Monitoring	Frequent follow-up appointments and use of standardized rating scales to monitor symptoms and side effects.	Regular visits helped detect and manage side effects early, improving adherence.
3	Psychoeducation and Psychotherapy	Educate patients about depression, treatment options, and coping strategies. Integrate with CBT to address psychological factors.	Sarah's knowledge about her condition reduced anxiety; CBT provided coping mechanisms.
4	Side Effect Management	Proactively identify and address specific side effects with interventions like dose adjustments, switching medications, or adding adjunctive treatments.	Bupropion was added to manage sexual dysfunction; lifestyle changes addressed weight gain; sertraline timing improved sleep.
5	Switching or Augmenting Strategies	Change to a different antidepressant or add adjunctive treatments when initial treatments are inadequate.	Mirtazapine was added to improve sleep without causing significant weight gain.



Highlights

- Outlines the different types of antidepressants including SSRIs, SNRIs, TCAs, MAOIs, atypical antidepressants, and NASSAs.
- Details the specific adverse effects associated with each class, highlighting both common and severe impacts.
- Discusses strategies to manage side effects in clinical practice, including patient education and pharmacological adjustments.

5. Conclusions

In conclusion, the review article underscores the multifaceted nature of managing antidepressant therapy amidst its diverse side effect profiles. Throughout the analysis, it becomes evident that while antidepressants offer significant benefits in treating depression, their efficacy must be weighed against potential adverse effects inherent to each class. The comparative analysis delves into the nuanced differences among SSRIs, SNRIs, TCAs, MAOIs, atypical antidepressants, and NaSSAs, providing valuable insights into their respective safety profiles and clinical considerations. From the meticulous examination of each class emerges a comprehensive understanding of the importance of tailored treatment approaches, regular monitoring, and proactive side effect management strategies. Furthermore, the discussion on switching or augmenting strategies underscores the dynamic nature of antidepressant therapy, emphasizing the need for

personalized interventions to optimize treatment outcomes. As the field of psychopharmacology continues to evolve, this comparative analysis serves as a valuable resource for clinicians, researchers, and healthcare providers, guiding evidence-based decision-making and enhancing patient care in the complex landscape of antidepressant medication management. Through continued research and collaborative efforts, we can move towards mitigating adverse effects and improving the overall safety and efficacy of antidepressant therapies, ultimately fostering better outcomes and quality of life for individuals battling depression.

6. Conflict of Interest

Not available

7. Financial Support

Not available

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