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Review Article

PHARMACOTHERAPEUTIC MANAGEMENT OF MAJOR DEPRESSIVE DISORDER: ANTIDEPRESSANT STRATEGIES AND PHARMACIST-LED CARE

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ABSTRACT

Major depressive disorder (MDD) is a disabling, prevalent psychiatric disorder that has a tremendous effect on emotional, cognitive, social, and physical functioning. The multifactorial pathophysiology, fluctuate clinical expression, and common comorbidities of it complicate and highly individualize the pharmacotherapeutic management of the disease. This review also brings to light the key areas of antidepressant treatment such as the selection of selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors as well as atypical antidepressants. It also addresses the significance of selecting different medications according to the patient, dose adjustment, exchange plans, monitoring therapeutic responses as well as treatment of the side effects and drug-drug interactions. Special emphasis is put on the growing role of pharmacists in maximizing antidepressant treatment by conducting medication reviews, aiding the adherence process, counseling patients, early detection of issues related to the treatment, and collaborative care. Besides that, non-pharmacological and lifestyle intervention is acknowledged to be useful supportive measures. The patient-centered approach led by pharmacists can enhance treatment safety, adherence and macro clinical outcomes of managing depression.

Keywords: Major Depressive Disorder, Antidepressant Pharmacotherapy, Pharmacist-Led Care, Medication Adherence, Patient-Centered Management.

INTRODUCTION

One of the most prevalent and debilitating mental disorders in the world is the major depression disorder (MDD), which impacts millions of people and critically deteriorates the emotional, cognitive and physical functioning. Depression is a significant burden of the disease with persistent sadness, loss of interest or pleasure in activities, appetite or sleep changes, fatigue, lack of concentration, worthlessness and in severe cases suicidal thoughts. The international health accounts suggest that the health condition of depression is one of the major causes of disability and has significant social and economic impacts because of decreased productivity, high healthcare use, and poor quality of life.[1,2] The condition has been reported to have no age-related or socioeconomic differences and is mostly found in women, though. Depression is in most cases underdiagnosed and undertreated due to stigmatization, ignorance and access to mental health care is limited especially in low- and middle-income nations. The recurrence and chronicity of the major depressive disorder make its management even more complicated since many patients have recurrent episodes during the entire lifespan and it is usually accompanied by comorbid psychiatric or medical illnesses like anxiety diseases,

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cardiovascular diseases, diabetes, or substance use diseases. Depression is a multifactorial and intricate pathophysiology that entails a combination of genetic predisposition, stressors in the environment, neurobiological alterations and psychosocial effects.[3] The neurochemical theories indicate that the dysregulation of neurotransmitters like serotonin, norepinephrine, and dopamine is important to develop depressive symptoms, but the changes related to the hypothalamic-pituitary-adrenal (HPA) axis, neuroinflammation, neuroplasticity, and structural alterations of the brain areas, such as the hippocampus and prefrontal cortex, also contribute to the development of the disease. Though the underlying mechanisms are not entirely understood, these findings have been used in the development of the pharmacological treatments aimed at restoring the neurotransmitters balance and enhancing the neuronal communication. Pharmacotherapy is one of the key elements of the clinical treatment of moderate to severe depression and is often used with the help of psychotherapy and lifestyle changes to attain the best results.[4] There is a plethora of antidepressants at the present: selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants. Such drugs have their therapeutic actions by virtue of their ability to balance the concentration of the neurotransmitters in the synapses of the central nervous system, which enhances mood control and emotional stability. Although several therapeutic alternatives are available, antidepressant pharmacotherapy has been difficult due to the fact that the reaction rate to treatment differs significantly in different people as well as the patients may delay or fail to heal their symptoms and have adverse reactions to the medication they are taking. Moreover, comorbid conditions and multiple drug use predispose the presence of clinically significant drug-drug interactions that further complicate the treatment decisions.[5,6] Medication compliance is also one of the most important areas of depression management since patients might leave the treatment process too soon because of the perceived ineffectiveness of the treatment, side effects, or poor perceptions regarding antidepressant treatment. Here, pharmacists can contribute more significantly to the optimization of pharmacotherapy of major depressive disorder because they possess greater knowledge in drug use, in counseling patients, and monitoring therapy. Pharmacists, being a source of easy access to healthcare professionals, can participate in enhancing the safe and effective use of antidepressants by examining prescription, detecting possible drug interactions, prescribing suitable medication choice depending on patient characteristics, and assisting clinicians in dose-titration or switching medication plans. They also educate patients about their treatment expectations, how long they should continue with the therapy, how to manage side effects and the effects of the need to adhere to their prescribed medications.[7] Moreover, pharmacists may help in tracking the effectiveness of the therapy by assessing the improvement of the symptoms, detecting the development of the adverse drug reactions, and warning signs like depression worsening or suicidal thoughts, which might need urgent clinical intervention. Their participation in patient-focused treatment, such as lifestyle education, stress management, and collaboration with other risk management specialists, contributes to an improved performance of depression treatment. Thus, incorporating pharmacist-led interventions into the pharmacotherapeutic treatment of the major depressive disorder can provide an opportunity to better address treatment outcomes, improve medication safety, and provide full mental health care to patients in the context of contemporary healthcare systems.[8]

Global Burden of Depression and Epidemiology.

Depression is a significant worldwide populace health issue and is one of the greatest causes of incapacity worldwide and greatly impacts individuals, families and the healthcare systems. Major depression disorder (MDD) is implied on a population of over 280 million individuals in the world making up a significant percentage of the cumulative of mental disorders. Estimates by international health organizations indicate that depression is one of the leading contributors to the world burden of disease in terms of the number of years lived with disability (YLDs), as well as, it is one of the greatest contributors to the burden of disease. Depression occurs at different rates, in different regions, among different age groups, and various socioeconomic groups, although it is always widespread and common to both developed and developing countries.[9] The frequency of depression in women is said to be almost a twice as often as in men, and it is possible to attribute it to biological and hormonal, social, and psychological causes. Depression in life may be experienced at any age adolescence or even in old age but the initiation is usually at the early adulthood. Adolescents and young adults are especially susceptible to it, because of the impact of academic stressors, social stress, and changes in the psychological development, and older people might develop depression as a result of the impact of the chronic disease burden, social isolation, and the loss of functional autonomy. The socioeconomic issues affecting the world have increased global burden of depression through unemployment, poverty, conflict and social inequality all of which are known to be risk factors of having mental health disorders.[10] Moreover, recent worldwide crises such as pandemics and economic turmoil have facilitated the significant rise in the depressive symptoms in most of the populations.

Depression is often related to other psychiatric and health comorbidities, such as anxiety disorders, substance use disorders, cardiovascular diseases, diabetes, and chronic pain disorders, which also make diagnosis and treatment more complicated. These comorbidities do not only aggravate clinical outcomes but also inflate the cost and quality of life. Depression has a significant economic cost, which is caused by healthcare costs, diminished productivity in the workplace, absenteeism, and cost of disability. Depression causes tremendous loss in the participation and productivity in the workforce in most countries, thus, impacting the economic growth and social development of a country.[11] Although depression is highly prevalent and has dire outcomes, a big percentage of the affected people fail to get proper diagnosis and treatment because of stigma, inaccessibility to mental health services, ignorance, and incurable access to healthcare services. This disparity in treatment is especially high in low- and middle-income nations, where the mental health provision is usually under-invested and understaffed. Moreover, untreated depression is closely linked with the high risk of suicide and this is one of the major causes of death among youth in different parts of the world. With its high rates of prevalence, chronicity, and health and societal devastation, depression is a serious health issue of concern in every corner of the world and has to have multi-tiered approaches such as early recognition, good management, general education, and incorporation of mental health into primary care systems to diminish its increasing worldwide burden.[12]

Significance of Pharmacist Intervention on Mental Health Care

The role of pharmacists in the mental health care is becoming a significant one, especially in treatment of psychiatric disorders like major depressive disorder, anxiety disorders, bipolar disorders and schizophrenia. Though pharmacists are easily available healthcare professionals with specialized understanding of pharmacotherapy, they play a significant role in maximizing the use of medications, enhancing patient safety, and improving therapeutic outcomes in mental healthcare. Mental diseases can need prolonged pharmacological treatment and patients can undergo complicated medication regimes, slow response to treatment and different adverse reactions to drugs and therefore continuous monitoring and patient care is paramount. [13]In this respect, the services offered by pharmacists like review of medication, possible drug-drug interactions, and evaluation of medication appropriateness depending on specific patients such as age, comorbidity and co-existing medications are valued. The pharmacists can assist the healthcare providers in choosing the best antidepressants or psychotropic drugs and reduce the occurrence of adverse effects and interactions through the management of medication therapy. Patient counseling and education is another important component of pharmacist involvement. People undergoing treatment of depression or any other psychiatric illness might fear the side effects of various medications, the time of treatment or the stigma that is attached to mental illness. Pharmacists can help in these issues by giving patients clear data on the anticipated treatment outcomes, expected response time of antidepressants, potential drug side effects and the need to take medications. [14]This counseling allows the patient to be more informed about their treatment plan and makes them willing to continue to be treated as prescribed which is vital since failure to take antidepressants early may result in a relapse or withdrawal as well as failure to be cured. Pharmacists also participate in the follow up of the therapeutic outcomes and the detection of the early symptoms of medication issues. Since pharmacists are in consistent contact with their patients, particularly when working at community pharmacy, they can identify a problem that may be worsening depressive symptoms, non-adherence or developing side effects and report these problems to physicians or mental health providers. By identifying such issues early enough, the therapy will be adjusted in time and the severity of complications will be less likely, including suicidal thoughts.[15] Moreover, pharmacists are important in controlling medication safety among patients with comorbidities that might be on numerous medications, which will decrease the chances of detrimental interactions. Besides the clinical roles, the pharmacist can be involved in public health programs to enhance mental health awareness, lower stigma, and early screening and referral to mental health disorders. Working together with physicians, psychologists, and other healthcare professionals, pharmacists also become an essential part of multidisciplinary teams of mental health care. Their engagement improves the quality of patient-centered care, safe and effective medication use, and eventually improves clinical outcomes and life quality of persons with mental health conditions.[16]

Pathophysiology of Major Depressive Disorder.

Major depressive disorder (MDD) is a complicated psychiatric disorder, which is marked by chronic mood swings and multiplicity of emotional, cognitive, and physical signs, which are caused by multifactorial biological and environmental processes. Pathophysiology of MDD is complex and entails interplay between genetic predisposition, neurochemical changes, neuroendocrine disruption, inflammatory mechanisms and brain structure and functional changes. The most popular of them is the monoamine hypothesis that suggests that the causes of depression are the shortage or malfunction of the primary neurotransmitters, serotonin, norepinephrine, and dopamine, in the central

nervous system. These neurotransmitters are important in controlling mood, motivation, sleep, appetite and emotions.[17] The decreased activity of neurotransmitters or altered sensitivity of receptors could be what disturbs the process of communication between neurons and helps to acquire the symptoms of depression. Nevertheless, the lack of neurotransmitters cannot be the only explanation of depression. There is growing evidence to suggest that hypothalamic-pituitary-adrenal (HPA) axis abnormalities also have a significant role in the pathophysiology of depression. Chronic stress may cause hyperactivity of the HPA axis, which causes the over secretion of the stress hormone cortisol that may have adverse effects on the functioning of the brain and lead to mood disorders. Long-term high cortisol levels have been linked to damage of neurons, decreased neurogenesis and structural alterations in emotional regulation brain regions, including the hippocampus, amygdala, and prefrontal cortex. Neuroplasticity or the detail that the brain can change and create new brain connections is also greatly influenced among the people with depression.[18] Research has demonstrated that patients with MDD have lower levels of the brain-derived neurotrophic factor (BDNF) that is a protein involved in the growth and survival of the neuron. Reduced levels of BDNF can compromise the synaptic plasticity and can potentially be a factor in the structural changes of the brain that occur in depressive disorders. Moreover, another valuable mechanism that has been identified as having a role in causing depression is neuroinflammation. Some people have been shown to have increased pro-inflammatory cytokines and immune mediators in depression, indicating that inflammatory mechanisms can mediate neurotransmitter metabolism and neuronal activity.[19] Genetics also contributes significantly to vulnerability to depression, where studies in families and twins have shown that those with a genetic predisposition could be more susceptible to an environmental stressor (such as in the forms of trauma, chronic stress, or other major life events). Biological processes are further interacted with environmental and psychosocial factors such as early life adversity, social isolation and continued psychological stress to initiate or increase the severity of depression events. The combined effects of these neurobiological and environmental processes have the eventual outcome of disrupter of normal brain circuitry which controls mood, reward processing and cognitive abilities. The multifaceted pathophysiology of the major depressive disorder is crucial to formulate an appropriate treatment approach and advance pharmacotherapeutic treatment methods to reestablish neurotransmitter equilibrium, boost neuroplasticity, and stabilize emotional balance of people with the mentioned disorder.[20]

Antidepressant Pharmacotherapy

Pharmacotherapy in terms of antidepressants is a key element in clinical treatment of major depressive disorder (MDD), especially when the patient has moderate to severe symptoms or when the patient is not responding suitably to psychotherapy on its own. Antidepressant drugs work by balancing the activity of neurotransmitters in the central nervous system, thus regaining the balance of major monoamines including serotonin, norepinephrine and dopamine that play a role in mood, motivation and emotional stability. There are currently a number of classes of antidepressant which vary in terms of their mechanisms of action, efficacy sub-profiles, and characteristics of adverse effects.[21] First-line treatment is typically suggested to be selective serotonin reuptake inhibitors (SSRI) fluoxetine, sertraline, escitalopram, and paroxetine, as they have a good safety profile, are tolerable, and few side effects may be severe in contrast to older antidepressants. The therapeutic action of SSRIs includes the inhibition of serotonin reuptake by the presynaptic neurons and, thus, an increase in serotonin in the synaptic cleft and improvement of serotonergic neurotransmission. Another popular type of antidepressants, which raises the level of serotonin and norepinephrine, in the synapses, thereby enhancing mood and functionality, is serotonin-norepinephrine reuptake inhibitors (SNRI) like venlafaxine, desvenlafaxine, and duloxetine. Besides these agents, non-SSRI, non-SNRIs like bupropion, mirtazapine and trazodone are commonly used in cases where the patients are not able to tolerate their responses to SSRIs or SNRIs.[22] Bupropion is mostly used in patients where other antidepressants cause fatigue or sexual dysfunction due to its main action on dopamine and norepinephrine receptors. Mirtazapine is an antagonist of certain presynaptic receptors and induces neurotransmission, which improves the noradrenergic and serotonergic transmission, is commonly prescribed as a sedative and appetite stimulant to patients with insomnia or weight loss. Older antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are still effective and are usually used in the case of treatment-resistant depression because of their potentially dangerous side effects and drug-drug interactions. The reuptake of norepinephrine and serotonin is prevented by TCAs which include amitriptyline and nortriptyline which can lead to anticholinergic side effects, orthostatic hypotension, and cardiac toxicity.[23] MAOIs such as phenelzine and tranylcypromine prevent the enzyme monoamine oxidase that breaks down neurotransmitters but their use is associated with dietary prohibitions and close observation because of the possibility of hypertensive crisis. The patient response to antidepressant treatment is usually determined after a few weeks, and antidepressant treatment is usually determined individually depending

on the characteristics of the patient, comorbidity, previous treatment history, and side effects. Close dose titration, observation of therapeutic response, adverse reactions, and potential drug interactions are also effective pharmacotherapy methods. Hence, effective antidepressant therapy is not only dependent on the choice of effective medications but also on an all-encompassing clinical monitoring and patient-based care to obtain the best therapeutic results.[24].

Pharmacist Initiated Optimization Plans.

The pharmacist-based optimization interventions are important in enhancing the effectiveness, safety, and overall results of the antidepressant pharmacotherapy in major depressive disorder (MDD) patients. Pharmacists being experts in medication and accessible healthcare professionals are best placed to help in the optimization of the treatment of mental health by managing medication comprehensively, counseling the patients, and working with physicians and other healthcare professionals. A pharmacist has one of the leading roles to provide a careful review of medications to make sure that antidepressant treatment suits the clinical status of the patient, comorbid and concomitant drug use. Depression in many patients is also accompanied by chronic pathologies like diabetes, cardiovascular diseases, anxiety disorders or substance use disorders and may be treated with several medications predisposing to drug-drug interactions. Pharmacists can prevent and recognize these interactions by assessing the medication history of the patient and prescribing less dangerous or changes in dose where needed.[25] The other significant attribute of pharmacist-led optimization is that it helps in the process of selection of the right antidepressant drugs depending on the patient-specific features like age, the severity of the symptoms, the previous response to treatment, comorbidity, and the possibility of developing adverse effects. Antidepressants that have a lower sedation potential can be prescribed by pharmacists to patients who need to be alert during the day or when there are minimal cardiovascular consequences on a patient with cardiac conditions or the elderly. Pharmacists also contribute significantly in terms of providing dose titration and switching plans, especially in patients that are not responding to the therapy adequately or with unbearable side effects. Pharmacists can assist prescribers by keeping close track of patients and ensuring that treatment regimens are optimized to produce the best therapeutic outcomes with the least adverse effects. Another significant element of pharmacist-led approaches is patient education and patient adherence.[14] A large proportion of people do not continue in antidepressant treatment because of the delayed effect, there is false belief that medication is addictive and fear of side effects. Pharmacists give a detailed counseling on the expected course of the therapeutic progression, how to receive the medication correctly, how to deal with the most frequent side effects, and why it is necessary that the treatment is taken regularly not to relapse. Pharmacists ensure the development of trust and adherence by engaging with the patient continuously, which forms the key to positive treatment results.[26] Moreover, pharmacists are involved in the follow-up of therapeutic response in the form of symptom improvement, early detecting the signs of treatment failure, and warning signs of depressive symptoms worsening or suicide thoughts, which are to be addressed by means of urgent medical care. They can also encourage non-pharmacological methods such as stress management, sleep hygiene, physical exercise, and referral to psychological counseling services as they support pharmacotherapy in the management of depression. Combining clinical expertise, patient education, and interprofessional healthcare, pharmacist-led optimization initiatives contribute to a substantial increase in medication safety, better treatment adherence, and personal approach and patient-centered care in the treatment of major depressive disorder.[27]

Medical Choice on Patient Profile.

The choice of medications on the basis of patient profile is an important part of successful pharmacotherapeutic management of major depressive disorder (MDD) as specific distinctive patient features have a great impact on the response to treatment, tolerability, and global clinical outcomes. Depression is a heterogeneous disorder and patients tend to manifest different patterns of symptoms, comorbid disorders, medical history and psychosocial factors, which should be taken into consideration in order to choose the right antidepressant drug. [14]The individual-based treatment choice maximizes the therapeutic returns at a minimum risk of treatment adverse effects and discontinuation. Severity and nature of depressive symptoms are one of the most important in choosing medication. As an example, antidepressants with anxiolytic properties, including selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRIs), can help patients with high levels of anxiety, agitation, and vice versa can be helped by activating agents, including bupropion. Another determinant is the age of the patient, which is more prone to drug adverse events such as orthostatic hypotension, anticholinergic effects and cardiac complications in the elderly population [28]. The antidepressants of a good safety profile and reduced risk of drug interactions are usually desired in this situation. Comorbid medical conditions are also significant in the choice of medication to use. CVD patients might need antidepressants with minimal cardiac weight whereas patients with chronic pain disorders may use antidepressants that have SNRI effects on them such

as antidepressants and analgesics. In the same vein, antidepressants such as mirtazapine which have sedative and appetite-stimulating properties might be effective in patients whose sleeplessness or weight loss cannot be attributed to any other cause. On the contrary, those who fear weight gain or are prone to drowsiness will be more advantageous to medications like bupropion, a more activating medication profile. The other critical factor is the history of previous treatment since patients who have previously reacted well to a specific antidepressant are more likely to respond to that medication in future incidences[29]. On the other hand, those drugs whose side effects were intolerable or their response was inadequate, should be avoided in general. The presence of potential drug to drug interaction should also be given serious consideration, especially when the patient is taking a number of drugs in case of chronic illnesses. To avoid the antidepressant-induced toxicity, pharmacists and clinicians should consider the drug history of patients to avoid interactions that can lead to a decrease in antidepressants or predisposition to toxicity. The preferences of the patients, their lifestyle, and their ability to adhere to the treatment should be included in the decision-making process as well since these may be a very significant factor in the success of the treatment. Through using antidepressant treatment according to patient profile, healthcare providers will be able to enhance the level of treatment tolerability, increase the level of medication adherence and eventually improve clinical outcome in the management of major depressive disorder.[30].

Switching Strategies and Dose Titration.

The use of dose titration and switching are very crucial elements of effective antidepressant therapy because the individuals have different responses to the pharmacological therapy and may need specific adjustments in order to gain maximum therapeutic benefits. The gradual dose titration of the antidepressant medications is usually necessary to reach the balance between the efficacy and tolerability as the clinician may observe the reaction of the patient without causing the adverse effects as much. In most instances, a low starting dose of treatment is used, especially in elderly, or patients with comorbid medical conditions to minimize the risks of side effects like gastrointestinal disturbances, sedation, dizziness, or anxiety.[31] The dose is then steadily raised with a series of weeks depending on clinical response and tolerance of the patient. Since it may take several weeks before the majority of antidepressants can provide their maximum curative effect, close patient follow-up at the initial phases of the therapy will be required to evaluate the progress in the symptoms and identify any adverse response. In the case where a patient experiences partial improvement yet does not completely get rid of the symptoms, clinicians can further increase the dose within the recommended therapeutic index before switching drugs. But when the patient does not provide responses satisfactorily after the due trial period which is generally four to eight weeks on therapeutic dose, the possibility of switching to an alternate antidepressant can be suggested. [32]In practice, the switch strategies are frequently used in cases where patients are not provided with an adequate therapeutic effect, where the side effects prove to be unacceptable or in case the patient exhibits certain clinical symptoms that demand a new pharmacological treatment. A number of switching techniques are applied in clinical practice such as direct switching, cross-tapering, and washout techniques. Direct switching refers to the requirement to stop taking antidepressant and immediately initiate a new antidepressant, which might be appropriate in cases of the transition of medications with a similar pharmacological profile. The idea behind cross-tapering is taking the time to wean the dose of the original antidepressant and at the same time start taking the medication, and up-tap, in order to cover the therapeutic area and minimise the amount of withdrawal symptoms.[33] Washout of some drugs like monoamine oxidase inhibitors (MAOIs) might be required when one decides to change to other antidepressants to avoid severe medication interactions like serotonin syndrome. The selection of switching strategy will be determined by such factors as the half-life of the medications discussed, possible drug-drug interactions, and the clinical stability of the patient. Besides changing drugs, augmentation plans can also be taken into consideration when partial response is identified, in which another drug like an atypical antipsychotic, mood stabilizer, or any other antidepressant is added to improve the effect of treatment. Pharmacists are essential in the management of dose titration and switching techniques by focusing on medication safety, finding possible interactions, providing information on dosage changes, and adherence during change of treatment. With proper dose optimization and the proper use of switching strategies, clinical and pharmacists can enhance effectiveness of antidepressants and reduce negative consequences of its use, finally helping to achieve better clinical treatment of major depressive disorder.[7]

Table 1: Major Antidepressant Classes Used in Major Depressive Disorder

Antidepressant class	Common examples	Main mechanism	Important clinical uses	Common adverse effects / precautions
Selective Serotonin Reuptake	Fluoxetine, Sertraline, Escitalopram,	Inhibit serotonin reuptake and increase	First-line in many patients due to good	Nausea, insomnia, sexual dysfunction,

Inhibitors (SSRIs)	Paroxetine	serotonin availability	efficacy and tolerability; useful in depression with anxiety	headache; caution with serotonin syndrome and drug interactions
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine, Desvenlafaxine, Duloxetine	Inhibit reuptake of serotonin and norepinephrine	Useful in depression with fatigue, pain symptoms, or partial SSRI response	Nausea, sweating, restlessness, increased blood pressure, withdrawal symptoms if abruptly stopped
Tricyclic Antidepressants (TCAs)	Amitriptyline, Nortriptyline, Imipramine	Block reuptake of serotonin and norepinephrine; also affect other receptors	Considered in selected or treatment-resistant cases	Anticholinergic effects, sedation, orthostatic hypotension, cardiac toxicity; caution in elderly and overdose
Monoamine Oxidase Inhibitors (MAOIs)	Phenelzine, Tranylcypromine	Inhibit monoamine oxidase and prevent breakdown of monoamines	Reserved for resistant or atypical depression in specialized settings	Hypertensive crisis with tyramine-containing foods, significant drug interactions, serotonin syndrome risk
Atypical Antidepressants	Bupropion, Mirtazapine, Trazodone	Vary by drug; may enhance norepinephrine/dopamine or serotonergic activity	Chosen according to symptom profile such as insomnia, low appetite, fatigue, or sexual dysfunction concerns	Bupropion: activating, insomnia; Mirtazapine: sedation, weight gain; Trazodone: sedation, dizziness

Table 2: Patient Profile–Based Selection of Antidepressants in Major Depressive Disorder

Patient profile / clinical situation	Preferred antidepressant approach	Rationale	Important caution
Depression with prominent anxiety	SSRI or SNRI	Effective for depressive symptoms with associated anxiety	Monitor for early agitation or anxiety worsening
Depression with fatigue / low energy	Bupropion or activating antidepressant	May improve energy, motivation, and reduce sexual side effects	Avoid or use carefully in patients prone to insomnia or seizure risk
Depression with insomnia	Mirtazapine or trazodone	Sedative properties may improve sleep and mood	Monitor daytime sedation and falls, especially in elderly
Depression with poor appetite / weight loss	Mirtazapine	May improve appetite and body weight	Use cautiously in patients concerned about weight gain
Elderly patients	SSRIs with safer tolerability profile	Better tolerated than TCAs and MAOIs in many cases	Watch for hyponatremia, falls, drug interactions, polypharmacy
Patients with cardiovascular disease	Antidepressants with lower cardiac risk, often selected SSRIs	Lower risk compared with TCAs	Avoid TCAs when cardiac toxicity risk is high
Patients with chronic pain syndromes	SNRI such as duloxetine	May improve both depressive symptoms and pain	Monitor blood pressure and tolerability
Patients with previous good response to a drug	Reuse previously effective antidepressant when appropriate	Past response often predicts future benefit	Review prior adverse effects and current comorbidities

Patients with polypharmacy	Drugs with lower interaction potential	Helps reduce clinically significant drug–drug interactions	Thorough medication review is essential
Patients concerned about sexual dysfunction	Bupropion or alternatives with lower sexual adverse effect burden	Can improve adherence and satisfaction	Assess suitability based on anxiety, sleep, and comorbidities

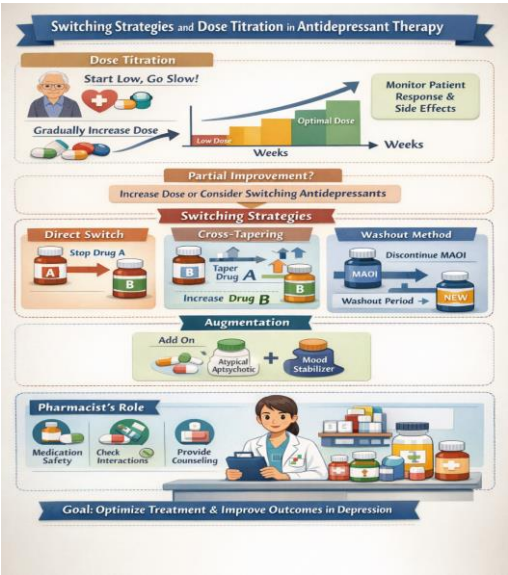

Figure: 1 Switching Strategies and Dose Titration.

Therapeutic Response Monitoring.

Therapeutic response monitoring is an important part of pharmacological treatment of the major depressive disorder (MDD) because of the need to provide evaluation of the treatment efficacy and patient safety as well as timely adjusting the treatment, where appropriate. The development of antidepressant drugs takes time in the form of several weeks and until the clinical change is evident, it is necessary to conduct methodical and constant observation during the initial stages of treatment and the subsequent stages. Clinicians typically determine therapeutic response by reviewing the core depressive symptoms like mood, interest in daily activity, sleep cycles, appetite, concentration, vitality and general ability to get about. Objective measures of symptom severity and tracking progress in time are most commonly done with standardized assessment tools like depression rating scales: the Patient Health Questionnaire (PHQ-9), Hamilton Depression Rating Scale (HDRS) or Beck Depression Inventory (BDI). Such tools present the clinician with a measurable information which assist him or her to decide whether the patient is in remission, partial response, or insufficient improvement.[7] Follow-up visits are usually advised in the first two to four weeks of antidepressant therapy to assess the tolerability of medication, and to identify the early symptoms changes. In these examinations, medication adherence is also checked since nonadherence is among the most frequent cause of subpar results of treatment in depression. Patients can stop taking medication because of side effects, misconceptions regarding antidepressants, or because they do not feel better which is why patient education and frequent communication are important parts of observation. Pharmacists have an important role in promoting this process by enhancing adherence rates, helping patients resolve issues related to the use of medication, and determining obstacles to regular therapy. Besides assessing the level of symptom improvement, the functional outcomes that should be monitored include the capacity of the patient to complete the daily activities, social relations as well as their capability to resume working or studying. Positive changes in the quality of life and functional recovery are valuable signs of effective treatment that cannot be limited to the reduction of symptoms.[30] Medical personnel should also be cautious of the possible negative consequences of antidepressant treatment since side effects can be a factor in compliance and general treatment outcome. Such adverse effects like nausea, insomnia, sexual dysfunction, weight changes, or even fatigue are to be monitored and handled accordingly. In case patients do not demonstrate any considerable progress at the end of the sufficient course of treatment typically four to eight weeks with a therapeutic dose, clinicians could rethink the dose, change medications, or use augmentation measures. Frequent monitoring can also be used to detect the

deterioration of symptoms or onset of suicidal thoughts especially at the beginning of the treatment process when patients are at the highest risk. So, therapeutic response monitoring is the key to maximizing antidepressant treatment, enhancing patient outcomes, and safety and effectiveness of managing major depressive disorder with the help of a collaborative healthcare system.[35]

CONCLUSION

Treatment of major depressive disorder with pharmacotherapeutic intervention needs to be holistic, personalized and carefully monitored since depression is a multifaceted and recurrent mental condition that can be caused by biological, psychological and social factors. Despite the existing variety of antidepressant drugs, such as the SSRIs, SNRI, TCA, MAOIs, and atypical antidepressants, the effective treatment is not only in the selection of drugs but also in paying close attention to the patient-specific features, comorbidity, adherence and the tolerance level to the drugs, and the potential of the interaction of the drugs. Delayed therapeutic response, partial or insufficient remission, and adverse effects of current medications, as well as options of exacerbating symptoms or suicide attempts at an early treatment stage, complicate depression treatment. Titration of dose, rotation, and frequent follow- up, as well as oral therapeutic supervision should be considered vital to enhance clinical outcome and minimize treatment failure. Besides this, there are the incorporation of lifestyle change and non-pharmacological interventions, including physical exercise, sleeps, nutritional enrichment, stress, and psychological interventions, which have valuable supplementary advantages that enhance the general treatment plan. In this context, pharmacists have a very useful and a more acknowledged role in depression care. Their knowledge of medication therapy management will allow them to make a significant contribution to the antidepressant choice, dose modification, screening of the interactions, educating the patient, encouraging adherence, and early recognizing of adverse event or warning signs that necessitate immediate action. Since pharmacists frequently are one of the most available health care providers, they are in a perfect position to sustain steady contact with patients and facilitate care continuity especially in community and outpatient environments. Their participation also enhances multidisciplinary mental health services as the communication among the patients, prescribers, and other members of the healthcare team is enhanced. In addition, patient education by pharmacists can lessen the stigma, explain expectations of treatment and motivate patients not to become inactive in the therapy despite the lag in benefit that is common with antidepressants. Pharmacist intervention may be of the essence to avoidable complications and safe medication use in patients with comorbid medical illnesses or polypharmacy. All in all, evidence-based, patient-centered, and collaborative approaches to managing major depressive disorder, which involve the combination of pharmacological with psychosocial and lifestyle interventions, are to be adopted. The role of pharmacists in mental health care might be strengthened to a large extent to improve medication safety, adherence, therapy response, and quality of life. Thus, pharmacist-led care can be regarded as a critical part of the modern approach to managing depression with the aim to enhance its long-term outcomes and decrease the personal and social impact of this significant mental health problem.

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