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AN OVERVIEW ON UNIPOLAR MAJOR DEPRESSION IN ADULTS DIAGNOSIS AND MANAGEMENT APPROACH

Hisham Fawaz Babagi[1], Noor Mohammed M Aljifri[2], Raghdah Suliman O Dali[3], Noran Salah M Jan[4], Lamya Mesfer Alqahtani[5], Wael Mohammed Abusrrah[5], Ali Saeed A Aladalah[5], Zahra Ali M Alqurus[6], Abdullah Mansour Alswilem[7]*, Dina Mohammad Aljabri[8], Ibrahim Saeed Alghamdi[9]

1. *Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.*
2. *Pharmacist, Fakeeh Hospital, Jeddah, KSA.*
3. *Pharmacist, International Extended care center, Jeddah, KSA.*
4. *Faculty of Medicine, Battarjee Medical University, Jeddah, KSA.*
5. *Faculty of Medicine, King Khalid University, Abha, KSA.*
6. *Faculty of Medicine, Medical University of Lodz, Lodz, Poland.*
7. *Faculty of Medicine, Almaarefa University, Riyadh, KSA.*
8. *Faculty of Medicine, Ibn Sina National College of Medicine, Jeddah, KSA*
9. *Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan*

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ABSTRACT.

Background: Unipolar major depression is commonly encountered in everyday clinical practice, especially in the primary-care setting. Its presentation is very variable, making missed diagnoses a common occurrence; with much dire consequence (e.g. suicide), careful examination of suspected cases and correct identification of affected patients becomes ever so important, not only to specialists but also to general practitioners, whom the majority of cases will present to. Unipolar major depression is a chronic, lifelong disease with a high recurrence rate and worsening prognosis with repeated episodes; therefore, appropriate, timely management in addition to patient education and guidance of their expectation is key to improving clinical outcomes and patient satisfaction. **Methodology:** The PubMed database and the MeSH tool were employed to collect the articles used in this review. Relevant articles were obtained, if possible, and reviewed. **Objectives:** Our goal was to perform a comprehensive review of recent review articles that examined unipolar major depression in adults in addition to etiology, epidemiology, pathogenesis, clinical features and types, diagnosis, management, or prognosis. **Conclusion:** Unipolar major depression is a common mental health problem presenting to the primary-care setting, with many missed diagnoses due to heterogenous presenting features. Management options include psychological therapy, pharmacological therapy, or a combination of both. Early detection and treatment considerably improve the clinical outcome; therefore, it's imperative that physicians, whether specialists or general practitioners, familiarize themselves with its clinical picture.

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Introduction

- **Definitions**

The term "depression" can mean a multitude of things; therefore, it is important to understand what such a term may refer to avoid confusion. Firstly, it can indicate a mere state of the mood in a particular period, in which a person may feel (e.g. sad, empty, hopeless, etc.), or is observed by other individuals around them (e.g. tearful appearance). A depressed mood by itself is not necessarily a pathologic condition, as it may manifest as a normal response to loss or failure, and may often be a healthy, adaptive response provided it does not happen too frequently or persist for too long. Nevertheless, a depressive mood can also be a clinical manifestation of multiple psychiatric and medical disorders [1-3]. Secondly, the term depression may refer to a psychiatric syndrome that includes depressed mood as a manifestation in addition to others. Commonly

Corresponding Author: Abdullah Mansour Alswilem, Faculty of Medicine, Almaarefa University, Riyadh, KSA. Email: Abdullah.m.alswailem @ gmail.com

encountered depressive syndromes include major depression, minor depression, as well as dysthymia. [4] Lastly, "depression may refer to a single, clinically distinct medical condition, namely unipolar major depression. This entity is the main focus of this review.

- **Epidemiology**

Depressions is a common psychiatric disorder with an increasing prevalence year after year, especially in developed countries. [5] In the United States, the 12-month prevalence of major depression was estimated to be around 6%, [6] while the life-time prevalence was 17%. [7] Depression is twice more common in females than males, [8] with a predominantly white distribution. [9] Also, older-aged individuals were found to be less likely to suffer from depression when compared with their younger counterparts, [9] although certain subgroups of the older population are more likely to have depression than others. [10] Globally, the prevalence of depressive disorders is comparable to the United States, with the persistence of female-predominance across all regions. [11]

Methodology

PubMed database was utilized for the selection of relevant articles, with the use of the MeSH tool to help filter the results. The following keywords were used in the MeSH search builder: (((depression) AND (classification)) OR (epidemiology)) OR (etiology) OR (pathophysiology) OR (diagnosis) OR (therapy) OR (prevention and control). Articles were included if their topic was relevant to the MeSH filters and their population of interest was adults. Articles were excluded if their topic was irrelevant to the MeSH filters or if the population examined was children or adolescents while placing articles focusing on older adults as low priority. Relevant articles were collected and reviewed where possible, and appropriate articles were cited in this report.

Etiology & Pathogenesis

The underlying pathophysiological mechanism in depression is complex and remains poorly understood to this day. [12] Nevertheless, the evidence we have available today points toward a complex molecular interplay between neurotransmitter availability and receptor sensitivity and regulation. [12] Environmental, epigenetics, and immunology play a predominant role in the pathogenesis as well, [12] with a 60-70% contribution from environmental factors compared to only 30-40% from genetic factors. [13] This contribution of environmental factors is thought to be mediated by stressful events throughout the patient's life that lead to alteration of the hypothalamic-pituitary-adrenal axis leading to the modification of the normal stress response. That, in addition to genetic contributors, leads to further alteration of the structure and function of the brain parenchyma and leads to changes in the level of available neurotransmitters. [13] These changes include a decrease in the levels of serotonin and its precursor tryptophan, as well as changes in dopamine and norepinephrine (the monoamine hypothesis). Correction of these abnormalities is the basis of many pharmacological therapies available today for depression. [13] Chronic inflammation has been also implicated in the pathogenesis of depression, with the observation that patients with chronic inflammatory diseases are at increased risk of developing depression, and that therapeutically administered cytokines, such as interferon-gamma, can trigger the onset of depression. [14] Furthermore, the ability of neurons to grow and organize adaptively (termed neurogenesis and neuroplasticity, respectively) is reduced in individuals with depression. Proteins that regulate neurogenesis are diminished in depressive patients as well, including brain-derived neurotrophic factor (BDNF). Also, structural brain changes have been linked to depression, including reduced hippocampal volume, as well as that of the dentate gyrus, in patients suffering from depression. [14] Functional brain changes have also been linked to depression, with the finding that the amygdala tend to have increased activity and connectivity in depressed patients, with hypoactivity and decreased connectivity in other areas of the brain, including insula and dorsal lateral prefrontal cortex. [15] In spite of the fact that our understanding of the pathophysiological mechanisms underlying depressive disorder has developed greatly in the past few decades, it remains considerably difficult to apply this knowledge into developing clinically relevant, disease modifying therapeutics.

Clinical Features [1]

The onset of unipolar major depression has bimodal distribution; the majority of patients presenting in their 20s, with a second peak occurring in the 50s. [8]

Risk factors for the development of depression include, as mentioned previously, being in the high-risk age groups, the female sex, in addition to high levels of stress, previous episodes of depression, divorce or separation from a spouse, previous history of trauma, and having a first-degree relative with a major depressive disorder. [16]

It is crucial to recognize that the clinical presentation of unipolar major depression is extremely variable and heterogeneous, especially when it comes to the age of onset, presenting symptoms, course of illness, and severity. Unipolar major depression is also part of a continuum of diseases, starting from isolated, subsyndromal depressive episodes, ending with unipolar major depression.

- **Dysphoria**

Depressed mood (dysphoric mood or dysphoria) is essential to the presentation of unipolar major depression. The patient may have many descriptions for such a symptom, including being sad, "blue", "under the weather", hopeless, or discouraged. Some patients may deny feeling depressed in contradiction with their sad or tearful appearance.

- **Anhedonia**

Anhedonia is the loss of interest or the loss of the ability to feel pleasure from previously pleasurable activities is also one of the cardinal clinical features of unipolar major depression. Patients may describe this symptom by saying that they "don't care anymore", or by stating that they have lost interest in people, hobbies, or previous interests (e.g. losing interest in sex).

- **Sleep disturbances**

Sleep problems are commonly present in unipolar major depression as well as other depressive disorders. Such problems can either be insomnia or hypersomnia.

- **Appetite/weight changes**

Change in appetite or weight is a common symptom of unipolar major depression. Such changes go both ways, as loss of appetite or increased appetite can both be a presenting complaint of a patient with depression; either weight loss or gain can be present in depressed patients as well.

- **Lethargy and fatigue**

Lack of energy may be a major complaint in a depressed patient. Patients may complain of constantly feeling tired, or exhausted.

- **Neurocognitive dysfunction**

Neurocognitive dysfunction can be defined by marked deficits in a wide array of functional domains, including concentration, attention, memory, speed of processing information, verbal fluency, executive function (e.g. problem solving, planning, reasoning, and impulsivity), social awareness, and cognition, and cognitive flexibility. Such symptoms tend to be more severe in older patients than younger patients.

- **Psychomotor disturbances**

Psychomotor disturbances can be either agitation, manifest by increased motor activity in a repetitious non-productive manner, or retardation, characterized by slowing of speech, thinking, or body movements, often with latency responding to questions. While psychomotor disturbances are not very common in depressed patients, their presence implies the presence of more severe disease.

- **Guilt and feeling of worthlessness**

Depressed patients frequently have a feeling of inadequacy, failure, inferiority, worthlessness, or inappropriate guilt. These patients may misinterpret minor setbacks as evidence of their failure.

- **Suicidal ideation**

Suicidal ideation can be passive, with the patient thinking that they are not worth living or that others would be better off if they were dead, or active, with frequent thoughts of wanting to die or attempt suicide; such thoughts may also be accompanied by active planning to commit suicide, and many patients eventually do so.

It is helpful to recognize that, while the presentation of unipolar major depression is variable, certain features are present in most patients and therefore are considered as core clinical features. [17] These include sad, irritable, or anxious mood; loss of interest or pleasure; impaired concentration and decision making; worthlessness and inappropriate guilt; hopelessness; fatigue or loss of energy. [18]

Clinical types

The Diagnostic and Statistical Manual, Fifth Edition (DSM-5) describes the following subtypes in an attempt to better classify patients to have greater therapeutic specificity: anxiety, atypical, catatonic, melancholic, mixed features, peripartum, psychotic, seasonal. The classification of patients into these subtypes can many therapeutic implications. For instance, depression with melancholia generally responds better to pharmacotherapy and electroconvulsive therapy. Similarly, psychotic depression usually responds very well to electroconvulsive treatment. [4, 14]

Diagnosis

The diagnosis of unipolar major depression is made after a major depressive episode has lasted for 2 weeks or longer. A major depressive episode is defined by the DSM-5 criteria cited in Table 1. [4] Sometimes the patient may have symptoms of depression that are insufficient in number or severity to satisfy the criteria, those are sometimes referred to as subthreshold depressive symptoms. It is important to recognize that subthreshold depressive symptoms are early indicators of a major depressive episode. [14]

Management

The management of unipolar depression can be achieved using psychological therapy, pharmacological therapy, or both. [18] The goal is to induce complete remission of the disease and minimize the recurrence of the episodes. Before initiating, however, it is important to implement some general measures such as withdrawing drugs that can affect the patient's mood (e.g. steroids) and encourage the patient to make lifestyle modifications that may improve the course of the disease such as maintaining good sleep hygiene, regular exercise, and healthy eating behaviors. [19] The general approach to management is that mild unipolar major depression can be treated with psychotherapy alone; in fact, psychotherapy is the first-line of treatment in mild depression. Psychotherapy can also be effective in cases with moderate disease, although often it has to be combined with pharmacotherapy to achieve satisfactory results. In severe cases of unipolar major depression, pharmacotherapy is the first-line of management, with electroconvulsive therapy being conserved for treatment-resistant cases. [14]

Table 1: DSM-5 Criteria*

Diagnostic Condition	Symptoms
Five or more of these symptoms during the same 14 days period, with these symptoms fulfilling two conditions: 1. a change from a previous state of function, 2. at least one symptom of depressed mood or loss of pleasure or interest	Depressed mood on most days
	Diminished interest in most activities on most days
	Significant weight loss or anorexia
	Insomina or hypersom,nia on most dauys
	Psychomotor agitation or retardation on most days
	Fatiguability on most days
	Feelings of worthlessness on most days
	Indecisiveness and decreased concentration on most days
	Recurrent thoughts of death on most days
*Excerpt from American Psychiatric A. Diagnostic and statistical manual of mental disorders: DSM-5 5th ed. Washington, D.C.: American Psychiatric Association; 2013.	

- **Psychological therapy**

Options for psychological therapy available include cognitive-behavioral therapy (CBT), interpersonal therapy, problem-solving therapy, psychodynamic psychotherapy, behavioral activation, and supportive psychotherapy. [20] Of those, CBT and interpersonal psychotherapy are by far the most popular and are frequently utilized as initial treatment as a result of them being more widely studied than other types of psychotherapies. [21] Nevertheless, there is no evidence to support that one of the major psychotherapies is superior to the other, and the ultimate choice may come down to availability and patient preference. [22, 23]

Table 2: DSM-5 Severity of Depression*

Depression Severity	Description
Mild	Few symptoms required for the depression diagnosis, minor impairment in social / occupational functioning
Moderate	Frequency and intensity of symptoms and functional impairment are in-between mild to severe
Severe	Frequency of symptoms is in excess of diagnostic criteria, distress and management resistance occur as symptoms interfere with daily living and occupation
*Excerpt from American Psychiatric A. Diagnostic and statistical manual of mental disorders: DSM-5 5th ed. Washington, D.C.: American Psychiatric Association; 2013.	

CBT involves helping patients identify negative thinking patterns that contribute to their depressed mood; it provides a reliable method for the patient to address these negative thoughts and, when possible, replace them with healthier, positive thoughts.

Interpersonal therapy, on the other hand, focuses on recognizing difficulties within the patient's relationships, particularly interpersonal conflict and problems in social interactions (e.g. marital difficulties).

In patients with mild to moderate depression, psychotherapies seem to be as effective as pharmacotherapy. This, however, is not true for severe depression, mainly because the disease prevents patients from engaging in psychotherapy, to begin with. [24] Psychological therapy has many advantages, including that their positive outcomes persist up to a year or more after cessation of therapy, in contrast to an antidepressant, whose effect lasts only for the period of administration. (Table 2) [14]. The safety profile of psychological therapy compared to antidepressants is also a major advantage. On the other hand, cost and availability are major disadvantages of psychological therapy as very few trained therapists available. [25]

- **Pharmacotherapy**

The basis of pharmacological therapy in depression is the monoamine pathway. Nevertheless, other pathways are being targeted by newer drugs, such as the N-methyl-D-aspartate (NMDA) receptor pathway.

Currently, the antidepressants used in the treatment of unipolar major depression are the second-generation antidepressant, these include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, and serotonin modulators. Older drugs that were previously used in the management of depression include tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).

SSRIs are usually the first choice of therapy in patients in need of pharmacotherapy, this is because of their good efficacy and safety profile demonstrated in clinical trials. [26] If other choices are desirable, any of the other second-generation antidepressants are a good choice, as they all offer comparable efficacy. [27] The first-generation antidepressant (TCAs and MAOIs) are not used in initial management anymore, as they have a questionable safety profile and numerous concerning adverse reactions in comparison with their newer alternatives. Furthermore, in some cases, certain medications are probably well more favorable for the patient's condition, both in terms of efficacy and tolerability, to specific subtypes of unipolar major depression, and can be chosen selectively for such cases. For example, the use of sedative antidepressants in depression with anxiety or insomnia can be particularly helpful; similarly, the utilization of activating antidepressants for depression with psychomotor retardation can be of extra benefit to the patient. [14]

Prognosis

Unipolar major depression usually has an insidious onset, although an abrupt onset can be reported sometimes. Its course throughout the patient's life is largely variable; in most patients, it takes an episodic course, and generally, the patients feel well between episodes. Nonetheless, unipolar major depression is a lifelong disease, with a very high lifetime recurrence rate of 80%. [28] Furthermore, the chance of recurrence increases with each episode. Older patients face a significantly less favorable outcome. [29] Even though more than half of patients recover within 6 months, and nearly 75% recover within a year, there is a significant proportion of patients (about 27%) who never recover and develop a chronic depressive state. [30]

Conclusion

Major depression is a prevalent mental health disorder with a varying clinical picture, which represents a challenge for the clinician to suspect it when appropriate and make an appropriate diagnosis, especially with most cases presenting in the primary-care setting. Most patients affected are early adults or senior citizens, and females are affected nearly twice as much as males. With a limited understanding of its widely complex pathogenesis, it is still not possible to target specific pathways in the pathogenetic process and individualize treatment for patients. Management options include psychological therapy, pharmacological therapy, or a combination of both.

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