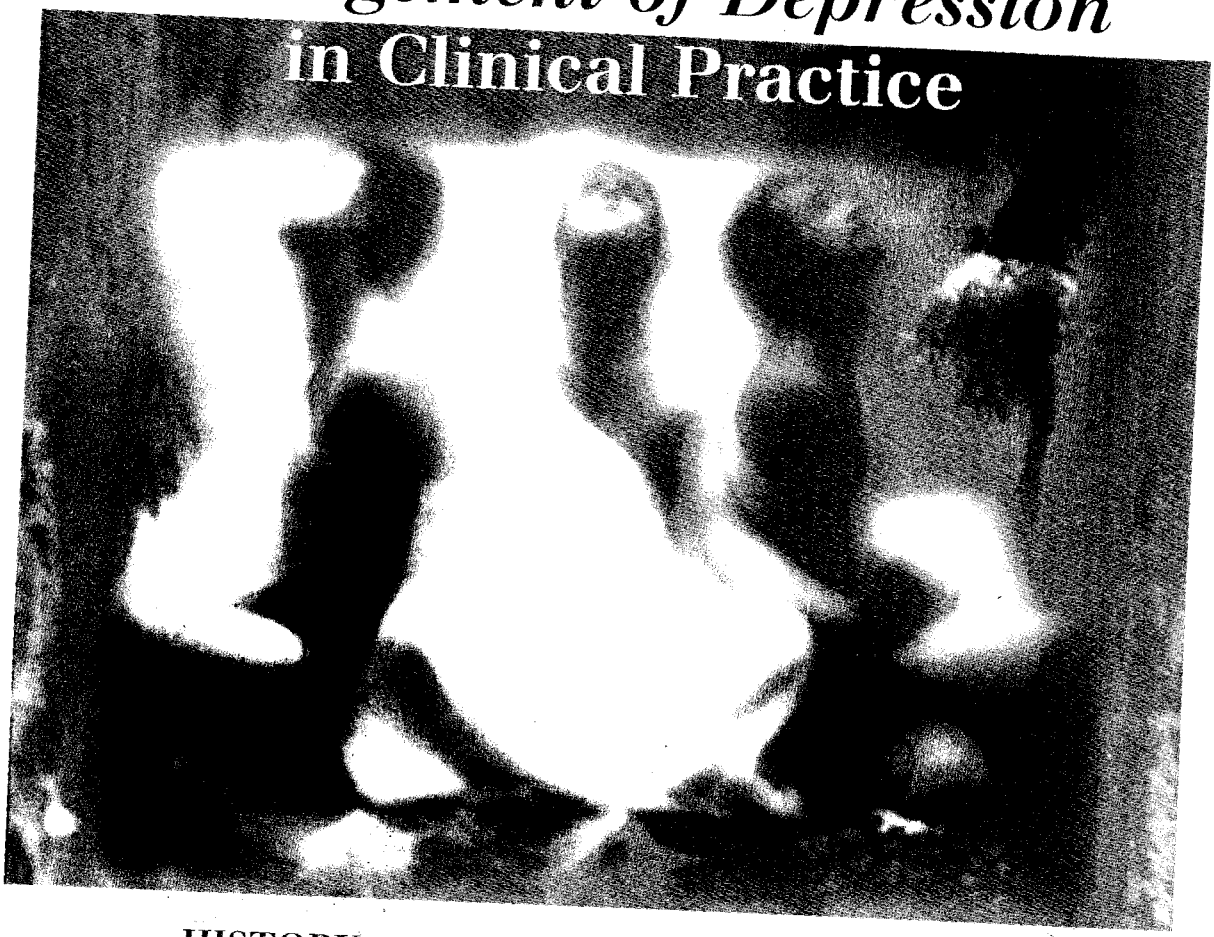
Management of Depression in Clinical Practice



HISTORY

Depression is the commonest psychiatric disorder encountered in clinical practice. It has been reported since antiquity. There has been mention about depression in Old Testament and Ramayana and Mahabharata, where Ram and Arjuna had episodes of depression.

EPIDEMIOLOGY

The lifetime prevalence of major depression varies from 5-15%. It is more common in women than men by a ratio of 3:2, which may be due to hormonal influences, effects of childbirth and differing psychosocial stressors for women and men. Its incidence is higher in primary care patients and in medical inpatients.

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The mean age of onset of depressive episode is about 40 years. It can also have its onset in childhood or in the elderly, though it is uncommon. Recent studies have shown an increasing incidence below 20 years which may be related to increased use of alcohol and other substances of abuse in that age group. Prevalence does not differ from race to race. Major depression occurs more in persons who have no close interpersonal relationship or who are divorced or separated.

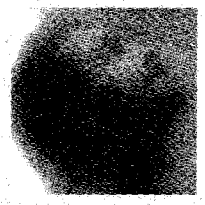
AETIOLOGY

The causal basis for depression is still not known. It can be artificially divided into biochemical, genetic and psychosocial with an interaction among themselves.

Biological factors

Biogenic amines

Abnormalities in serotonergic activity namely diminished availability of L-tryptophan - the precursor of serotonin, impaired serotonin synthesis, release and decreased density of $5HT_1$ receptor in the hippocampus and amygdala have been reported in depression. Depressed patients are also characterized by an elevated central metabolite of norepinephrine (NE) namely MHPG, a compensatory mechanism for reduced NE activity. GABA levels in plasma and CSF have also been found to be low in depressives, that may be a trait marker of depression. Dopamine also has a speculative role in depression with decreased levels being reported. Elevation of dopamine transmission in nucleus accumbens is the final common pathway in the behavioral action of antidepressants. Recent research is focusing on the underlying intracellular changes in depression namely adenyl cyclase, phosphatidyl inositol, calcium regulation etc after binding of neurotransmitters to its receptors.



Neuroendocrine dysregulation

A number of studies have reported hypercortisolemia, elevated CRF, pituitary and adrenal hypertrophy in depression. Depression is associated with non-suppression of cortisol production on challenge with external administration of dexamethasone (dexamethasone non-suppresion test) and this correlates with severity of depression. In the same way there is blunted ACTH response to exogenous CRF administration. TRH challenge produces blunted TSH response in depression. Depressed patients also have blunted growth hormone response to clonidine challenge. Other endocrine dysregulations reported are decreased nocturnal secretion of melatonin, decreased FSH and LH, reduced testosterone levels in men and decreased prolactin response to tryptophan challenge in women.

Neuroimaging

Structural and functional brain imaging studies show ventricular enlargement, increased sulcal prominence, reduced blood flow to frontal lobes and smaller putamen and caudate volumes. All these suggest involvement of limbic circuit and related connections in depression.

Polysomnography

Sleep EEG studies have reported reduced REM latency, increased length of REM sleep in first half of sleep and diminished delta or slow wave sleep in depression.

Genetic studies

Family studies, adoption studies and twin studies show high risk of depression in first-degree relatives and higher concordance rate in monozygotic twins.

Psychosocial factors

Life events

In many depressed patients, the episode may be precipitated by life events such as death of close relatives, martial or family conflicts, financial problems etc, but it is difficult to separate the life event and onset of depression as independent factors in many cases.

Premorbid personality

No single personality is prone to develop depression. However some characteristics such as dependency, introversion, obsessionality, breakdown under stress and lack of energy are more frequently seen in premorbid personality of depressed patients.

Psychoanalytic and other theories

Some of these theories are "aggression turned inward" (Abraham), traumatic separation from loved object (Freud), and faulty thinking pattern like negative view of self, world and future (Beck) etc.

SYMPTOMATOLOGY

Depressed mood

This is the characteristic feature of depression. Patients complain of feeling unhappy, miserable or may have weeping spells. Some patients may show undue irritability instead of depressed mood.

Loss of interest or anhedonia

Loss of interest and inability to enjoy pleasurable activities like film or music is another frequent complaint.

Anxiety

Many patients feel tense; are unable to relax and have difficulty paying attention and concentrating. This is usually accompanied by somatic symptoms like dryness of mouth, palpitation, indigestion, sweating, headache, giddiness, etc.

Sleep disturbance

This can be in the form of delay in getting sleep or getting up 2 or 3 hours before the usual time of awakening or frequent awakening during night. Some atypical cases can have hypersomnia as well. Another complaint is that sleep is not refreshing.

Suicidal ideas

Depressed patients usually have a feeling of worthlessness, hopelessness and helplessness. Almost half may have suicidal ideas and 15% may be successful in their attempt.

Guilt feeling

It varies from culture to culture. They may feel that they have done some unpardonable sin or mistake and depression is a punishment given by God.

Somatic symptoms

Many times this may dominate the clinical picture and these unexplained somatic symptoms may pose a great dilemma to the physician unless they specifically look for signs of depression. Gastrointestinal symptoms like decrease in appetite, loss of interest in food, constipation and loss of weight are common. Hypochondriacal beliefs of some fatal illness is another presentation. Loss of libido, difficulty in erection, ejaculatory difficulties are also common. Women may have amenorrhoea and loss of sexual interest.

Retardation or agitation

A retarded patient walks slowly and speaks with slow and fading voice. They may also have slowness in thinking, difficulty in concentration and indecisiveness. An agitated patient may be restless and pace up and down, may be anxious and pluck at his fingers and make restless movements of his legs.

Diurnal variation of symptoms

This is characteristic of endogenous depression with worsening of all symptoms in the morning and feeling better towards evening.

Panic attacks

It can very well occur in depression with sudden occurrence of palpitation, nervousness, pain in the chest, feeling dizzy, choking, sweating, and a sense of impending doom.

DIAGNOSIS

Unlike physical disorders where there are specific investigations to confirm diagnosis, in psychiatry there is no gold standard for establishing the diagnosis. DSM IV (American Psychiatric Association, 1994) has laid out polythetic criteria for the diagnosis of depressive episode (Table - 1). If the patient satisfies minimum required number of symptoms and signs, it is a diagnosis of depression.

Table - 1

How to diagnose Major Depression

Depressed mood or loss of interest or pleasure with 5 (or more) of the following symptoms for a period of 2 weeks.

1. Depressed mood most of the day
2. Markedly diminished interest or pleasure in almost all activities
3. Significant weight loss or weight gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive inappropriate guilt
8. Diminished ability to think or concentrate or indecisiveness
9. Recurrent thoughts of death, suicidal ideation, attempt or specific plan

Table - 2

Medical and pharmacological causes of depressive symptoms

Neurological disorders	Cerebrovascular diseases, dementia, Parkinson's disease, neoplasm, infections (including HIV and neurosyphilis)
Endocrine disorders	Hypo- and hyperthyroidism, Addison's disease, Cushing's disease, menses- related, postpartum.
Infections and inflammatory diseases	AIDS, tuberculosis, pneumonia, mononucleosis, connective tissue disorders
Analgesics	Opiates, NSAIDs
Antibiotics	Ampicillin, griseofulvin, metronidazole, tetracycline, streptomycin, etc
Anticancer drugs	Vincristine, azathioprime, trimethoprim
Neurological & Psychiatric drugs	Amantidine, levodopa, bromocriptine, antipsychotics, sedatives and hypnotics
Steroids & hormones	Corticosteroids, oral contraceptives, prednisolone
Miscellaneous conditions	Cancer (especially pancreatic and other G.I), Vitamin deficiencies (B12, C, folate, niacin, thiamine), cardio - pulmonary/renal failure
Psychiatric disorders	Alcohol and other substance abuse disorders, schizophrenia and related disorders, somatoform disorders, adjustment disorders, eating disorders like anorexia nervosa and bulimia nervosa, generalised anxiety disorder, panic disorder, obsessive-compulsive disorder.

CAUSES OF SECONDARY DEPRESSION

Some common medical and psychiatric causes of depressive disorder are shown in Table 2. One has to always rule out these conditions first and if they are present, treatment of these conditions will resolve depression.

MANAGEMENT

Hospitalisation

It is indicated when there is a risk of suicide, homicide or if the patient is not taking food or fluids.

Antidepressants

Antidepressants are the main stay in the management of depression. Some of the commonly used antidepressants and their profile are shown in Table 3. Several problems may be encountered during antidepressant therapy. In the beginning of therapy, patients may develop side effects like drowsiness, dryness of mouth, constipation, etc especially with tricyclic antidepressants; whereas the antidepressant effect may start at 4th or 6th week of therapy. Due to this, there are high chances for drug discontinuation. Hence patients and their relatives should be educated about the illness and its treatment, including side effects at the beginning of the therapy. The dosage of the drug should be titrated slowly depending on the clinical response and side effects. A suicidal patient should never be given medicines for more than 1 week because of the risk of suicidal overdose, especially with tricyclic antidepressants. However, with the introduction of newer generation antidepressants like SSRIs, venlafaxine, mirtazapine, bupropion etc. the treatment of depression has become more easy as they have lesser side effects, early onset of action, fewer drug interactions and low lethality with suicidal overdose.

In every case, the drug therapy should be maintained for 6 months or for the length of previous episode whichever is longer. When antidepressants are stopped it should be tapered gradually over 1 to 2 weeks. Around 20% of patients may show only partial response to adequate dose and duration of the antidepressant therapy. The response in such patients can be augmented with the addition of lithium, T3 (triodothyronine), L-tryptophan, adding another antidepressant or switching to a different class of drug.

Electroconvulsive therapy

It is an effective and rapidly acting treatment for depression. It is indicated for patients who are unresponsive to pharmacotherapy, those who can't tolerate drugs and in situations so severe that rapid response is needed (suicidal, homicidal, stuporous).

Psychosocial therapies

Rather than individual treatment, combined pharmacotherapy and psychosocial therapy is the most effective treatment for depression. Cognitive behaviour therapy aims to correct the faulty thinking pattern supplemented with behavioral modification programs. Interpersonal therapy focuses on the current interpersonal problems and tries to rectify it. Family therapy is supportive therapy to the patient and counseling family members of the patient.

COURSE AND PROGNOSIS

An untreated episode will last for 6-13 months, most treated episodes last for 3 months. Premature withdrawal of antidepressants almost always results in relapse of depression. As the disease progresses, patients tend to have more frequent and longer episodes. Over a 20-year period, the mean number of episodes are 5 to 6.

Table - 3

Commonly used antidepressants and their profile

Drug	Adult dose range (mg /day)	Common side effects
Tricyclic Antidepressants		
Impiramine	150-300	Orthostatic hypotension, anticholinergic side effects, conduction abnormalities, moderate sedation
Amitriptyline	150-300	High sedation, anticholinergic side effects, conduction abnormalities
Clomipramine	150-250	Sedation, anticholinergic side effects, conduction abnormalities
Nortriptyline	150-300	Mild to moderate anticholinergic side effects, sedation
Doxepin	150-300	Sedation, anticholinergic side effects, orthostatic hypotension, weight gain
Dothiepin	150-300	Sedation, low anticholinergic side effects
Tetracyclic antidepressants		
Mianserin	30-90	Mild anticholinergic side effects
Amoxapine	200-300	Moderate anticholinergic side effects, extrapyramidal side effects, rarely seizures
Selective Serotonin Reuptake Inhibitors		
Fluoxetine	20-80	Sedation, insomnia, headache, fatigue, mild anticholinergic side effects, tremor, mild orthostatic hypotension, GIT-disturbances, anorgasmia, delayed ejaculation
Fluvoxamine	50 - 300	Sedation, insomnia, orthostatic hypotenison, mild anticholinergic side effects, headache, tremor, GIT disturbances, anorgasmia, delayed ejaculation, excitement
Sertraline	50 - 200	Insomnia, sedation, excitement, mild anticholinergic side effects, mild orthostatic hypotension, GIT distress, sexual disturbances, tremor

In conclusion, depression is a commonly occurring, correctly diagnosable and completely treatable psychiatric disorder. It has a definite biological etiology with an interaction of psychosocial factors. As with any physical disease, the fatal complication of depression is death that can occur by suicide in 15 percent of the patients.