Major Depressive Disorder

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Depression in its various forms is a commonly seen disorder in general practice. Indeed, over 90% of patients suffering from depression are seen, diagnosed and treated in primary care. The most severe, chronic and complicated cases are referred on to a psychiatrist.

Background

The World Health Organization (WHO) predicts that by 2020, depression will become the second leading cause of disability adjusted life-years lost worldwide, after ischaemic heart disease. About 20 per cent of the population will develop a depressive episode at some point in their lives, with up to 85 per cent of patients having more than one episode. Further, one in 10 patients with depression will commit suicide, and up to 20 per cent of patients with depression will have symptoms for two years or more (chronic depression)[1]

General practitioners are immensely variable in their ability to recognize depressive illnesses, with some recognizing virtually all the patients found to be depressed at independent research interview, and others recognizing very few. The communication skills of the GP make a vital contribution to determining their ability to detect emotional distress, and those with superior skills allow their patients to show more evidence of distress during their interviews, thus making detection easy. Those doctors with poor communication skills are more likely to collude with their patients, who may not themselves wish to complain of their distress unless they are asked directly about it.[2]

Those patients with more severe disorders, and those presenting psychological symptoms to their doctor, are especially likely to be recognized as depressed, while those presenting with somatic symptoms for which no cause can be found are less likely to be recognized.[3]

Pathophysiology

The underlying pathophysiology of major depressive disorder (MDD) has not been clearly defined. Clinical and preclinical trials suggest a disturbance in CNS serotonin (i.e., 5-HT) activity as an important factor. Other neurotransmitters implicated include norepinephrine (NE) and dopamine (DA).

The role of CNS serotonin activity in the pathophysiology of MDD is suggested by the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of MDD. Furthermore, studies have shown that an acute, transient relapse of depressive symptoms can be produced in research subjects in remission using tryptophan depletion, which causes a temporary reduction in CNS serotonin levels. Serotonergic neurons implicated in affective disorders are found in the dorsal raphe nucleus, the limbic system, and the left prefrontal cortex.[4]

Clinical experience indicates a complex interaction between neurotransmitter availability, receptor regulation and sensitivity, and affective symptoms in MDD. Drugs that produce only an acute rise in neurotransmitter availability, such as cocaine, do not have efficacy over time as antidepressants. Furthermore, an exposure of several weeks' duration to an antidepressant usually is necessary to produce a change in symptoms. This, together with preclinical research findings, implies a role for neuronal receptor regulation over time in response to enhanced neurotransmitter availability.

All available antidepressants appear to work via 1 or more of the following mechanisms: (1) presynaptic inhibition of uptake of 5-HT or NE; (2) antagonist activity at presynaptic inhibitory 5-HT or NE receptor sites, thereby enhancing neurotransmitter release; or (3) inhibition of monoamine oxidase, thereby reducing neurotransmitter breakdown.[5]

Symptoms

Depression refers to a wide range of mental health problems characterized by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms. Distinguishing the mood changes between major depression and those occurring 'normally'

remains problematic: persistence, severity, the presence of other symptoms and the degree of functional and social impairment form the basis of that distinction.

Commonly, mood and affect in a major depressive illness are unreactive to circumstance, remaining low throughout the course of each day, although for some people mood varies diurnally, with gradual improvement throughout the day only to return to a low mood on waking. A person's mood may be reactive to positive experiences and events, although these elevations in mood are not sustained, with depressive feelings re-emerging, often quickly.

Behavioural and physical symptoms typically include tearfulness, irritability, social withdrawal, reduced sleep, an exacerbation of pre-existing pains, and pains secondary to increased muscle tension and other pains,[6] lowered appetite (sometimes leading to significant weight loss), a lack of libido, fatigue and diminished activity, although agitation is common and marked anxiety frequent. Along with a loss of interest and enjoyment in everyday life, feelings of guilt, worthlessness and deserved punishment are common, as are lowered self-esteem, loss of confidence, feelings of helplessness, suicidal ideation and attempts at self-harm or suicide. Cognitive changes include poor concentration and reduced attention, pessimistic and recurrently negative thoughts about oneself, one's past and the future, mental slowing and rumination.[7]

Diagnosis

In order to diagnose depressive illness, diagnostic classifications such as the 'International classification of diseases' 10th edition (ICD-10) and the 'Diagnostic and statistical manual of mental disorders' 4th edition (DSM-IV), an American system, have been developed. In both these classifications (see below), a diagnosis of depression is made from the presence of a number of specific symptoms, or a syndrome, for a minimum of two weeks. It therefore relies on one of the most fundamental medical skills, that of recognizing patterns of symptoms. The two systems differ in that ICD-10 provides guidelines in making a diagnosis, whereas
DSM-IV ismore explicit in the symptoms required to make a diagnosis. However, both systems allow the coding of somatic symptoms, psychotic symptoms, and other illness characteristics.

The ICD-10 Classification System for Depression

Classification Symptoms of a Depressive Episode. Typical Features for a Period of Around Two Weeks:

- Depressed mood
- Loss of interest and enjoyment
- Reduced energy or increased tiredness
- Reduced activity

Other Common Symptoms:

- Reduced concentration and attention
- Reduced self-confidence and self-worth
- Guilt and unworthiness
- Bleak and pessimistic regarding the future
- Self-harm or suicidal ideas
- Disturbed sleep
- Reduced appetite

Somatic Symptoms:

Low mood may vary over the course of the day
Motor activity may be slowed or increased
Sexual appetite my be reduced
Patient may lose weight
Loss of interest and unreactivity of mood may be present

Psychotic symptoms (usually hallucinations or delusions) may be present in severe depression. Determination of the severity of depression is based upon a clinical judgement involving the number, type and severity of symptoms.

Diagnostic Guidelines

F32.0 Mild Depressive Episode

The presence of at least two of the typical symptoms of depression plus at least two of the other symptoms. None of the symptoms should be present to an intense degree. Minimum duration of the whole episode is about 2 weeks. An individual with a mild depressive episode is usually distressed by the symptoms and has some difficulty in continuing with ordinary work and social activities, but will probably not cease to function completely.

A fifth character may be used to specify the presence of the somatic syndrome:

F32.00 Without Somatic Symptoms

The criteria for mild depressive episode are fulfilled, and there are few or none of the somatic symptoms present.

F32.01 With Somatic Symptoms

The criteria for mild depressive episode are fulfilled, and four or more of the somatic symptoms are also present. (If only two or three somatic symptoms are present but they are unusually severe, use of this category may be justified).

Moderate Depressive Episode

The presence of at least two of the three most typical symptoms noted for mild depressive episode should be present, plus at least three and preferably four of the other symptoms. Several symptoms are likely to be present to a marked degree, but

this is not essential if a particularly wide variety of symptoms is present overall. The minimum duration of the whole episode is about 2 weeks. An individual with a moderately severe depressive episode will usually have considerable difficulty in continuing with social, work or domestic activities. A fifth character may be used to specify the occurrence of somatic symptoms:

F32.10 Without Somatic Symptoms

The criteria for moderate depressive episode are fulfilled, and few if any of the somatic symptoms are present.

F32.11 With Somatic Symptoms

The criteria for moderate depressive episode are fulfilled, and four or more or the somatic symptoms are present. (If only two or three somatic symptoms are present but they are unusually severe, use of this category may be justified).

Severe Depressive Episode

All three of the typical symptoms noted for mild and moderate depressive episodes should be present, plus at least four other symptoms, some of which should be of severe intensity. However, if important symptoms such as agitation or retardation are marked, the patient may be unwilling or unable to describe many symptoms in detail. An overall grading of severe episode may still be justified in such instances. The depressive episode should usually last at least 2 weeks, but if the symptoms are particularly severe and of very rapid onset, it may be justified to make this diagnosis after less than 2 weeks. During a severe depressive episode it is very unlikely that the sufferer will be able to continue with social, work, or domestic activities, except to a very limited extent.

Severe Depressive Episode with Psychotic Symptoms

A severe depressive episode which meets the criteria given for severe depressive episode without psychotic symptoms and in which delusions, hallucinations, or depressive stupor are present. The delusions usually involve ideas of sin, poverty, or imminent disasters, responsibility for which may be assumed by the patient. Auditory or olfactory hallucinations are usually of defamatory or accusatory voices or of rotting filth or decomposing flesh. Severe psychomotor retardation may progress to stupor. If required, delusions or hallucinations may be specified as mood-congruent or mood-incongruent.[8]

DSM-IV Diagnostic Criteria

a. A minimum of five symptoms from the following list have been present during the same 2-week period and represent a change from previous functioning. One of the symptoms must be 1 or 2, as listed below: 1) Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful) 2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, as indicated either by subjective account or observation made by others. Do not include symptoms that are clearly due to general medical condition or mood-incongruent delusions or hallucinations 3) Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day 4) Insomnia or hypersomnia nearly every day 5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down) 6) Fatigue or loss of energy nearly every day 7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick) 8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others) 9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide
b. The symptoms do not meet the criteria for a mixed episode
c. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
d. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)
e. The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.[9]

Differential Diagnosis

The differential diagnosis in patients presenting with alterations in mood is extensive and should include consideration of the following:

1. Personality disorders: Certain personality disorders (e.g., borderline personality disorder) may present with mood changes as a prominent symptom. The presence of a personality disorder can be difficult to determine in the setting of acute affective symptoms. Many patients who are depressed who appear labile, demanding, or pathologically

dependent look dramatically different once the depressive episode has been treated adequately.[10]

2. Mood disorders secondary to CNS conditions: These include a broad range of physiologic and structural CNS processes that can produce changes in mood and behaviour. Major Depressive Disorder (MDD) can produce measurable cognitive deficits or a worsening of preexisting dementia. This decline in cognitive functioning, which, on formal testing, appears to arise from impaired concentration or motivation, is referred to as dementia of depression and should remit with successful treatment of the depressive episode. MDD does not cause focal neurological signs. Such findings should prompt an evaluation for other organic syndromes.
3. Alzheimer disease: This disease and other degenerative and vascular dementias can be associated with affective symptoms. Mood disorders are very prominent in Parkinson's disease, Huntington's disease, multiple sclerosis, stroke, and seizure disorders.[5]
4. Neoplastic lesions of the CNS: These lesions also can cause changes in mood and behaviour before the onset of focal neurological signs.
5. Inflammatory conditions: Conditions such as systemic lupus erythematosus (SLE) can produce a wide range of neuropsychiatric signs and symptoms, likely because of alterations in the blood-brain barrier and an autoimmune cerebritis.
6. Sleep disorders: Obstructive sleep apnea, especially, can cause significant medical and psychiatric symptoms and often is missed as a diagnosis. Patients, and, if necessary, their partners, should be interviewed regarding their sleep quality, daytime sleepiness, and snoring. Polysomnography can help make the diagnosis and guide treatment.
7. Infectious processes: These include syphilis, Lyme disease, and HIV encephalopathy, which can cause mood and behavior changes.
8. Pharmacologic agents: Substances that can produce changes in mood include antihypertensive medications (especially beta-blockers, reserpine, methyldopa, and calcium channel blockers); steroids; medications that affect sex hormones (e.g., estrogen, progesterone, testosterone, gonadotropin-releasing hormone [GnRH] antagonists); H2 blockers (e.g., ranitidine, cimetidine); sedatives; muscle relaxants; appetite suppressants; and chemotherapy agents (e.g., vincristine, procarbazine, L-asparaginase, interferon, amphotericin B, vinblastine).
9. Endocrinologic disorders: Disorders involving the hypothalamic-pituitary-adrenal axis or thyroid are especially likely to produce changes in mood. These include Addison disease, Cushing disease, hyperthyroidism, hypothyroidism, prolactinomas, and hyperparathyroidism.
10. Substance use, abuse, or dependence: These can cause significant mood symptoms. This is especially true of alcohol, cocaine, amphetamines, marijuana, sedatives/hypnotics, and narcotics. Inhalant abuse also should be considered, particularly among young male patients. Other substance-related and psychiatric processes either can present with mood disturbance as the primary symptom or can occur together with MDD.
11. Dysthymia: This mood disorder presents with low mood as a primary symptom. Dysthymia can predate a depressive episode. The symptoms of dysthymia alone do not meet criteria for MDD and must be present for at least 2 years.
12. Anxiety disorders: Patients with anxiety disorders are at higher risk for developing comorbid depression. In such patients, it is important to identify the anxiety disorder because they often require specific treatment approaches. Commonly encountered anxiety disorders include panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, posttraumatic stress disorder, and phobia.
13. Eating disorders: People with eating disorders (EDs) also have a high rate of comorbid MDD and require specific treatment approaches. These disorders include bulimia, anorexia nervosa, and ED not otherwise specified.[5]
14. Bereavement: Depressed mood, disturbed sleep, and crying occur in over 50 per cent of bereaved subjects, but there is no disturbance of self-esteem. However, about one-third of the subjects have feelings of guilt concerning the dead person.[11]
15. Schizophrenia: Patients with schizophrenia may develop pronounced depressive symptoms. Persistent non-affective delusions or hallucinations, and even depressive hallucinations that are continuous rather than occasional, suggest schizophrenia.[11]

Aetiology

Depression is a broad and heterogenous psychiatric disorder that affects people of all ages, from childhood to old age. It varies in severity and duration, and there is a difference in incidence between sexes, being more common in women with a prevalence twice that observed in men. Boys and girls are affected equally. It is unlikely that there is only one cause of depression. Rather, its aetiology is multifactorial.

Aetiology can be divided into predisposing, personality and provoking factors.

Predisposing Factors

Genetic influence: It has been recognized for over 50 years that mental disorders, including mood disorders, aggregate in families. By means of twin studies and studies of adopted children, the genetic contribution to affective disorders has been established. In twin studies, for example, concordance is 80 per cent for bipolar disorders and 60 per cent for recurrent depression. Early childhood environment: Challenges are faced in trying to identify the influence of an individual's early life experiences on his or her predisposition to affective disorders. For example, much research has been carried out on investigating the importance of the parent-child relationship. Clear evidence suggests that lack of adequate parental care may be a developmental risk factor for adult depression. Many studies have also shown that early bereavement – especially loss of mother by death or separation- makes people more vulnerable to later loss experiences. An influential study by Brown et al argued that the loss of the mother before the age of 11 years was associated with a greater risk of adult depression, suggesting a direct causal link.[12] Maternal over – protection has also been incriminated in several studies in which depressed patients remembered their childhoods.

Personality Factors

Those who develop depressive illnesses are more likely to have low self – esteem and are rather more likely to be introverted and obsessional. Low self – esteem greatly increases the risk of a depressive illness following a stressful life event. Negative views about oneself, one's future and one's surroundings are said to constitute the "cognitive triad" which renders people vulnerable to depressive illness.[11]

Provoking Factors

Loss events may be the loss of a relationship, bereavements, threatened future losses or even failure to be promoted. These are especially likely to precipitate depression in those with low self – esteem. The loss may precede the episode of depression by as much as one year.

Physical illness commonly contributes to the genesis of depressive illnesses seen in general medical settings. For example illnesses as stroke, a heart attack, cancer, Parkinson's disease, and hormonal disorders can cause depressive illness, making the sick person apathetic and unwilling to care for his or her physical needs, thus prolonging the recovery period.

Stressful social circumstances such as having unsatisfactory living conditions, poor interpersonal relationships and very little social support can favour the release of depressive phenomena.[11]

Management

A wide range of effective treatments is available for depressive disorder. Brief psychotherapy (e.g., cognitive behavioral therapy (CBT), interpersonal therapy) has been shown in clinical trials to be an effective treatment option, either alone or in combination with medication. Medication alone also can relieve symptoms. However, the combined approach generally provides the patient with the quickest and most sustained response.

Mild Depressive Episode

The large majority of patients with depression are cared for solely in primary care.

For a significant number of people with mild to moderate depression, brief interventions delivered by the primary care team are effective; for others – particularly if they have not responded to the initial brief intervention – more complex interventions, which could be provided in primary or secondary care, are required.

Many patients with milder depression respond to interventions such as exercise e.g. advice is given to follow a supervised and structured exercise programme of approximately 45 minutes three times a week for a period of 10 to12 weeks.

Guided self-help, although many improve while being monitored without additional help, may be beneficial. More structured therapies, such as problem-solving, brief Cognitive Behavioural Therapy (CBT) or counselling can be helpful. Antidepressant drugs and psychological therapies, such as longer-term CBT or interpersonal psychotherapy (IPT), are not recommended as an initial treatment; these may be offered when simpler methods (for example, guided self-help or exercise) have failed to produce an adequate response.

Antidepressants are not recommended for the initial treatment of mild depression, because the risk–benefit ratio is poor.

The use of antidepressants should be considered for patients:

- with mild depression that is persisting after other interventions.
- whose depression is associated with psychosocial and medical problems.
- with a past history of moderate or severe depression present with mild depression[13]

Moderate or Severe Depressive Episode

In moderate or severe depression, the choice of treatment will reflect patient preference, past experience of treatment and the fact that the patient may not have benefited from other interventions as explained above.

With more severe depression, the risk of suicide should always be considered. Referral to secondary services should be

based on this assessment, the degree of functional impairment and the presence of significant comorbidities or specific symptoms.

Where a patient presents considerable immediate risk to self or others, for example patients with symptoms of psychotic depression, urgent referral for specialist treatment should be arranged.[13]

Antidepressant Drugs

There is more evidence for the effectiveness of antidepressant medication in moderate to severe depression than in milder depression. Careful monitoring of symptoms, side effects and suicide risk (particularly in those aged under 30) should be routinely undertaken, especially when initiating antidepressant medication. It is also important to monitor patients for relapse and withdrawal symptoms when reducing or stopping medication and they should be warned about the risks of reducing or stopping medication. Treatment failures often are caused not by clinical resistance, but by medication noncompliance, inadequate duration of therapy, or inadequate dosing.

Patients started on antidepressants who are not considered to be at increased risk of suicide should normally be seen after two weeks. Thereafter they should be seen on an appropriate and regular basis, for example, at intervals of two to four weeks in the first three months and at longer intervals thereafter, if response is good. Antidepressants should be continued for at least six months after remission of an episode of depression, because this greatly reduces the risk of relapse. When a patient has taken antidepressants for six months after remission, healthcare professionals should review with the patient the need for continued antidepressant treatment. This review should include consideration of the number of previous episodes, presence of residual symptoms, and concurrent psychosocial difficulties.[13]

Tricyclic Antidepressants (TCAs) include amitriptyline, nortriptyline, desipramine, clomipramine, doxepine, protriptyline, trimipramine, and imipramine.

This group has a long record of efficacy in the treatment of depression and has the advantage of lower cost. The disadvantages include the need to titrate the dose to a therapeutic level and considerable toxicity in overdose.

Adverse effects largely are due to their anticholinergic and antihistaminic properties and include sedation, confusion, dry mouth, orthostasis, constipation, urinary retention, sexual dysfunction, and weight gain. Caution should be used in patients with cardiac conduction abnormalities.[5]

Selective Serotonin Reuptake Inhibitors (SSRIs) include fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram. This group has the advantage of ease of dosing and low toxicity in overdose. Common adverse effects include GI upset, sexual dysfunction, and changes in energy level (i.e., fatigue, restlessness).[5]

Selective Serotonin/Norepinephrine Reuptake Inhibitors

(SNRIs) include venlafaxine and duloxetine. Safety, tolerability, and side effect profiles are similar to that of the SSRIs, with the exception that the SNRIs have been associated (rarely) with a sustained rise in blood pressure. SNRIs can be used as first-line agents, particularly in patients with significant fatigue or pain syndromes associated with the episode of depression. The SNRIs also have an important role as second-line agents in patients who have not responded to SSRIs.[5]

Atypical Antidepressants include bupropion, nefazodone, mirtazapine, and trazodone. This group also shows low toxicity in overdose and may have an advantage over the SSRIs by causing less sexual dysfunction and GI distress.

Bupropion is associated with a risk of seizure at higher doses, especially in patients with a history of seizure or eating disorders.

Mirtazapine is a potent antagonist at 5-HT2, 5-HT3, alpha2-, and histamine (H1) receptors and, thus, can be very sedating. Adverse effects such as drowsiness and weight gain may tend to improve over time and with higher doses.

Trazodone is very sedating and usually is used as a sleep aid rather than as an antidepressant.

Monoamine Oxidase Inhibitors (MAOIs) include phenelzine and tranylcypromine.

MAOIs are widely effective in a broad range of affective and anxiety disorders. However they are potentially toxic drugs and side effects are common.

Because of the risk of hypertensive crisis, patients on these medications must follow a low-tyramine diet. Other adverse effects can include insomnia, anxiety, orthostasis, weight gain, and sexual dysfunction.[5]

Non Pharmacologic Treatment

Electroconvulsive Therapy (ECT) involves the induction of a modified epileptic seizure given through electrodes placed bitemporally or with both on the non-dominant hemisphere. It is a highly effective treatment for depression and may have a more rapid onset of action than drug treatments. Advances in brief anaesthesia and neuromuscular paralysis have improved the safety and tolerability of this modality. Risks include those associated with brief anaesthesia, postictal confusion, and, more rarely, short-term memory difficulties. ECT is indicated when a rapid antidepressant response is needed, when drug therapies have failed or when there is a history of good response

to ECT. It is particularly effective in the treatment of delusional depression.[14]

Prognosis

The average age of the first episode of a major depression occurs in the mid-20s and although the first episode may occur at any time, from early childhood through to old age, a substantial proportion of people have their first depression in childhood or adolescence.[15] It is generally thought that depression is usually a time-limited disorder lasting up to six months with complete recovery afterwards. However around 20% of patients remain depressed for 2 years or more.

While around half of those affected by depression will have no further episodes, depressive illnesses, have a strong tendency for recurrence. At least 50% of people following their first episode of major depression will go on to have at least one more episode,[16] with early onset depression (at or before 20 years of age) particularly associated with a significantly increased vulnerability to relapse.[17] After the second and third episodes, the risk of further relapse rises to 70% and 90% respectively.[16] Thus, while the outlook for a first episode is good, the outlook for recurrent episodes over the long term can be poor, with many patients suffering symptoms of depression over many years.

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