# BAP GUIDELINES FOR THE MANAGEMENT OF

# DEPRESSIVE DISORDERS

1st Edition, 2022

বাংলাদেশ এসোসিয়েশন অব সাইকিয়াট্রিস্টস (বিএপি)
BANGLADESH ASSOCIATION OF PSYCHIATRISTS (BAP)

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**BAP Guidelines for the Management of Depressive Disorders**



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# PREFACE TO THE FIRST EDITION

Depressive disorders are the most common mental disorders in the community except for anxiety disorders and contribute greatly to the global burden of disease. Apart from personal sufferings, impact of depression on overall health, well-being, economic, social and occupational functioning is huge. The Bangladesh Association of Psychiatrists (BAP) felt the need to develop a management guideline for depression for psychiatrists and also for physicians working in non-specialized settings to improve clinical practice while recognizing, assessing, diagnosing and treating depressed patients.

This guideline is based on available evidence on epidemiology, diagnosis and treatment of depression obtained mainly through desk review of established guidelines. The suggestions in this guideline represent the view of BAP, arrived at after careful consideration of different evidence. However, we expect that the users will exercise their judgement, alongside with the individual needs, preferences and values of the patients.

I want to thank everyone who worked rigorously during this guideline development process. I believe this guideline will greatly help to improve mental health care practices in Bangladesh and consequently our patients' lives.

**Prof. Dr. Md. Waziul Alam Chowdhury**
President
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# ACKNOWLEDGEMENT

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# ABBREVIATIONS

| | |
|---|---|
| CBT | Cognitive-Behavior Therapy |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| ECT | Electroconvulsive Therapy |
| HbA1c | Hemoglobin A1c |
| HIV | Human Immunodeficiency Virus |
| ICD | International Classification of Diseases |
| IPT | Interpersonal Psychotherapy |
| NaSSAs | Noradrenaline and Selective Serotonin Antidepressants |
| NICE | National Institute for Health and Care Excellence |
| PCOD | Polycystic Ovarian Disease |
| PLID | Prolapsed Lumbar Intervertebral Disc |
| SNRIs | Serotonin Norepinephrine Reuptake Inhibitors |
| SSRIs | Selective Serotonin Reuptake Inhibitors |
| TCAs | Tricyclic Antidepressants |

# CONTENTS

# BACKGROUND

# INTRODUCTION

Depressive disorders are the most common of all mental illnesses. According to the Global Burden of Disease, depressive disorders are second (7.5%) and by the end of 2030, will be the first rank of global burden of disease. Depressive disorders are the 13th cause of disability in terms of disability-adjusted life years (DALYs). It contributes greatly to the global burden of disease. Along with personal sufferings, impact of these disorders on overall health, well-being, economic, social and occupational functioning is huge.

Terms like sadness, depressive disorders are often mistakenly synonymously used. Knowing the distinction between them is necessary as it has important diagnostic and treatment implications

| Feature | Sadness | Depressive disorders |
|---|---|---|
| Definition | Sadness is a human emotion; a natural reaction to emotional upset or pain, distressing, discouraging events, a loss, disappointment, problems, or other adverse situations. | Depressive disorders are a group of mental disorders whose common features are presence of sad, empty, irritable mood accompanied by somatic changes (e.g., sleep, appetite) and cognitive changes (e.g., guilt, worthlessness) that significantly affects an individual's capacity to function. |
| Characteristics | Sad, unhappy, blue, miser, regretful, pessimistic, bitter. | Persistent sadness, depressed mood, irritable, empty, hopeless, anhedonia, pessimistic. |
| Persistence | Transient, situation related. | Persistent and pervasive with duration of at least 2 weeks. |
| Functional impairment | None or mild | Marked |
| Presumed etiology | Adverse life events | Adverse life events, endogenous, secondary to physical illness, drug (medicine) or substance use.It can be comorbid with other physical or mental illnesses. |
| Treatment | Usually none. Reassurance and support. | Pharmacotherapy and psychotherapy. |

# CLASSIFICATION

Based on the duration of symptom presence, timing of symptom onset and presumed etiology, DSM-5 categorizes depressive disorders into following category.

**DSM-5 Classification of Depressive Disorders**

- Disruptive Mood Dysregulation Disorder
- Major Depressive Disorder (including major depressive episode)
- Persistent Depressive Disorder (Dysthymia)
- Premenstrual Dysphoric Disorder
- Substance/Medication-Induced Depressive Disorder
- Depressive Disorder Due to Another Medical Condition
- Other Specified Depressive Disorder
- Unspecified Depressive Disorder

Major depressive disorder (MDD) is the most commonly diagnosed depressive disorder. The symptom pattern will give us some idea about what a typical depressive disorder presents like. The diagnosis of MDD requires the presence of five (or more) of the core symptoms that should be present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure.

**Core symptoms of Major Depressive Disorder**

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all activities
- Significant weight loss or gain
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feeling of worthlessness or excessive, inappropriate guilt
- Diminished ability to think or concentrate or indecisiveness
- Recurrent thoughts of death, suicidal ideation, plan or suicidal attempt

According to symptoms severity and impact, depressive disorders are further classified into mild, moderate and severe type.

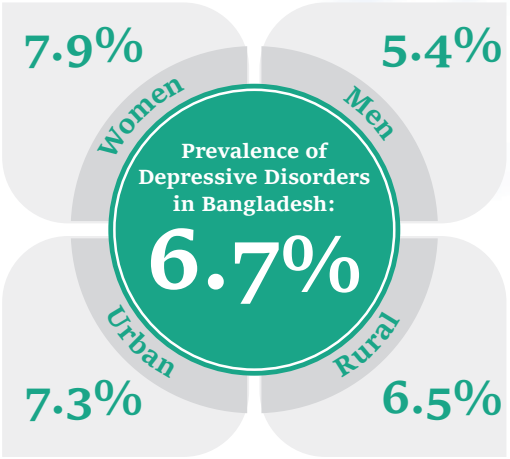
| | |
|---|---|
| **Mild** | • Few, if any, symptoms in excess of those required to make the diagnosis are present<br>• The intensity of the symptoms is distressing but manageable<br>• The symptoms result in minor impairment in social or occupational functioning. |
| **Moderate** | • The number of symptoms, intensity of symptoms, and/or functional impairment are between those specified for “mild” and “severe.” |
| **Severe** | The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning. |
| **Severe with psychotic features** | Delusions and/or hallucinations are present. |

# EPIDEMIOLOGY

Globally, life time estimates of proportion of depression vary widely due to geographical, racial, methodological and other issues. Research has identified certain risk factors for depression such as early parental deprivation, unemployment, job loss, separation, divorce, bereavement and other negative life events.

- Best estimates of life time prevalence of depression in the community lie between 4% to 10%.
- Average age of onset of major depressive episodes varies and occurs usually in the mid-20s.
- A substantial proportion of people have their first episode started in childhood or adolescent.

- Prevalence rate was consistently found 1.5 to 2.5 times higher in women than men.




# RATIONALE

Overall prevalence of mental disorders among Bangladeshi population of 18 years and above is 18.7% where depression was found to be 6.7% in the National Mental Health Survey Bangladesh, 2018-19. Depressive disorders have been associated with significant personal distress, functional impairment and contributes greatly to the global burden of disease. It is estimated that 70% of the suicide occurs due to depressive illness and 10-20% of depressive patients may commit suicide. It has emerged from focus group discussions that general physicians are not trained and skilled enough to diagnose and manage depression. Especially where a patient in Bangladesh presents with mostly somatic complaints rather than low mood, they are misdiagnosed. A patient also delays in seeking help and there is no clear referral system at work in Bangladesh. Till date there is no single uniform management guideline for depression published in Bangladesh. Bangladesh Association of Psychiatrists (BAP) felt the need to develop a national clinical management guideline for the psychiatrists and for other physicians that can be incorporated at all levels of health care services, from community to tertiary.

## Why this guideline is unique and uniform and very much compatible with Bangladesh context

- Diagnosis of depressive disorders can be made by psychiatrists as well as by the physicians working in a setting with low resources.
- The concepts, assessment, management (both pharmacological and non-pharmacological) and referral pathways are clearly described here.
- The clinical features ranges from mild to severe illness and special population with depression (pregnant & lactating mothers, persons with physical comorbidities, etc.) are also considered in this guideline.
- A nationwide referral pathway for the management of depressive disorders is included in this guideline that makes it more usable for psychiatrists and other physicians, which also develops a basis for rational liaison psychiatric service.
- The evidence-based principle of management developed here after considering country context, cultural compatibility and available resources.
- This guideline comprises for use in both inpatient and outpatient settings.
- A comprehensive management plan including follow up and compliance issues also discussed here.
- This guideline will be updated periodically.

# OBJECTIVES

The objective of this guideline is to provide clear, concise and uniform information to all psychiatrists as well as other physicians on the current concept in the management of depressive disorders considering country context. Since patients with depressive disorders first contact with primary care physicians, here this guideline provides necessary directives and primary management algorithm along the referral pathways for them.

**Uniform** | **Updated** | **Culturally compatible** | **Contextualized evidence based** | **Comprehensive**

# TARGET USERS

| | |
|---|---|
| **Physicians in non-specialized settings** | • Primary management protocol *(what to do and what not to do)*<br>• Referral pathway *(when to refer, where to refer, how to refer)*<br>• Non-pharmacological approach for the management of depression |
| **Psychiatrists** | • Advanced and updated management protocol for clinical practice<br>• Cover management of major depressive disorder and other catagories of depressive disorders<br>• Management guideline for special conditions / situations |

# METHODOLOGY

This guideline has been developed after considering the desk review of updated clinical practice guidelines from several authorities like American Psychiatric Association (APA), National Institute for Health and Care Excellence (NICE guidelines), Depression Management Guidelines of Indian Psychiatric Society, etc., expert consensus, clinical experience and the findings from the focus group discussions (FGD) with the psychiatrists, general practitioners and persons with living experience of depression in Bangladesh.

Treatment recommendations used in this guideline are developed by considering the efficacy of each treatment modality across various phases of illness as well as safety and tolerability obtained from levels of evidence from various types of studies.

**Definition of levels of evidence criteria used in depressive disorders treatment recommendations**

| Level | Evidence | BAP evidence gathering |
|---|---|---|
| I | Systematic review/meta-analysis of all relevant randomized controlled trials | Obtained from desk review |
| II | One or more properly designed randomized controlled trial | |
| III | Well-designed prospective trial (non-randomized controlled trial); comparative studies with concurrent controls and allocation not randomized; case-controlled or interrupted time series with a control group | |
| IV | Case series, either post-test or pretest/post-test | |
| V | Expert opinion | Consensus among experts, focus group discussion with experts |

# MANAGEMENT

# ASSESSMENT

Patients with symptoms of depression should receive a thorough biopsychosocial assessment, to determine the diagnosis of major depressive disorder and to identify the presence of other psychiatric or general medical conditions.

## Components of assessment and evaluation

### Comprehensive assessment of patient

- **Complete history with information from all possible sources**
- **Areas to be evaluated**
  Symptom severity
  Symptom dimensions
  Comorbid physical conditions
  Other psychiatric and substance use conditions
  Risk of self-harm, suicide and risk of harm to others
  Level of functioning
  Problem in maintaining relations and socio-cultural milieu of the patient
- **History of previous mood disturbance**
  Depression
  Mania
  Hypomania
- **Personal history**
  Birth history, development history, menstrual history, sexual history (including history of sexual abuse or assault)
  Identification of early life trauma, abuse or neglect
  Determination of responses to life transitions, major life events, or significant traumas
- **Family history**
  Any psychiatric illness including history of depression or other mood disorders, substance use disorders, suicide
- **Past treatment history**
  Type of antidepressant used which includes dose of medication, compliance, response to treatment, any side effects experienced.

Medications used to treat general medical conditions may induce depressive syndromes.

- **Social resources of the patient**
  Work, finances, family life, social activities, general living conditions and physical health
  Enquiries should cover family, friends, and work

## Physical Examination

- Blood pressure, pulse rate, weight, body mass index and waist circumference
- Anaemia
- Thyroid swelling
- Evidence for malnutrition or any specific nutritional deficiency

### Physical conditions associated with depressive disorders

**Neurological-** Stroke, Parkinson's Disease, Multiple Sclerosis, Degenerative Brain Disease, PLID, Head injury, Brain infection

**Coronary Artery Disease-** MI, Ischemic Heart Disease

**Endocrine-** Hypothyroidism, Diabetes mellitus, Hyperparathyroidism, Cushing's Syndrome, Addison's Disease, PCOD

**Malignancy**

**Infection**

**Medications-** Steroids, betablockers, antihypertensives, anticonvulsants, oral contraceptive pills, some antibiotics, chemotherapeutic agents

**Others-** Collagen tissue disorders, nutritional deficiencies

## Mental state examination

- Appearance and behavior
- Speech
- Mood and affect
- Thought
- Perception
- Cognitive function
- Insight

## Basic investigations

- Complete Blood Count (CBC)
- Blood sugar, HbA1c
- Lipid profile
- Liver and renal function tests
- Thyroid function tests
- Electrocardiogram (ECG)
- Chest X-ray

## Establish the diagnosis

- The diagnosis must be confirmed as per the current diagnostic criteria (DSM-5/ICD-11)
- Rule out bipolar disorder, other psychiatric disorders, depressive disorder secondary to any medical conditions or medications
- Assess the severity, specifier, subtype of depression

## Risk assessment

- ***Assess suicidal risk***
  - Presence of suicidal ideation and behaviors.
  - Extent to which the patient has made plans for or begun to prepare for suicide.
  - Availability and lethality of the means for suicide and the degree to which the patient intends to act on suicidal plans.
  - History of previous attempts and aborted attempts.
  - Family history of past or recent exposure to suicide.
- ***Assess life events***
  - Presence of acute or chronic psychosocial stressors, such as financial difficulties or changes in socioeconomic status, family discord, domestic violence, and sexual or physical abuse or neglect.
  - History of childhood traumas, particularly sexual and physical abuse.
  - Absence of psychosocial support, such as loss/poor relationship with family, unemployment, living alone, unstable or poor therapeutic relationship.
  - Absence of protective factors, such as children in the home, sense of responsibility to family, pregnancy, life satisfaction, cultural beliefs, or religiosity.
- ***History of substance use, violence and aggression***
- ***Presence of psychotic symptoms such as hallucinations and/or delusions***
- ***Presence of major psychiatric disorders, substance use disorders, cluster B personality disorders***
- ***Presence of disabling medical illness, especially with poor prognosis, such as chronic pain, brain and spinal cord injury, malignant neoplasm, HIV.***

## Evaluate functional impairment and quality of life

Depression can impair function and threaten the quality of life. The patient's overall quality of life should also be assessed, which can be done by asking patients what bothers them the most about their depression and determining how their current activities and enjoyment of life have been altered by their depressive symptoms. The psychiatrist should address impairments in functioning and help the patient to set specific goals appropriate to his or her functional impairments and symptom severity.

## Possible referral points (liaison)

- **National Institute of Mental Health (NIMH)**
  Sher-E-Bangla Nagar, Dhaka
- **Pabna Mental Hospital**
  Pabna, Bangladesh
- **Psychiatry Department, Bangabandhu Sheikh Mujib Medical University Hospital (BSMMU)** Shahbagh, Dhaka
- **Psychiatry Department**
  All Government Medical College Hospitals
- **Consultant Psychiatrist**
  District level Government Hospitals or Sadar Hospitals
- **Psychiatry Department/Psychiatric Service**
  Private Medical College Hospitals and Corporate Hospitals
- **Doctors who received training on Mental Health Upazila Health Complexes (UHC)**

### When to refer to a psychiatrist

- When depressive symptoms are chronic, severe and disabling.
- The patient is elderly, pregnant or is a child or adolescent.
- During post-partum period.
- Psychotic symptoms (e.g., delusions, hallucinations), water and food refusal or catatonia is present.
- Comorbid illicit drug use is present.
- Comorbid medical or mental illness is present (e.g., heart disease, diabetes, OCD, personality disorder).
- There is risk of suicide or self-harm.
- Persons who cannot get to work or maintain usual activities.
- The diagnosis is uncertain.
- Poor response to standard treatment. The response should be evaluated within a period of 4-8 weeks.

# BIOLOGICAL TREATMENT

## Pharmacological treatment

The mainstay treatment of depressive disorder is the prescription of antidepressants, although psychological treatments can be applied in milder form of depression.

Before starting pharmacological treatment, these factors must be considered and severity assessment is essential.

## Basic principles of prescribing antidepressants

- Discuss with the patient about his/her condition, choice of drug and utility/availability of other.
- Discuss the likely outcomes, such as gradual relief from depressive symptoms over 4-6 weeks.
- Prescribe a dose of antidepressant (after titration, if necessary) that is likely to be effective.
- For a single episode, continue treatment for at least 6-9 months after resolution of symptoms.
- Patients who have had multiple episodes, maintenance treatment should be for at least 2 years.
- Withdraw antidepressants very gradually; always inform patients of the risk and nature of discontinuation symptoms.

## Factors to consider for choosing an antidepressant

***Patient factors***

- Clinical features and dimensions
- Patient profile- age, sex, body weight
- Comorbid psychiatric and/or general medical conditions
- Nature of prior response to medication
- Side effects during previous use of antidepressant
- Patient preference

***Medication factors***

- Comparative efficacy
- Safety, tolerability and anticipatory side effects
- Potential drug interactions
- Half-life and simplicity of use
- Cost and availability of treatment

| Recommended antidepressants in depressive disorders | | |
|---|---|---|
| **Class** | **Drug** | **Recommendation** |
| Selective serotonin reuptake inhibitors (SSRIs) | Fluoxetine<br>Paroxetine<br>Fluvoxamine<br>Sertraline<br>Citalopram<br>Escitalopram | Generally recommended as first-line pharmacological treatment of depression |
| Tricyclic antidepressants (TCAs) | | Should be used cautiously for elderly people due to its side effects |
| Tricyclic tertiary amines | Amitriptyline<br>Imipramine<br>Clomipramine | |
| Tricyclic secondary amines | Desipramine<br>Nortriptyline | |
| Tetracyclic | Maprotiline | |
| Unicyclic | Bupropion | |
| Serotonin norepinephrine reuptake inhibitors (SNRIs) | Venlafaxine<br>Duloxetine<br>Milnacipran<br>Desvenlafaxine | In patients with more severe depression, SNRIs are slightly more effective than SSRIs |
| Noradrenaline and specific serotonin antidepressants (NaSSAs) | Mirtazapine | Effective in moderate to severe depression |
| Serotonin partial agonist and reuptake inhibitor (SPARI) | Vilazodone | |
| Others | Agomelatine | |

## Psychoeducation

Management of all patients with depressive disorders should begin with psychoeducation. The aim is to provide information about the nature of illness, its treatment and the key coping strategies to patient and family. Listed below are the essential components of psychoeducation for depressive disorders.

| Essential components of psychoeducation for depressive disorders |
|---|
| • Etiological factors |
| • Common signs and symptoms |
| • Awareness regarding the early signs of relapse/recurrence |
| • How to cope with the situation |
| • Various treatment options available |
| • When and how to seek treatment |
| • Need for adherence to treatment as per the guidance of treating team |
| • Long-term course and outcome |
| • Dos and don'ts for family members while dealing with the patient |
| • Clearing myths and misconceptions about the illness and dispelling stigma |
| • How to deal with self-harm and suicidal behavioral |

## Stepped care management of depression

- For the treatment of simple sadness, antidepressants are not recommended.
- Patients with short-lived, mild depression who may recover quickly without treatment should be offered an early review (active monitoring).
- Patients with persistent milder form of depression, antidepressants and/or guided self-help program based on cognitive-behavior therapy (CBT), an exercise program can also be recommended.
- For patients with persistent mild depressive symptoms who do not respond to these measures, consider drug treatment with SSRI.
- Patients who present with moderate or severe depression, should be treated with a combination of antidepressant medication and psychological intervention (e.g., CBT)

- Patients who respond to antidepressant medication should continue treatment for at least 6-9 months.

## Combination therapy

- Combination therapy is widely used in patients who have failed to respond to initial antidepressant.
- In patients who are unresponsive or partly responsive to medication, it may be more appropriate to add a second compound to the antidepressant. This is called combination therapy where the second compound is itself considered to be an antidepressant.

**Some recommended combination therapy of antidepressants**

- SSRI+Mirtazapine
- TCA+SSRI
- Venlafaxine+Mirtazapine
- Bupropion+SSRI

## Augmentation of antidepressants

Augmentation refers to the addition of a drug to an antidepressant that is not by itself regarded as an effective antidepressant but is able to produce a therapeutic response when added to an ineffective antidepressant medication.

**Some commonly used drugs for augmentation of antidepressants**

- **Atypical antipsychotics**
  - Olanzapine
  - Quetiapine
  - Aripiprazole
- **Lithium**
- **Tri-iodothyronine**

## Switching antidepressants

- If a patient does not respond to an antidepressant (no improvement at all is seen by 3 to 4 weeks), the first step is usually to stop the first medication and try another.

- When changing from one to another, abrupt withdrawal should be avoided unless there has been a serious adverse event.
- Cross-tapering is preferred, in which the dose of the ineffective or poorly tolerated drug is slowly reduced while the new drug is slowly introduced.
- Cross-tapering may not be necessary in some cases, for example when switching from one SSRI to another or switching to drug with a similar mode of action.

## Continuation phase treatment

- After symptomatic remission, follow-up for several months is usually recommended, continuing antidepressant treatment for 6 to 9 months after remission reduces relapse rate.
- In case of high relapse rate, treatment should be continued for at least 2 years, occasionally lifelong treatment is needed in various forms.

## Maintenance treatment

- Maintenance treatment should be considered if a patient has had two previous episodes of depression within a 5-year period.
- If there is a family history of recurrent major depression, or personal and social factors predictive of recurrence.
- Maintenance treatment may be needed for two years or more on the basis of clinical or psychological assessment.
- Maintaining the dose of medication.

**Risk factors to consider for maintenance treatment with antidepressants**

- Frequent recurrent episodes
- Severe episodes, e.g., psychosis, severe impairment, suicidality
- Chronic episodes
- Presence of co morbid psychiatric and other medical conditions
- Difficult to treat episodes
- Family history of psychiatric illness, particularly mood disorders
- Ongoing psychosocial stressors or impairment
- Negative cognitive style
- Persistent sleep disturbance

## Discontinuation of treatment

- The decision to discontinue maintenance treatment may be based on the same factors considered in the decision to initiate maintenance treatment.
- Patient should be advised not to discontinue medications before holidays, significant events (e.g., wedding) or other stressful events.
- Patient should be carefully monitored during and immediately after discontinuation of treatment to ensure that remission is stable.
- The highest risk of relapse is seen in the first two months after discontinuation of treatment.
- It is important to schedule a follow-up visit during this period to ensure stability.
- About half of the patients will experience withdrawal symptoms on reducing or stopping their antidepressants. So, it should be stopped by tapering gradually.
- The process normally takes between 3 months and 2 years but in some people can require longer periods.
- The range of reductions is equivalent to about 10 -20% dose reduction at each step.

## Treatment resistant depression

Depression is usually considered resistant when at least two trials with antidepressants from different pharmacologic classes (adequate in terms of dosage, duration, and compliance) fail to produce a significant clinical improvement.

***Steps to follow to treat treatment resistant depression***

### Step 1

- **Re-evaluate the diagnosis**
  Possibilities of bipolar II disorder, dementia in case of elderly or other organic cause should be considered first
- **Clinical assessment**
  Review treatment history
  Adherence to medication
  Engagement of psychotherapy
  Potential personality problem
  Psychiatric and medical comorbidities
- **Psychological stressors**

### Step 2

- In case of partial response, increase the dose of the antidepressant
- Consider combining pharmacotherapy with psychotherapy

### Step 3

- If there is no improvement, first consider augmentation and/or combination therapy.
- **Augmenting agents**
  Lithium
  Second generation antipsychotics, e.g., Olanzapine; Quetiapine; Aripiprazole
  Thyroid hormones
- **Combination therapy**
  SSRI+Mirtazapine
  TCA+SSRI
  Venlafaxine+Mirtazapine
  Bupropion+SSRI

### Step 4

- If step 3 does not work, consider alternative strategies such as switching

### Step 5

- ECT is an effective therapy for treatment resistant depression and should be considered lastly.
- It should be approached on the basis of individual patient and illness factor.

## Electroconvulsive therapy (ECT)

ECT is a rapid and effective treatment for severe depressive disorder. It is a practical procedure, so it should be given in a pleasant, safe surrounding and adequate emergency equipment should be available, including a sucker, endotracheal tubes, adequate supplies of oxygen, and facilities to carry out full resuscitation. The nursing and medical staff who give ECT should receive special training and accreditation.

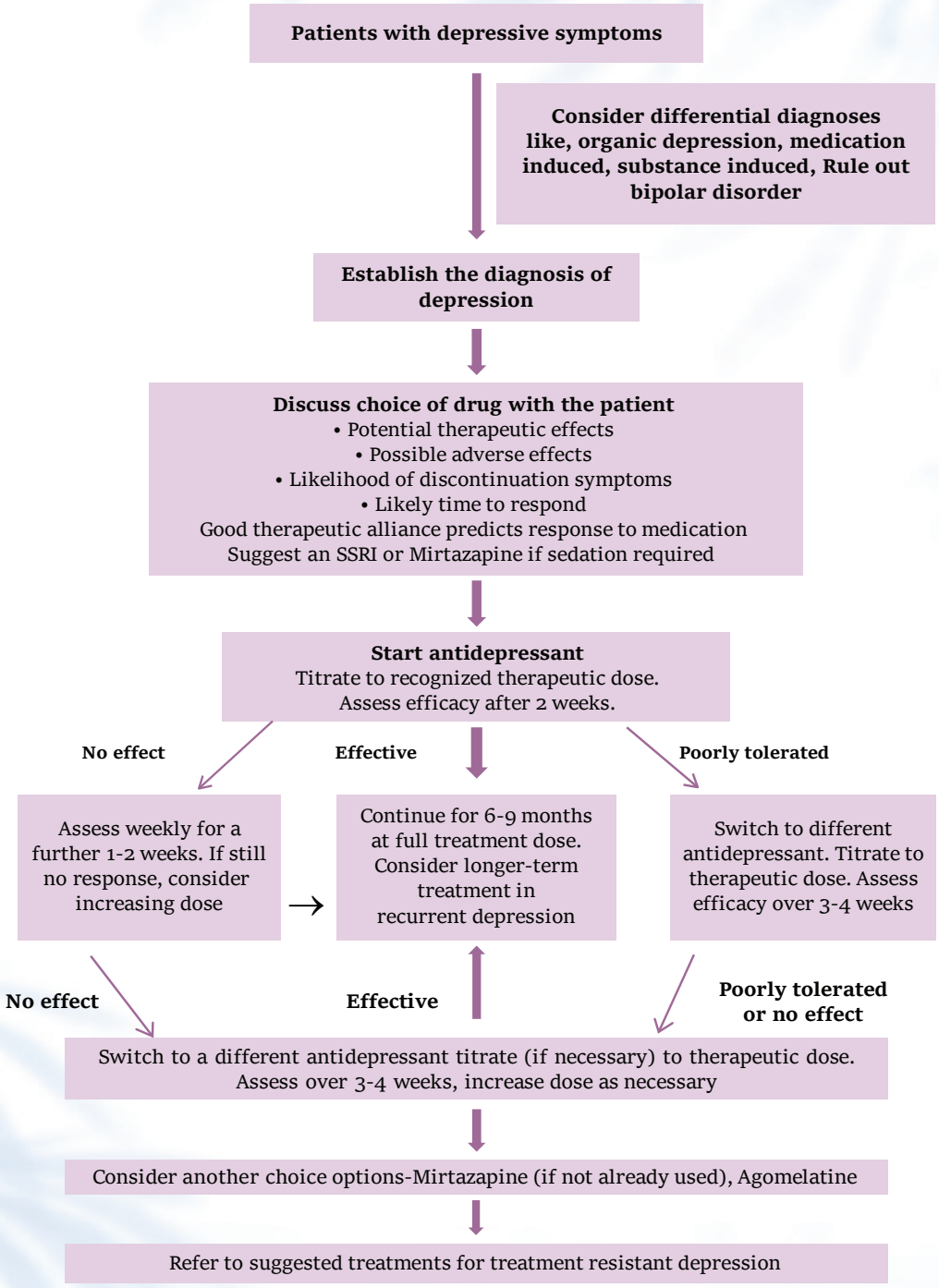
### Indications of ECT in depression

- Severe depression with refusal of food, fluid and medication
- High suicidal risk
- Severe depressive illness with stupor and marked psychomotor retardation
- Psychotic depression
- Pregnancy and postpartum depression
- Depressive illness that is not responsive to antidepressant drugs
- Catatonia

### Contraindications of ECT

- Any medical illnesses that increase the risk of anesthetic procedures, e.g., respiratory infections, serious heart disease, serious pyrexial illness, etc.

## Treatment algorithm of depressive disorders



# PSYCHOLOGICAL INTERVENTIONS

Decisions about providing psychological treatment should be made after considering the severity of the disorder, the preference of the informed patient, the durability of the treatment effect and the availability of the treatment in question.

Psychotherapy when needed should be provided by either psychiatrists or clinical psychologists.

For children, pregnant women and older adults with depressive disorders, psychotherapy is recommended by some experts. Given the limited availability of psychotherapy in Bangladesh, decision should be made on individual patient basis along with the consideration of the severity of the disorder and impact on patient life.

| | Advice | Counselling | Psychotherapy |
|---|---|---|---|
| **Definition** | A relevant piece of information provided by a health professional to resolve a problem or overcome from difficulty | Professional advice given by a counselor to an individual to help him overcome personal or psychological problems | Established psychological treatment that require a specific and elaborate training |
| **Aim** | Provide reassurance and support | A clear set of instructions with underlying theoretical principles which focuses on specific problem and changing behavior of patient | Explore the cause of the current problems and try to change the personality, cognition, etc. of the patient |
| **Who can provide it?** | Physician from any discipline (non-mental health professional) | Health professionals | Psychiatrists and clinical psychologists |

| Recommended psychotherapies in depressive disorders | |
|---|---|
| **First line** | • Cognitive-behavior therapy (CBT)<br>• Interpersonal psychotherapy (IPT) |
| **Others** | • Mindfulness-based cognitive therapy<br>• Problem-solving therapy<br>• Marital and family therapy |

## Cognitive-behavior therapy (CBT)

CBT combines cognitive and behavior therapies and includes comprehensive assessment and management. CBT eradicates irrational thoughts/believes, reduces symptoms of depression and improves functioning of the patients. Cognitive therapy and behavior therapy can be separately given but usually they are delivered as a package.

## Interpersonal psychotherapy (IPT)

In IPT the goal is to intervene by identifying the current trigger of the depressive episode, facilitating mourning in case of bereavement, promoting recognition of related affects, resolving role disputes and role transitions, and building social skills to improve relationships and to acquire needed social supports.

## Non-specific techniques used to control depression

For patients who have some symptoms of depression but not depressive disorder, guided self-help (e.g., written materials from BAP), psychoeducational group might be useful. Some non-specific techniques can be useful in controlling depressive symptoms. However, in case of depressive disorders, they are not effective alone; these techniques need to be incorporated with psychotherapy.

**Non-specific techniques used to control depression**

- Behavioral activation
- Relaxation therapy
- Supportive psychotherapy
- Problem solving counselling
- Mindfulness
- Coping skills development
- Stress management
- Physical activity and healthy lifestyle

# PROGNOSIS

- Depressive disorders are best conceptualized as chronic relapsing conditions.
- The average length of a depressive episode is about 6 months.
- Around 25% of patients have episodes that run for more than 1 year and 10-20% develop a chronic unremitting course.
- About 80% patients with major depressive episode will have further episodes.
- About 25% of patients experience a recurrence of major depressive episode within 6 months, 30-50% in the following 2 years and 50-75% in 5 years.
- About 50% of depressed patients continue to experience subsyndromal depression of fluctuating severity.
- Only about 25% of patients with recurrent depression can maintain a 5 years period of clinical stability.
- The rates of suicide are 15 times higher than general population in patients with depressive disorders.
- The best predictor of the future course is the history of previous episodes. The risk of recurrence is much higher in persons with history of several previous episodes.

**Factors that predict higher risk of another depressive episode**

- Incomplete symptomatic remission
- Early age of onset
- Poor social support
- Poor physical health
- Comorbid substance misuse
- Comorbid personality disorder
- Presence of psychotic symptoms
- First-degree family members with major depressive disorder

# SPECIAL PRESENTATIONS

| Special presentation | Features | Treatment |
|---|---|---|
| **Somatic symptoms** | • Changes in appetite (weight loss or weight gain)<br>• Sleep disturbance (insomnia or hypersomnia)<br>• Decreased libido<br>• Lack of energy/fatiguability<br>• Pain in different parts of the body (e.g., headache, abdominal pain)<br>• Burning sensation | **First line**<br>Duloxetine<br>Venlafaxine<br>Mirtazapine<br>Amitriptyline<br>**Second line**<br>Sertraline<br>Escitalopram |
| **Comorbid anxiety** | • Feeling tensed<br>• Restlessness<br>• Difficulty in concentration<br>• Anticipation<br>• Fear of losing control | **First line**<br>Escitalopram<br>**Second line**<br>Mirtazapine<br>Benzodiazepines (clonazepam, alprazolam)<br>Non-selective β-blockers (propranolol)<br>Anticonvulsants (lamotrigine, gabapentin)<br>Atypical antipsychotics (aripiprazole, quetiapine)<br>CBT |
| **Psychotic depression** | • Psychotic features (hallucinations or delusions) may be present sometimes<br>• Psychomotor disturbance is more frequent in this group of patients<br>• This condition constitutes a risk factor for recurrent major depression and indicates the need for maintenance treatment<br>• In case of postpartum depression with psychotic features prescribe antipsychotic in combination with antidepressant | **First line**<br>Imipramine<br>Clomipramine<br>Fluoxetine+Olanzapine<br>**Second line**<br>Sertraline<br>Fluvoxamine<br>Venlafaxine<br>Mirtazapine<br>Antipsychotics (olanzapine, quetiapine, aripiprazole)<br>**Third line**<br>ECT should be considered where rapid response is required or in treatment failure cases |
| **Atypical depression** | • Variably depressed mood with mood reactivity to positive events<br>• Over-eating and over-sleeping | **First line**<br>Sertraline<br>Fluoxetine<br>**Second line**<br>Nortriptyline<br>Imipramine |

| | | |
|---|---|---|
| | • Extreme fatigue and heaviness in the limbs (leaden paralysis)<br>• Pronounced anxiety<br>• Common co-existing diagnoses include panic disorder, substance misuse and somatization disorder | |
| **Melancholic features** | • Loss of interest or pleasure in all, or almost all, activities, or a lack of reactivity to usually pleasurable stimuli<br>• Worsened depression in the morning<br>• Early morning awakening<br>• Significant anorexia or weight loss<br>• This group of patients may have increased risk of suicide and recurrence | **First line**<br>Fluoxetine<br>Escitalopram<br>Paroxetine<br><br>**Second line**<br>Venlafaxine<br>Amitriptyline<br>Nortriptyline<br>Imipramine |
| **Catatonia** | • Catatonic depression is characterized by not responding to what is going on around the patients<br>• The patient may be silent and motionless (in a stupor); may show excessive motor activity<br>• Important differential diagnoses include<br>• General medical conditions (i.e., organic disorders)<br>• Bipolar mood disorder<br>• Schizophrenia | **First line**<br>Oral/intramuscular benzodiazepines (lorazepam, diazepam)<br>**Second line**<br>ECT<br><br>**Once a person's catatonic symptoms improve, antidepressants and psychotherapy can be added to treat the underlying depression |
| **Persistent depressive disorder (dysthymia)** | • A chronic/continuous form of depression<br>• Usually lasts for more than 2 years | **First line**<br>Fluoxetine<br>Sertraline<br>**Second line**<br>Amitriptyline<br>Imipramine<br>Nortriptyline<br>Venlafaxine<br>**Third line**<br>CBT |
| **Premenstrual dysphoric disorder** | • Symptoms usually begin 7 to 10 days before the menstrual period and may continue for the first few days of the period<br>• Prominent features include<br>- Sadness or hopelessness<br>- Anxiety<br>- Frequent mood changes<br>- Marked irritability or anger | **First line**<br>Sertraline<br>Escitalopram<br>Fluoxetine<br>**Second line**<br>Venlafaxine |

# SPECIAL POPULATION

| Special population | Recommendations | Treatment |
|---|---|---|
| **Pregnancy** | • Consider antidepressant in case of moderate to severe depression in combination with psychotherapy.<br>• Try to prescribe single antidepressant.<br>• If a woman has a history of a good response to an antidepressant, consider that antidepressant first.<br>• Electroconvulsive therapy is recommended as a treatment option in moderate to severe depression in all trimesters who are non-responsive to medication or who are not suitable for pharmacotherapy. | Sertraline<br>Escitalopram<br>Fluoxetine<br>Maprotiline<br><br>***Avoid Paroxetine* |
| **Postpartum period and lactating mother** | • Prescribe SSRIs to treat moderate to severe major depressive disorder in combination with psychotherapy. | Fluoxetine<br>Sertraline<br>Escitalopram |
| **Elderly** | • Consider SSRIs, SNRIs.<br>• ECT is effective in treating depression in older age and has better outcome than the younger. | **First line**<br>Escitalopram<br>Sertraline<br>Fluoxetine<br><br>**Second line**<br>Nortriptyline<br>Duloxetine<br>Agomelatine |
| **Child and adolescent** | • Prescribe antidepressant medication to a child or young person with moderate to severe depression in combination with psychological therapy.<br>• Monitoring of adverse drug reactions, as well as reviewing mental state and general progress is necessary. | **First line**<br>Fluoxetine<br><br>**Start fluoxetine at 10 mg daily or 20 mg on every alternate day. This can be increased to 20 mg daily after 1 week if clinically necessary* |

| Special population | Recommendations | Treatment |
|---|---|---|
| | • In psychotic depression, augmenting the current treatment plan with a second-generation antipsychotic medication should be considered.<br>• ECT is not recommended in the treatment of depression in children (5–11 years). | **Second line**<br>Sertraline<br>Citalopram<br><br>**Third line**<br>Nortriptyline<br><br>***Avoid Paroxetine and Venlafaxine* |

# COMORBID MEDICAL CONDITIONS

| Comorbid medical condition | Recommendations | Treatment |
|---|---|---|
| **Ischemic heart disease** | • Prescribe SSRIs and SNRIs.<br>• TCAs should be used cautiously. | **First line**<br>Escitalopram<br>Sertraline<br>Fluoxetine<br><br>**Second line**<br>Desvenlafaxine<br>Duloxetine<br>Agomelatine |
| **Post stroke depression** | • Prescribe antidepressant to treat depression in post stroke patients to facilitate rehabilitation, improve global cognitive functioning, enhance motor recovery and reduce mortality.<br>• Antidepressants also have prophylactic effect against post stroke depression as depression increases the risk of stroke; depression is seen in at least 30-40% survivors of stroke. | Fluoxetine<br>Escitalopram<br>Sertraline<br>Mirtazapine<br>Nortriptyline<br><br>***as SSRIs may increase bleeding tendency, use cautiously* |
| **Epilepsy** | • Major depressive disorder significantly increases the risk of unprovoked seizures even after the adjustment of age, sex, length of medical follow up and medical therapies for depression.<br>• Consider Concomitant prescription of an anticonvulsant or elevating the dose of an existing anticonvulsant. | **First line**<br>Sertraline<br>Escitalopram<br><br>**Second line**<br>Mirtazapine |
| **Parkinson's disease** | • Patients with Parkinson's disease experience alteration of serotonergic and noradrenergic systems that may induce depression. | **First line**<br>Sertraline<br>Escitalopram<br>Fluoxetine<br>Citalopram |

| Comorbid medical condition | Recommendations | Treatment |
|---|---|---|
| | | **Second line**<br>Venlafaxine<br>Duloxetine<br>Agomelatine<br><br>**Third line**<br>ECT |
| **Diabetes mellitus** | • Prescribe SSRIs as the first line treatment.<br>• Consider SNRIs in patients with diabetic neuropathy.<br>• Try to avoid TCAs and MAOIs | Fluoxetine<br>Duloxetine |
| **Renal impairment** | • Start antidepressant at a low dose and increase slowly. In renal impairment, the half-life of a drug is usually prolonged.<br>• Prescribe a single drug.<br>• Monitor patient for adverse effects.<br>• Avoid TCAs.<br>• Monitor renal function weekly, at least initially. | Escitalopram<br>Sertraline<br>Fluoxetine<br>Mirtazapine<br><br>***as SSRIs may cause electrolyte imbalance, use cautiously* |
| **Hepatic impairment** | • Start an antidepressant at a lower dose.<br>• Prescribe a single drug.<br>• Consider longer intervals between dosage or alternate day dosing.<br>• Always monitor carefully for side effects that may develop later than the usual.<br>• Avoid drugs that are very sedative.<br>• Avoid drugs that are known to be hepatotoxic (e.g., MAOIs).<br>• Monitor liver function tests (LFTs) weekly, at least initially. | Escitalopram<br>Sertraline<br>Amitriptyline |

# MISCELLANEOUS

| Summary Recommendations for Antidepressants | |
|---|---|
| **Line of recommendation** | **Antidepressants** |
| **First-line** | Agomelatine<br>*Bupropion*<br>Citalopram<br>Desvenlafaxine<br>Duloxetine<br>Escitalopram<br>Fluoxetine<br>Fluvoxamine<br>*Mianserin*<br>Milnacipran<br>Mirtazapine<br>Paroxetine<br>Sertraline<br>Venlafaxine<br>*Vortioxetine* |
| **Second-line** | Amitriptyline, clomipramine, and others TCA<br>Levomilnacipran<br>*Moclobemide*<br>Quetiapine<br>*Selegiline*<br>*Trazodone*<br>Vilazodone |
| **Third-line** | *Phenelzine*<br>*Tranylcypromine*<br>*Reboxetine* |

First line Level 1 or Level 2 Evidence, plus clinical support; Second line Level 3 Evidence or higher, plus clinical support; Third line Level 4 Evidence or higher, plus clinical support.

Alphabetically arranged, Italics are not available in Bangladesh market

# MANAGING UNWANTED EFFECTS OF MEDICATION

Patients may impose a different value than the doctor to a certain unwanted effect, so drug choice should always involve patients' opinions.

An important component of management of unwanted effects of medication is educating patients about the common side effects. However, for some patients discussing side effects may make them anxious and magnify concerns resulting in premature discontinuation or switching to another medication. Some side effects require prompt evaluation (e.g., rash, agitation, worsening of suicidal ideations).

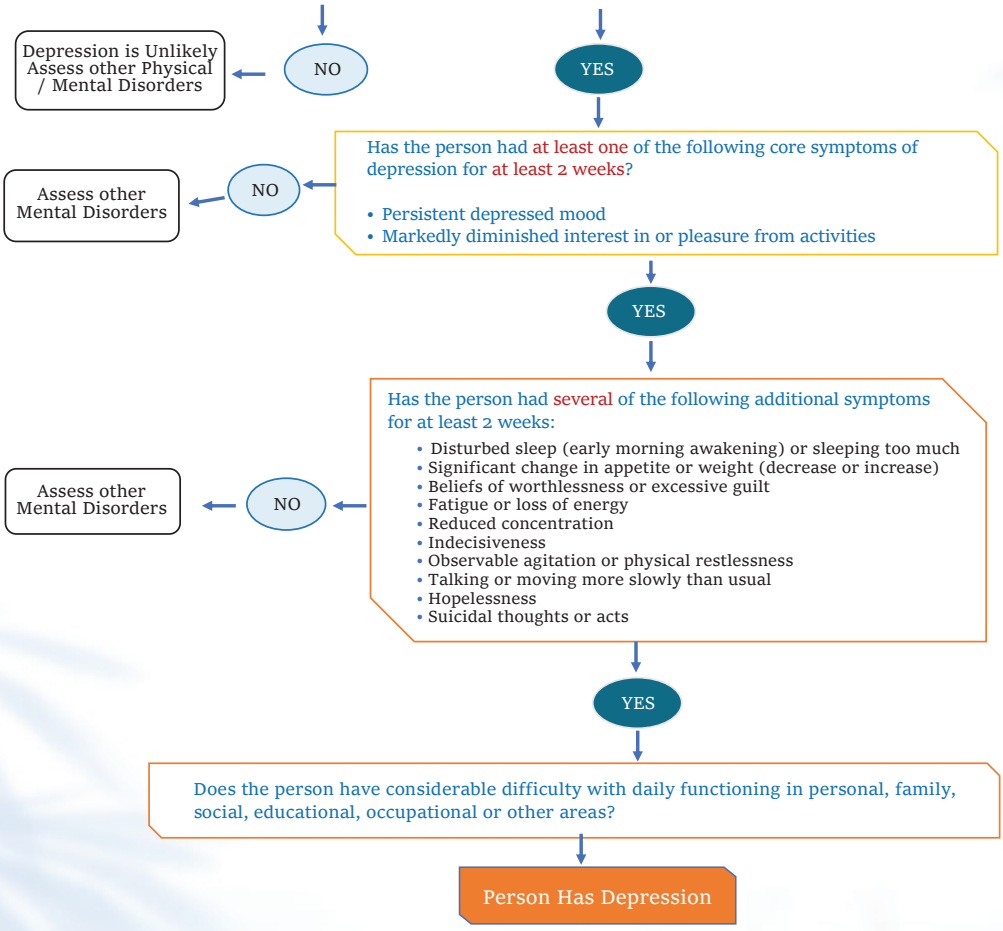
| Unwanted effect | Drugs responsible | Management |
|---|---|---|
| **Nausea, dyspepsia, vomiting** | • SSRIs<br>• SNRIs | Common side effect (17-26%)<br>• Take medication after food or<br>• Small amount of food like toast, crackers, ginger containing food<br>• Divided dosing<br>• Omeprazole<br>• Ondansetron, mirtazapine (5-HT3 receptor blocking properties) |
| **Diarrhea** | • SSRIs | Usually transient, resolves within weeks<br>• Loperamide<br>• Cyproheptadine |
| **Constipation** | • TCAs<br>• SSRI (esp. paroxetine) | • Physical activity<br>• Fluid, fiber intake<br>• Bulk-forming laxative, stool softeners, osmotic agents, etc. |
| **Fatigue and somnolence** | • SSRIs more likely to cause fatigue<br>• Mirtazapine, TCAs more likely to cause somnolence | • Exclude sleep apnea, substance use<br>• Sleep hygiene, exercise<br>• Morning to nighttime shift in administration or evening administration<br>• Divided dosing<br>• Use of slower release preparations<br>• Psychostimulants – bupropion, modafinil |

| Unwanted effect | Drugs responsible | Management |
|---|---|---|
| **Insomnia** | • Reboxetine<br>• SSRIs | Found in 12-22% of outpatients<br>• Benzodiazepines<br>• Zolpidem, eszopiclone<br>• Melatonin<br>• Trazodone, mirtazapine, etc. |
| **Tremor** | • Venlafaxine<br>• SSRIs<br><br>** *Fine and rapid tremor more common* | Anxiety needs to be excluded<br>• B-Blockers<br>• Benzodiazepine<br>• Caffeine intake reduced |
| **Weight gain** | • Mirtazapine<br>• SSRIs<br>Venlafaxine | • Identify who are at risk of weight gain by medical history and lifestyle.<br>• Improve physical activity and diet.<br>• Bupropion, nortriptyline is not associated with weight gain |
| **Antidepressant-induced arrhythmia** | • TCAs<br>• Citalopram<br>• Escitalopram | • ECG monitoring<br>• Use lofepramine, sertraline, mirtazapine when there is chance of arrhythmia |
| **Hyponatremia** | • SSRIs<br>• SNRIs | • Common in elderly<br>• Monitor patients<br>• Refer if serum sodium level <125 mmol/L |
| **Sexual side-effects** | • Potentially all antidepressants (less evidence for mirtazapine and bupropion) | • Can be minimized by starting with low doses or reducing the dose to the minimal effective dose<br>• Drug holiday: trying a once-weekly, one-day drug holiday before engaging in sexual activity<br>• Switching to another SSRI<br>• Adding a counteracting pharmacologic agent<br>• For restoring libido: Amantadine, Buspirone, Yohimbine, Ginkgo Biloba extract, Cyproheptadine<br>• For restoring erection and orgasmic ability: Sildenafil, Tadalafil, Vardenafil. |

# MANAGEMENT IN NON-SPECIALIZED SETTINGS

## Common presentations of depression

- **Multiple persistent physical symptoms**
- **Low energy, fatigue**
- **Sleep problems**
- **Persistent sadness or depressed mood**
- **Anxiety**
- **Loss of interest or pleasure in activities that are normally pleasurable**



## Management

Assessment: Thorough history taking with mental state examination and exclude any history of mania to exclude bipolar disorder. If any current /previous history of mania, avoid any sort of antidepressant and follow protocol of Bipolar Guideline and refer the patient to psychiatrist.

If no features of mania, provide treatment for depression.

## Pharmacological

- Antidepressant: adequate dose and duration
- Antidepressant works slowly, so patients and doctors both need patience
- Need to continue at least 6-9 months after resolution of symptoms
- Regular follow-up

## Non-pharmacological

- Psychoeducation to the person and their carers about treatment options and medications
- Reduce stress and strengthen social supports
- Promote functioning in daily activities and community life
- If available, consider referral for one of the following brief psychological treatments:
  Cognitive-behavior therapy (CBT), interpersonal psychotherapy (IPT), behavior activation and problem-solving counselling.

**Antidepressants**

- **TCA (Amitriptyline, nortriptyline, impipramine):** Start 25 mg at bedtime. Increase by 25-50 mg per week. Minimum effective dose in adults is 75 mg.
- **SSRI: Fluoxetine:** Start 20 mg daily. If no response in 6 weeks, increase to 40 mg.
- **Sertraline:** Start 25 mg at morning/daytime. Increase by 25-50 mg per week to 100-150 mg

# FOCUS GROUP DISCUSSION FINDINGS

Bangladesh Association of Psychiatrists (BAP) organized several focus group discussions (FGD) with senior psychiatrists to understand the current treatment approach and pattern in managing patients with depressive disorders in Bangladesh. They each had more than 25 years of psychiatric clinical experience, practiced in variety of settings ranging from very low resource settings, government hospitals to top notch corporate hospitals. They were enquired about their usual treatment choices in different depressive disorders.

SSRIs and in some cases SNRIs were found to be their first-choice of medication in depression. SSRIs are chosen for their improved side effect profile, tolerability and cardiac friendly properties. In case of dysthymia, TCAs are also chosen. When medical comorbidities are present, SSRIs are usually prescribed as first-line option.

Drug non-compliance is a point of concern and to ensure compliance strategies like psychoeducation, involvement of family members, starting drugs at lower dosage, choosing more tolerable drug, regular monitoring of side effects, regular follow up were suggested.

# GLOSSARY

## DSM-5 criteria for major depressive disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
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.
(Note: In children, consider failure to make expected weight gain.)
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 a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
Note: Criteria A-C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of

intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

## ICD-11 description of depressive disorder

Single episode depressive disorder is characterized by the presence or history of one depressive episode when there is no history of prior depressive episodes. A depressive episode is characterized by a period of depressed mood or diminished interest in activities occurring most of the day, nearly every day during a period lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. There have never been any prior manic, hypomanic, or mixed episodes, which would indicate the presence of a bipolar disorder.

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# ANNEXURES

| Antidepressant | Usual dose range (mg/day) | Maximum dose (mg/day) |
|---|---|---|
| **Selective serotonin reuptake inhibitors (SSRIs)** | | |
| Fluoxetine | 20-60 | 60 |
| Paroxetine | 20-50 | 60 |
| Fluvoxamine | 100-300 | 300 |
| Sertraline | 50-200 | 200 |
| Citalopram | 20-40 | 40 |
| Escitalopram | 10-20 | 20 |
| | | |
| **Tricyclic antidepressants (TCAs)** | | |
| Tricyclic tertiary amines | | |
| Amitriptyline | 75-150 | 150 |
| Imipramine | 75-150 | 200 |
| Clomipramine | 50-150 | 250 |
| Tricyclic Secondary Amines | | |
| Desipramine | 100-200 | 300 |
| Nortriptyline | 75-100 | 150 |
| Tetracyclic | | |
| Maprotiline | 50-75 | 225 |
| Unicyclic | | |
| Bupropion | 150-450 | 450 |
| Serotonin norepinephrine reuptake inhibitors (SNRIs) | | |
| Venlafaxine | 150-375 | 375 |
| Duloxetine | 30-60 | 120 |
| Milnacipran | 50-200 | 200 |

| | | |
|---|---|---|
| **Desvenlafaxine** | **10-50** | **400**<br>***There is no evidence that doses greater than 50 mg /day provide additional benefit* |
| **Noradrenaline and Specific Serotonin Antidepressant (NaSSA)** | | |
| **Mirtazapine** | **15-45** | **45** |
| **Serotonin partial agonist and reuptake inhibitor (SPARI)** | | |
| **Vilazodone** | **10-20** | **40** |
| **Others** | | |
| **Agomelatine** | **25-50** | **50** |

| Common side effects of antidepressants |
| --- |
| **Selective serotonin reuptake inhibitors (SSRIs)** |
| Headache |
| GI distress |
| Weight loss/gain |
| Anxiety |
| Sleep disturbance |
| Sexual dysfunction |
| **Tricyclic antidepressants (TCAs)** |
| Anticholinergic effects (dry mouth, blurred vision, urinary retention, constipation) |
| Drowsiness |
| Orthostasis |
| Conduction abnormalities |
| Mild GI distress |
| Weight gain |
| Sexual dysfunction |
| High risk of seizure after 450 mg/day |
| **Serotonin norepinephrine reuptake inhibitors (SNRIs)** |
| Mild anticholinergics effects |
| Drowsiness |
| Conduction abnormalities |
| GI distress |
| **Noradrenaline and specific serotonin antidepressants (NaSSAs)** |
| Mild anticholinergic effects |
| Drowsiness |
| Orthostatic hypotension |
| Conduction abnormalities |
| GI distress |
| Weight gain |

| Serotonin partial agonist and reuptake inhibitors (SPARIs) |
| --- |
| Sedation |
| Dizziness |
| Hepatotoxicity |
| **Others** |
| Mild anticholinergic effects |
| Drowsiness |
| Orthostatic hypotension |
| Conduction abnormalities |
| GI distress |
| Weight gain |

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