وزارة الصحة
Ministry of Health

MOH Protocol for the Management of Major Depressive Disorder

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- **Introduction**

Major depressive disorder (MDD) is a prevalent mental disorder. In Saudi Arabia, the annual prevalence of MDD in the general population is 3.8 %, and lifetime prevalence is 6.0 %. Women have a greater lifetime prevalence of MDD (8.9%) than men (3.1%).[1]

Depressive disorders were the second biggest cause of disability worldwide, according to the Global Burden of Disease Study 2010. MDD also is associated with severe impairment in quality of life and has a significant economic impact owing to occupational costs, medical service costs, and suicide-related costs. In addition, many chronic medical issues, such as heart disease, arthritis, asthma, back pain, chronic pulmonary disease, hypertension, and migraine, are linked to MDD. [2, 3, 4]

A. Purpose

Major depressive disorder (MDD) is very common in clinical practice, and they are frequently associated with other psychiatric and medical issues. A comprehensive grasp of pharmacological and psychological treatments' efficacy and side effect profiles is necessary for optimal management. There is a clear need to create a MOH protocol for the management of MDD due to highly variable practice. As a result of an initiative of the Ministry of Health of the Kingdom of Saudi Arabia, a group of expert psychiatrists reviewed multiple published protocols of Management of MDD and created adapted protocols for MOH health care providers.

B. Aim & Scope

These protocols aim to deliver evidence-based recommendations on the non-pharmacological and pharmacological management of Major depressive disorder. This protocol also aims to reduce unnecessary use of multiple psychotropic medications and some psychotropic like antipsychotics in the management of MDD and to ensure that, where unavoidable, they are prescribed according to best practice.

C. Targeted Population

The protocol is intended to be a practical protocol and ready reference for health professionals who work in settings where they will be caring for patients with Major Depressive Disorder. Given the extensive range of expertise, disciplines, and positions of employees at the MOH, it's impossible to capture the whole scope of specialist practice that can be used by experienced professionals across different disciplines and settings. As a result, this protocol can be applied in several cases. It provides an overview of fundamental principles and practical resources for less experienced employees, which they may implement and discuss with their supervisors. Multidisciplinary teams can utilize it as a shared reference point to aid in coordinated treatment, and more experienced professionals can use it as a refresher or training resource. The protocol should be applied within a framework of local policies and procedures.

D. Setting

- Iradah Complex / Hospital and Mental Health.
- Psychiatric clinics in MOH General Hospitals.

E. Methodology

This is the first version of the Saudi practical protocol on the management of Major depressive disorder. This protocol development is completed through 2 phases:

Phase 1: literature review, the MOH formulary adaptation, and reviewing multiple published protocols by a teamwork of a group of psychiatric consultants. The published protocols were evaluated using the Appraisal of Protocols, Research and Evaluation II (AGREE II) scale. A total of 3 protocols were reviewed, including The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition and UK National Institute for Health and Care Excellence (NICE) protocol, The APA Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition, and the Canadian Clinical Practice Guidelines for the Management of Adults with Major Depressive Disorder meet the criteria for use in the development this protocol.

Phase 2: The protocol was sent to a group of experts in psychiatric Disorders to put their input and provide their review. Their input was collected over three weeks, followed by further meetings and assessment for the feedback by the committee.

F. Updating

The first version of this protocol was created in 2021. The protocol will be updated every three years or if any changes or updates are released by international/national protocols, pharmacotherapy references, or MOH formulary.

G. Conflict of Interest

This protocol was developed based on valid scientific evidence. No financial relationships with pharmaceutical, medical device, and biotechnology companies.

H. Funding

No fund was provided.

I. DISCLAIMER

This Clinical protocol is an evidence-based decision-making tool for managing health conditions. It is based on the best information that is available at the time of writing and is to be updated regularly. This protocol is not intended to be followed as a rigid treatment protocol. It is also not meant to replace the clinical judgment of practicing physicians but is only a tool to help manage patients with Major Depressive Disorder. Treatment decisions must always be made on an individual basis, and prescribing physicians must customize care and tailor treatment regimens to patients' unique situations and health histories. Physicians should check the approved product monographs within their institution's formulary for each drug for dosage, special warnings and precautions for usage, contraindications, and monitoring of side effects and potential risks. When choosing treatment options, take into account any constraints imposed by the institution's formulary. Prescribing physicians should consult their institution's formularies during the decision-making process for picking specific drugs within a recommended specific class.

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- **Protocol Overview (Summary)**

- **Establish Assessment and diagnosis of Major Depressive Disorder.**
- **Keep in mind that Depressive Disorder might be secondary to a medical condition (e.g., Hypothyroidism), or drug induce (e.g., Corticosteroids), and comorbidity with other psychiatric disorders (e.g., substance use disorder).**

Initial treatment based on multiple factors, including severity:

- Mild to:

Non-pharmacological options (Exercise, Light therapy, Psychotherapy)

- Moderate to Severe:

Medication, psychological treatments.

1st line treatment options:

Pharmacological Treatments:

SSRIs, SNRIs, agomelatine, bupropion, mirtazapine, and vortioxetine.

Non-Pharmacological Treatments

a. Exercise: mild to moderate MDD.
b. Psychological Treatments
   1. Cognitive-behavioral therapy (CBT)
   2. Interpersonal therapy (IPT)
   3. Behavioral activation (BA)
c. Light therapy Seasonal (winter) MDD
d. Repetitive Transcranial Magnetic Stimulation (rTMS): First line for patients who have failed at least one antidepressant.
e. Electroconvulsive Therapy (ECT): some clinical situations (Acute suicidal ideation, Psychotic features, Treatment-resistant depression)

2nd line treatment options:

Pharmacological Treatments:

TCAs, quetiapine and trazodone, moclobemide and selegiline, levomilnacipran, and vilazodone.

Non-Pharmacological Treatments

a. Exercise: adjunctive treatment for moderate to severe MDD.
b. Psychological Treatments
   1. Mindfulness-based cognitive therapy (MBCT)
   2. Cognitive-behavioral analysis system of psychotherapy (CBASP)
   3. Problem-solving therapy (PST)
   4. Short-term psychodynamic psychotherapy (STPP)
   5. Telephone-delivered CBT and IPT
   6. Internet- and computer-assisted therapy
c. Light therapy: nonseasonal MDD
d. Electroconvulsive Therapy (ECT)

3rd line treatment options:

Pharmacological Treatments:

MAO inhibitors and reboxetine.

Non-Pharmacological Treatments

a. Psychological Treatments
   1. Long-term psychodynamic psychotherapy (PDT)
   2. Acceptance and commitment therapy (ACT)
   3. Videoconferenced psychotherapy
   4. Motivational interviewing (MI)
b. Sleep deprivation: SD is recommended as a third-line adjunctive treatment for more severe and refractory forms of MDD

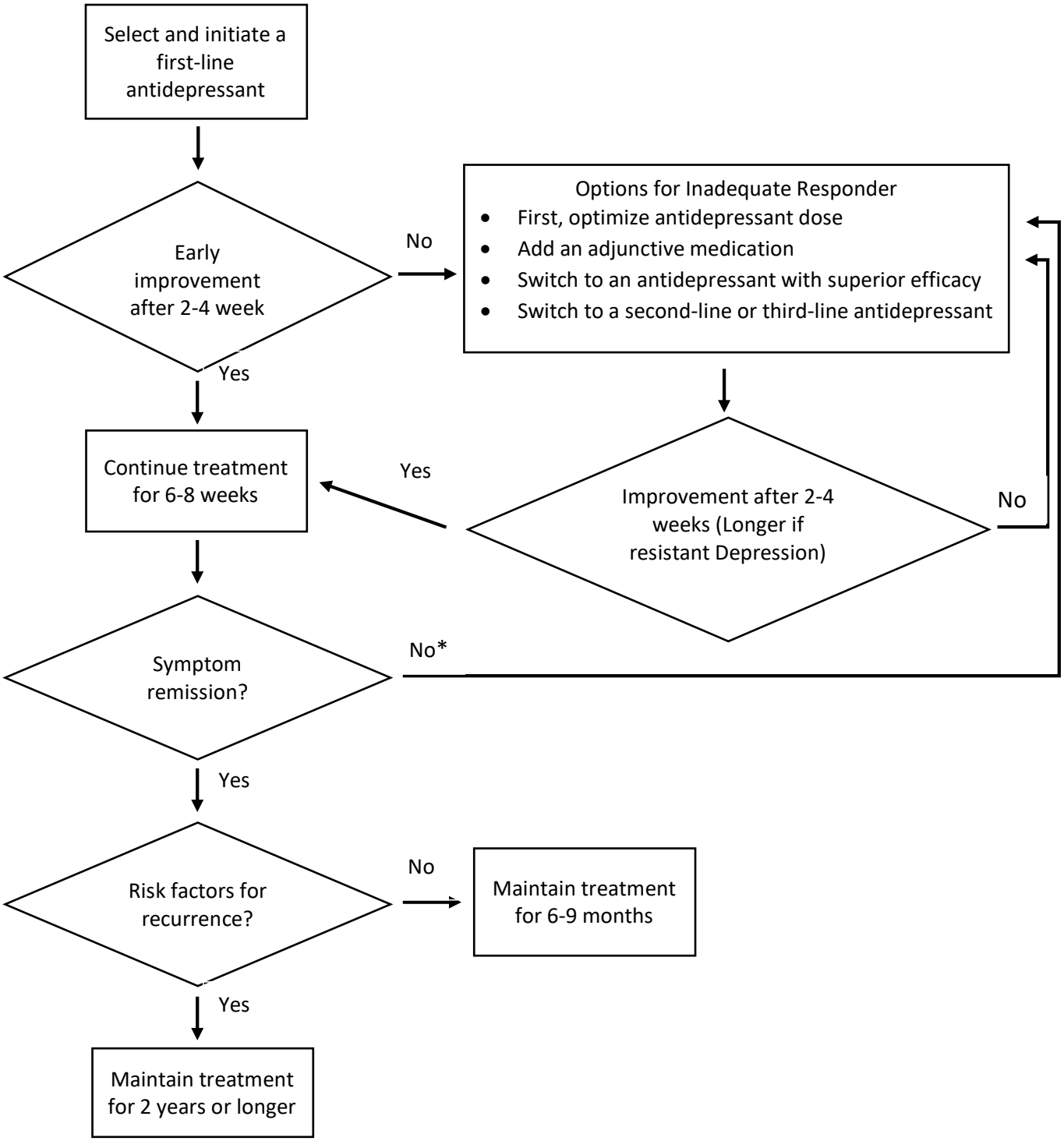
Recommendations for Adjunctive drugs for Non-response or Partial Response to an Antidepressant:

First line: Aripiprazole, Quetiapine, Risperidone.

Second line: Brexpiprazole, Bupropion, Lithium, Mirtazapine/mianserin, Modafinil, Olanzapine, Triiodothyronine.

Treatment-resistant depression (TRD): Esketamine.

- **Summary Algorithm for Pharmacological Treatment**



*In case of more chronic and resistant depressions, consider a chronic disease management approach that focuses on improving functioning and quality of life more than symptom remission.

- **General principles in Assessment and Management of Major Depressive Disorder**

A. Assessment:

- Those who meet the DSM-5 Criteria for Major Depressive Episode. Five (or more) of the symptoms set out below have been present for at least two weeks and indicate a change in functioning; at least one of the symptoms is (1) or (2). [5]

  1. Depressed mood throughout the majority of the day, almost every day, as indicated by either a subjective report (e.g., feels sad, empty, and hopeless) or an observation made by others (e.g., appears tearful). Note: it can be an irritable mood in children and adolescents.
  2. There is a noticeable decrease in interest or pleasure in all, or nearly all, activities during most of the day, almost every day (as indicated by either subjective account or observation).
  3. Losing or gaining weight significantly while not dieting (e.g., a shift of more than 5% of weight in a month) or a decrease or increase in appetite almost every day. Consider inability to make expected weight gains in children.
  4. Insomnia or hypersomnia almost every day.
  5. Psychomotor agitation or retardation almost every day (noticeable by others, not just subjective feelings of restlessness or being slowed down).
  6. Losing energy or fatigue almost every day.
  7. Feelings of worthlessness or extreme or improper guilt (which may be delusional) almost every day (not just guilt about being sick or self-reproach).
  8. Loss of ability to concentrate or think, or indecisiveness, almost every day (either by subjective account or as noticed by others).
  9. Recurrent thoughts of death (not merely being afraid of dying), repeated suicidal thoughts without a plan, or a suicide attempt or a particular plan for suicide.

- The symptoms result in clinically severe distress or impairment in social, occupational, or other vital areas of functioning.
- The episode is not caused by the physiological effects of a substance or by another medical condition.
- Note: The above three criteria represent a major depressive episode.
- Schizoaffective disease, schizophrenia, schizophreniform disorder, delusional disorder, or other schizophrenia spectrum and other psychotic disorders do not better explain the occurrence of the major depressive episode.
- A manic episode or a hypomanic episode has never existed.
- There are clinical presentations for MDD that have implications for prognosis and therapy; DSM-5 categorizes these subtypes (Episode Specifiers) as follows: [5]

  1. With melancholic features: Nonreactive mood, anhedonia, weight loss, guilt, psychomotor retardation or agitation, morning worsening of mood, early morning awakening, excessive or inappropriate guilt.

2. With atypical features: Reactive mood, oversleeping, overeating, leaden paralysis, interpersonal rejection sensitivity.
3. With psychotic features: Hallucinations or delusions.
4. With catatonic features: Catalepsy (waxy flexibility), catatonic excitement, negativism or mutism, mannerisms or stereotypes, echolalia or echopraxia (uncommon in clinical practice).
5. With anxious distress: Feeling keyed up or tense, restless, worried, something awful may happen, or afraid of losing control.
6. With mixed features: Elevated mood, inflated self-esteem or grandiosity, more talkative, racing thoughts, increased energy and activity, decreased need for sleep, risky and impulsive activities.
7. Seasonal pattern: Regular onset and remission of depressive episodes during a particular season (usually fall/winter onset).
8. With peripartum onset: Onset of depressive episode during pregnancy or within four weeks postpartum.

- Examples of Validated Scales.[6]
  1. Hamilton Depression Rating Scale (HAM-D, HAM-7)
  2. Montgomery-Asberg Depression Rating Scale (MADRS)
  3. Inventory for Depressive Symptomatology (IDS)
  4. Patient Health Questionnaire (PHQ-9)

B. Management:

- Choosing a pharmacological or non-pharmacological management model depends on multifactor including the severity of the symptoms, patient preference and motivation, the ability of the patient to engage in the treatment, availability of the medication or psychotherapy services, the initial response to treatment, side effect profile, and the presence of comorbid medical or psychiatric disorders.[6]

- All patients should be educated about their disorder, efficacy (including expected time to onset of therapeutic effects) and tolerability of treatment choices, aggravating factors, and signs of relapse.[6]

- Combined Psychological Treatment with Medication: A recent meta-analysis shows that psychological treatment combined with antidepressants is more effective than antidepressants alone.[7]

- **Recommendations for Pharmacological Treatment**

A. Step 1: Select and initiate a first-line antidepressant:

- The process of choosing an antidepressant should include both physician expertise and patient perceptions and preferences through conducting a detailed clinical assessment, and evaluating previous treatments, then to discuss the evidence-based pharmacologic and nonpharmacologic treatment options and taking into consideration the patient preference in the decision.
  - Recommendations for pharmacological treatment (see the appendix for doses):[9]
    1. The first-line agents include selective serotonin reuptake inhibitors (SSRIs), SNRIs, agomelatine, bupropion, mirtazapine, and vortioxetine.
    2. The second-line agents include TCAs, quetiapine and trazodone (due to increased side effect burden), moclobemide and selegiline (potential serious drug interactions), levomilnacipran (shortage of comparative and relapse-prevention data), and vilazodone (shortage of comparative and relapse prevention data and the need to titrate and take with food).
    3. Third-line agents include MAO inhibitors (owing to higher side effect burden and potential serious drug and dietary interactions) and reboxetine (lower efficacy).

- Within the first 2 weeks, reassess patients for tolerability, and safety.

- After 2-4 weeks, assess patients for early improvement:
  - The early improvement is correlated with response and remission at 6 to 12 weeks. [8]
  - The lack of early improvement
    - For non-improvers and the medication is tolerated increase the antidepressant dose.[10,11]
    - For non-improvers and the medication is poorly tolerated switch to another antidepressant.

- After achieving symptomatic remission, maintain treatment with antidepressants for 6 to 9 months, while those with risk factors for recurrence (Frequent, recurrent episodes, extreme episodes (psychosis, extreme impairment, suicidality), Chronic episodes, existence of comorbid psychiatric or other medical conditions, existence of residual symptoms, Difficult-to-treat episodes) extend antidepressant treatment to 2 years or more.[9]

B. Step 2: Management of Inadequate Responder to an Antidepressant:

- The clinician should then reassess the diagnosis and consider treatment issues (subtherapeutic doses, inadequate duration of treatment, poor adherence). that may be affecting response.[12]

- Management options for Inadequate Responder
  - Adjunctive strategy:
    - It refers to the addition of a second medication to an initial medication.

    - Consider an adjunctive medication when: [9]
      a. There have been 2 or more antidepressant trials.
      b. The first antidepressant appears to be well tolerated.
      c. The first antidepressant has partial response (>25% improvement).
      d. The first antidepressant has specific residual symptoms or side effects that can be targeted.

e. It requires less time for a response (more severe, more functional impairment).
f. Patient prefers to add on another medication.

- Recommendations for Adjunctive drugs for Nonresponse or Partial Response to an Antidepressant: [9]
  a. First line: Aripiprazole 2-15 mg, Quetiapine 150-300 mg, Risperidone 1-3 mg.
  b. Second line: Brexpiprazole 1-3 mg, Bupropion 150-300 mg, Lithium 600-1200 mg, Mirtazapine/mianserin 30-60 mg, Modafinil 100-400 mg, Olanzapine 2.5-10 mg, Triiodothyronine 25-50 mcg.
  c. Treatment-resistant depression (TRD): an esketamine nasal spray (56–84mg and 28mg in older people) has been developed and approved for use in TRD (in conjunction with an oral antidepressant) in Europe and the United States.[13-16]

- Switching Strategy:
  - The evidence is showing that switching non-responders to another antidepressant results in good response and remission rates.

  - Consider switching to another antidepressant when: [9]
    a. It is the first antidepressant trial.
    b. The first antidepressant has poorly tolerated adverse effects.
    c. There is no response (25% improvement) to the first antidepressant.
    d. It requires more time for a response (less severe, less functional impairment).
    e. Patient prefers to switch to another antidepressant.

  - It is recommended to switch to an antidepressant with evidence of superior efficacy.

  - (Escitalopram, Mirtazapine, Sertraline, and Venlafaxine have modest superiority for treatment response over duloxetine, fluoxetine, fluvoxamine, paroxetine, Also, Escitalopram over Citalopram, and Mirtazapine over sertraline, venlafaxine). [17]

  - Consider a chronic disease management approach for more chronic and resistant depressions, with a focus on enhancing functioning and quality of life rather than symptom remission.[18]

- **Recommendations for Psychological Treatments**

Recommendations for Psychological Treatments for Acute and Maintenance Treatment of Major Depressive Disorder. [19]

A. Acute Treatment

- First line:
  1. Cognitive-behavioral therapy (CBT)
  2. Interpersonal therapy (IPT)
  3. Behavioral activation (BA)

- Second line:
  1. Mindfulness-based cognitive therapy (MBCT)
  2. Cognitive-behavioral analysis system of psychotherapy (CBASP)
  3. Problem-solving therapy (PST)
  4. Short-term psychodynamic psychotherapy (STPP)
  5. Telephone-delivered CBT and IPT
  6. Internet- and computerassisted therapy
- Third line:
  1. Long-term psychodynamic psychotherapy (PDT)
  2. Acceptance and commitment therapy (ACT)
  3. Videoconferenced psychotherapy
  4. Motivational interviewing (MI)

B. Maintenance Treatment (Relapse Prevention)

- First line:
  1. Cognitive-behavioral therapy (CBT)
  2. Mindfulness-based cognitive therapy (MBCT)
- Second line:
  1. Interpersonal therapy (IPT)
  2. Behavioral activation (BA)
  3. Cognitive-behavioral analysis system of psychotherapy (CBASP)
- Third line: Long-term psychodynamic psychotherapy (PDT)

- **Recommendations for Other Options of MDD Treatments**

A. For Mild to Moderate MDD:

- Exercise: Recent meta-analyses and systematic reviews reported the effectiveness as monotherapy and adjunct to antidepressants or psychotherapy. It is recommended as first-line monotherapy for mild to moderate MDD and as second-line adjunctive treatment for moderate to severe MDD. [22]
- Light therapy: A recent meta-analysis and an RCT found evidence to support the efficacy of LT as monotherapy and adjunct to antidepressants in nonseasonal MDD (recommended as Second Line) and as monotherapy for Seasonal (winter) MDD (recommended as First Line). [22]

B. For Moderate to severe MDD:

- Repetitive Transcranial Magnetic Stimulation (rTMS): rTMS uses powerful focused magnetic field pulses to induce electrical currents in neural tissue noninvasively, via an inductor coil placed against the scalp.[21] It is recommended as First line for patients who have failed at least 1 antidepressant. [20]

- Electroconvulsive Therapy (ECT): ECT is a therapeutic procedure that entails induction of a seizure by applying an electrical stimulus to the brain. It is recommended as Second line and in some clinical situations (Acute suicidal ideation, Psychotic features, and treatment-resistant depression) as First line. [20]
- Sleep deprivation: SD is recommended as a third-line adjunctive treatment for more severe and refractory forms of MDD, in combination with other chronotherapeutic techniques. [22]

Appendix (Summary Recommendations for Antidepressants)

First line

- Bupropion 150-300 mg
- Duloxetine 60 mg
- Escitalopram 10-20 mg
- Fluoxetine 20-60 mg
- Fluvoxamine 100-300 mg
- Mirtazapine 15-45 mg
- Venlafaxine 75-225 mg
- Vortioxetine 10-20 mg

Second line

- Amitriptyline, clomipramine, and others TCA
- Quetiapine 150-300 mg
- Trazodone 150-300 mg

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