This guideline addresses the acute, continuation, and maintenance phases of major depressive disorder through standardized processes of screening, diagnosis, and symptom management. Unipolar depression with psychosis and bipolar depression are not addressed in this guideline.

The Patient Health Questionnaire PHQ-9 is recommended as a screening tool for depression.

For cases requiring linkage with community mental health centers, contact Netcare, 614-276-CARE.

Screening

The Patient Health Questionnaire PHQ-9 is recommended to screen for major depression.

Diagnostic Criteria

DSM-V* Criteria for Major Depressive Disorder

<table>
<thead>
<tr>
<th>Signs / Symptoms</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood / energy:</td>
<td></td>
</tr>
<tr>
<td>• Depressed mood</td>
<td>≥ 1</td>
</tr>
<tr>
<td>• Diminished interest / enjoyment/ pleasure</td>
<td></td>
</tr>
<tr>
<td>Behavior:</td>
<td></td>
</tr>
<tr>
<td>• Sleep (insomnia / hypersomnia)</td>
<td>≥ 3 (if 2 of above)</td>
</tr>
<tr>
<td>• Appetite / weight (decrease or increase)</td>
<td></td>
</tr>
<tr>
<td>• Psychomotor activity (retardation/ agitation)</td>
<td></td>
</tr>
<tr>
<td>• Reduced energy / increased fatigue</td>
<td></td>
</tr>
<tr>
<td>Cognition:</td>
<td></td>
</tr>
<tr>
<td>• Reduced concentration / attention</td>
<td>≥ 4 ( if 1 of above)</td>
</tr>
<tr>
<td>• Ideas of guilt / worthlessness</td>
<td></td>
</tr>
<tr>
<td>• Ideas of death / self-harm / suicide</td>
<td></td>
</tr>
<tr>
<td>• Reduced self-esteem and self confidence</td>
<td></td>
</tr>
<tr>
<td>Total number of symptoms</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Additional unique criteria</td>
<td>Impaired functioning</td>
</tr>
</tbody>
</table>

*DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.

Phases of Treatment

• Acute Phase (6-12 weeks):
  - Initial phase of treatment with active signs and symptoms.
  - Treatment targets response and remission.

• Continuation (4-9 months):
  - Following remission, treatment continues with a focus on achieving functional improvement.

• Maintenance (years):
  - Treatment continues until signs and symptoms have fully remitted and functional recovery has been achieved.

Treatment Strategies

Optimize Existing Treatments

- If patient is taking an antidepressant, optimize dose when possible.
  - Note: Check levels of tricyclic antidepressants (TCAs); venlafaxine and duloxetine generally have antidepressant activity across a broader dose range.

Substitution Strategy

- Before altering any treatment, allow a trial of appropriate duration, usually 2–6 weeks (sometimes longer), at adequate dosage for pharmacological or psychological treatments.
- When substituting antidepressants, alter antidepressant class unless reason for substitution is poor tolerability, which has prevented an adequate trial.
- Consider dual-acting agents (e.g., venlafaxine and duloxetine), tricyclics and tetracyclics (TCAs), or monamine oxidase inhibitors (MAOIs) (e.g., phenelzine) if adverse effects and dietary restrictions can be tolerated.

Note: Substitution strategy includes changing between antidepressants and psychological treatments, or substituting class of antidepressant.
Augmentation and/or Combination Strategy

- Add psychological treatment (cognitive behavioral therapy) or antidepressant medication as indicated.
- Level I strategies include:
  - Lithium:
    - Lithium can be administered in conjunction with all antidepressants.
    - As an augmentation strategy, lithium is the most studied approach.
  - Atypical anti-psychotics:
    - Aripiprazole
    - Olanzapine
    - Risperidone
    - Quetiapine
  - Thyroid hormone.
  - Short-term benzodiazepines may be helpful for symptom management.
- Combine antidepressants:
  - There is limited controlled evidence to support this approach, but it can be considered to treat resistant depression.
  - Logical combinations include combining serotonergic- and noradrenergic-acting drugs or two agents with different pharmacology.

Caution: When employing augmentation strategies or if combining antidepressants, monitor carefully for side-effects and potential toxicity.

Review

- Review patient’s adherence to treatment plan and dose of medication if taking an antidepressant.

Re-evaluate

- Re-evaluate diagnosis:
  - Frequently consider continuing factors of depression, substance abuse, and personality issues.
  - Reconsider alternative causes such as life events or social stress.

Re-assess

- Reassess comorbidities, especially for anxiety, substance abuse, and personality disorders.
- Assess for medical comorbidities.

Note: In conjunction with clinical management, structured rating scales such as the PHQ-9 or other depression rating scales can assist in quantifying treatment response and determining change in clinical profile.

Continuation Treatment

- Following an initial response, consider treatment with a focus on stabilizing or achieving further improvement and ultimately remission.
- To improve clinical outcome, combine psychotherapy with pharmacological treatments and, during longer term treatment (>12 weeks), consider enhancement approaches to medication management.
- Schedule planned follow-up with regular monitoring of side-effects and adjustment of treatment dosage as needed.
- If there is no response to antidepressant treatment within the first 2 weeks or if the patient fails to respond adequately within 6 weeks, consider a treatment change.
- After remission it is important to continue medication treatment for at least 6-12 months to prevent relapse.
- If remission is not achieved by 3 months, seek consultation or a second opinion and continue active treatment.
- If an initial episode included psychotic features, then continue treatment for at least 3 years.

Stages of Illness

- Response:
  - Significant reduction in clinical signs/symptoms (e.g., 50% reduction in PHQ-9 scores).
- Remission:
  - State of minimal or no signs/symptoms but lacking full recovery.
- Recovery:
  - Stable state of minimal or no signs/symptoms.
- Relapse:
  - The return of signs and symptoms after a patient has experienced a remission.
  - See “Risk of Relapse” section below.
- Recurrence:
  - Emergence of signs/symptoms following recovery.

Risk of Relapse

- Relapse rates are the highest immediately following remission and diminish with time.
- The risk of relapse during the continuation phase of treatment is relatively high and is increased by a variety of factors, such as:
  - Comorbid medical illness.
  - Lack of adherence to treatment plan.
  - Life events/social stress.
  - Female gender.
  - Greater number of prior depressive episodes.
Longer duration of current depressive episodes.
Greater severity of depression.
Residual symptoms.
Presence of psychosis.
Treatment resistance.

Refer and Consult

- For patients with emerging current suicidal intent, contact the Psychiatric Consult Team.
- Include Social Work in discharge planning for referral and preauthorization of mental health services.
- For patients who do not have private health insurance covering mental health services, contact NetCare, 614-276-CARE.

Antidepressant Medications

Evidence reveals that the greater the severity and duration of depression symptoms, the clearer the benefit of antidepressants.

Sub-Threshold Depression and Dysthymia

- Generally, sub-threshold depression should be treated with support, psycho-education and active monitoring.
- If patients have had a history of major depressive episodes or if the symptom duration has lasted longer than 2 years, antidepressant medication may be indicated.

Mild Depression

- Low intensity psychosocial interventions and psychological interventions are indicated.
- If these interventions fail, then antidepressants are recommended.

Moderate Depression

- Antidepressants alone are indicated for moderate depression.
- Antidepressants and evidenced-based psychotherapy (e.g., cognitive behavioral therapy, dialectical behavioral therapy, etc.) may be used together for patients with significant psychosocial problems or co-morbid Axis II disorders.

Severe Depression

- A combination of antidepressant medication and evidenced-based psychotherapy is indicated.
- Electroconvulsive therapy may also be considered first line in severe depression.

Typical First Choices

- Typical first choices are selective serotonin reuptake inhibitors (SSRIs) provided the side-effects are generally more tolerable compared to those of other types of anti-depressants.
- SSRIs include:
  - fluoxetine (Prozac®, Sarafem®)
  - paroxetine (Paxil®)
  - sertraline (Zoloft®)
  - citalopram (Celexa®)
  - escitalopram (Lexapro®)
- Other common first choices include:
  - Serotonin and norepinephrine reuptake inhibitors (SNRIs).
  - Norepinephrine and dopamine reuptake inhibitors (NDRIs).
  - Combined reuptake inhibitors and receptor blockers.
  - Tetracyclic antidepressants.
- A report in Lancet, 2009 Feb 28;373(9865):746-58, indicated that mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, and paroxetine.
  - Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, and venlafaxine.

Typical Second Choices

- Typical second choices are tricyclic antidepressants (TCAs), which tend to have more numerous and more severe side-effects; therefore, they are often not prescribed until SSRIs have been tried first without an improvement.

Typical Last Choices

- Typical last choices are monoamine oxidase inhibitors (MAOIs).
  - They are often prescribed as a last resort, when other medications haven not worked, because they can have serious harmful side-effects.
  - They also require strict dietary restrictions because of rare but potentially fatal interactions with certain foods.
  - The newer skin-patch versions of MAOIs may have fewer side-effects.

Other Medication Strategies

- Other medication strategies include:
  - Stimulants.
  - Mood-stabilizing medications.
  - Antianxiety medications.
  - Antipsychotic medications.
Categories of Antidepressant Medications

Note: Starting at lower doses can minimize side-effects without compromising efficacy. See page 5 for notes about withdrawal potential and QTc prolongation.

<table>
<thead>
<tr>
<th>Medication*</th>
<th>Typical Effective Dose Range</th>
<th>QT-Interval Prolongation Risks/Other Considerations and Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors (SSRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram (Celexa®)</td>
<td>20-40 mg</td>
<td>Dose response-associated increase in QTc interval demonstrated in clinical studies</td>
</tr>
<tr>
<td>Escitalopram (Lexapro®)</td>
<td>10-20 mg</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>20-60 mg</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine (Luvox®) NF</td>
<td>50-300 mg</td>
<td></td>
</tr>
<tr>
<td>Paroxetine (Paxil®)</td>
<td>20-60 mg</td>
<td>Increased potential for withdrawal symptoms if abruptly discontinued</td>
</tr>
<tr>
<td>Sertraline (Zoloft®)</td>
<td>50-200 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Tricyclics and Tetracyclics (TCAs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline (Elavil®)</td>
<td>100-300 mg</td>
<td>Dose response-associated increase in QTc interval demonstrated in clinical studies</td>
</tr>
<tr>
<td>Amoxapine (Asendin®) NF</td>
<td>100-400 mg</td>
<td></td>
</tr>
<tr>
<td>Clomipramine (Anafranil®)</td>
<td>100-200 mg</td>
<td></td>
</tr>
<tr>
<td>Desipramine (Norpramin®)</td>
<td>100-300 mg</td>
<td></td>
</tr>
<tr>
<td>Doxepin (Sinequan®)</td>
<td>100-300 mg</td>
<td></td>
</tr>
<tr>
<td>Imipramine (Tofranil®)</td>
<td>100-300 mg</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline (Pamelor®)</td>
<td>50-300 mg</td>
<td></td>
</tr>
<tr>
<td>Trimipramine (Surmontil®) NF</td>
<td>100-300 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desvenlafaxine (Pristiq®)** NF</td>
<td>50-100 mg</td>
<td></td>
</tr>
<tr>
<td>Duloxetine (Cymbalta®)</td>
<td>60-120 mg</td>
<td>Rare cases of hepatic failure (including fatalities) have been reported with use. Discontinue use in patients who develop jaundice or other evidence of clinically significant liver dysfunction without other explanation.</td>
</tr>
<tr>
<td>Venlafaxine (Effexor®)</td>
<td>75-300 mg</td>
<td>Increased potential for withdrawal symptoms if abruptly discontinued</td>
</tr>
<tr>
<td><strong>Norepinephrine and Dopamine Reuptake Inhibitors (NDRIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin®)</td>
<td>300-450 mg</td>
<td>Decreased QTc interval demonstrated in clinical studies</td>
</tr>
<tr>
<td><strong>Noradrenaline and Selective Serotonergic Receptor Antidepressant (NaSSAs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine (Remeron®)</td>
<td>15-45 mg</td>
<td></td>
</tr>
<tr>
<td>Nefazodone (Serzone®)</td>
<td>300-600 mg</td>
<td></td>
</tr>
<tr>
<td>Trazodone (Desyrel®)</td>
<td>100-300 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Monamine Oxidase Inhibitors (MAOls)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phelenezine (Nardil®)</td>
<td>15-90 mg</td>
<td></td>
</tr>
<tr>
<td>Tranylcypramine (Parnate®)</td>
<td>30-60 mg</td>
<td></td>
</tr>
<tr>
<td>Selegiline (Emsam®)** Transdermal NF</td>
<td>6-12 mg</td>
<td></td>
</tr>
</tbody>
</table>

* For more information about medications, including relative costs, see the OSUMC Pharmacy Website.
** Generics not currently available for these medications.

**NF = Non-formulary**
Withdrawal Potential

• When clinically feasible, all antidepressants should be tapered to avoid withdrawal symptoms such as:
  o Flu-like symptoms.
  o Insomnia.
  o Sensory disturbances.
  o Hyperarousal.

• Agents most commonly associated with withdrawal symptoms are paroxetine (Paxil®) and venlafaxine (Effexor®).
  o Consider prolonged taper when discontinuing either of these agents
  o Fluoxetine (Prozac®) is least likely to elicit withdrawal due to prolonged half-life of the drug and metabolites

• Symptoms usually begin and peak within one week, lasting one day to three weeks, and are usually transient and mild.

QTc Prolongation

• All classes of antidepressants appear to carry some degree of risk of QT prolongation, with the highest degree of association for QT prolongation noted in clinical studies of citalopram and amitriptyline.

• Antidepressants should be used with caution in patients with risk factors in addition to age and gender for QT prolongation.

• An ECG should be considered at baseline, steady state, at the time of dose increases and if another QT prolonging medicine is added to the treatment regimen.

Drug Interactions of Antidepressants Commonly Used in Primary Care

• All antidepressants have the potential for drug interactions

• Lower risks are demonstrated with the following:
  o citalopram (Celexa®).
  o escitalopram (Lexapro®).
  o sertraline (Zoloft®).
  o venlafaxine (Effexor®).

Side Effects of Antidepressants

• Although all antidepressants can cause unwanted side effects, not everyone experiences the same number or intensity of side effects.

• Side effects often go away or lessen within several weeks of starting an antidepressant.

The table below gives the side effect associated with the principal classes of antidepressants.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>SSRI</th>
<th>TCA</th>
<th>SNRI</th>
<th>NDRI</th>
<th>NaSSA</th>
<th>MAOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI distress</td>
<td>+++</td>
<td>0/+</td>
<td>+++</td>
<td>0/+</td>
<td>0/+</td>
<td>+/+</td>
</tr>
<tr>
<td>Sexual disturbance</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>0/+</td>
<td>0/+</td>
<td>+/+</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0/+</td>
<td>++</td>
<td>0/+</td>
<td>+++</td>
<td>+++</td>
<td>++/++</td>
</tr>
<tr>
<td>CNS effects</td>
<td>+/+</td>
<td>+/+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+/+</td>
</tr>
<tr>
<td>Anti-cholinergic effects</td>
<td>+</td>
<td>++/+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>ECG changes</td>
<td>0/+</td>
<td>++</td>
<td>0/+</td>
<td>0/+</td>
<td>0/+</td>
<td>0/+</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>0/+</td>
<td>++/+++</td>
<td>0/+</td>
<td>+</td>
<td>++/+++</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0/+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

Order Sets

• OSU IP ED: PSYCHIATRIC CARE (2642)

References

• New Zealand Guidelines Group. Identification of Common Mental Disorders and Management of Depression in Primary Care: An Evidence Based Best Practice Guideline. Published by New Zealand Guidelines Group; Wellington: 2008.
Resources

- Depression and Bipolar Support Alliance
- National Institute of Mental Health
- National Mental Health Association

Information about Augmentation Strategies

- Acute and longer-term outcomes in depressed outpatients requiring one of several treatment steps: A STAR*D Report. Am J Psychiatry November 2006.163:11,

Quality Measures

- Percent of patients identified, treated, and managed for depression
- Percent of patients with psychiatric consult
- Percent of patients screened with the PHQ-9 screening tool

Guideline Authors

- James V. Campo, MD
- James Young, MD
- Nicholas Lungociu, PharmD
- Kenneth Yeager, LISW, PhD
- Natalie Lester, MD

Guideline Approved


Disclaimer: Clinical practice guidelines and algorithms at The Ohio State University Wexner Medical Center (OSUWMC) are standards that are intended to provide general guidance to clinicians. Patient choice and clinician judgment must remain central to the selection of diagnostic tests and therapy. OSUWMC’s guidelines and algorithms are reviewed periodically for consistency with new evidence; however, new developments may not be represented.