

## Depression

### Depression Guideline Team

#### Team leaders

Thomas L Schwenk, MD  
*Family Medicine*

Linda B Terrell, MD  
*General Medicine*

#### Team members

R Van Harrison, PhD  
*Medical Education*

Amy L Tremper, MD  
*Obstetrics & Gynecology*

Marcia A Valenstein, MD  
*Psychiatry*

#### Consultant

Jolene R Bostwick, PharmD  
*College of Pharmacy*

#### Updated

August 2011

#### Ambulatory Clinical Guidelines Oversight

Connie J Standiford, MD  
Grant M Greenberg, MD,  
MHSA, MA

R Van Harrison, PhD

#### Literature Search Service Taubman Medical Library

For more information call  
GUIDES: 734- 936-9771

© Regents of the  
University of Michigan

These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

**Patient population.** Adults with depressive disorders

- Objectives.** (1) Improve the early recognition and treatment of depression in the primary care setting.  
(2) Improve patient's understanding of depression and its treatment.  
(3) Familiarize clinicians with appropriate treatment options, i.e. medications and psychotherapies.  
(4) Identify when referral is indicated.

### Key points

#### Epidemiology

- **Common.** Depression is common, under-diagnosed, and under-treated.
- **Recurrent.** Depression is frequently a recurrent/chronic disorder, with a 50% recurrence rate after the first episode, 70% after the second, and 90% after the third.
- **Care provider.** Most depressed patients will receive most or all of their care through primary care physicians.

**Diagnosis.** Depressed patients frequently present with somatic complaints to their primary care doctor rather than complaining of depressed mood [C\*].

**Treatment.** Mild major depression can be effectively treated with either medication or psychotherapy. Moderate to severe or chronic depression may require an approach combining medication and psychotherapy [IIA\*].

- **Drug treatment.** 40-50% of patients respond to the first antidepressant [A\*]. No particular antidepressant agent is superior to another in efficacy or time to response. Choice is often guided by matching patients' symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response [IIA\*]. Relative costs can also be considered because of the large selection of antidepressants available in generic form. Patients treated with antidepressants should be closely observed for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose increases or decreases [IC\*].
- **Frequent initial visits.** Patients require frequent visits early in treatment to assess response to intervention, suicidal ideation, side effects, and psychosocial support systems [ID\*].
- **Continuation therapy.** Continuation therapy (9-12 months after acute symptoms resolve) decreases the incidence of relapse of major depression [IA\*]. Long-term maintenance or life-time drug therapy should be considered for selected patients based on their history of relapse and other clinical features [IIB\*].
- **Education/support.** Patient education and support are essential. Social stigma and patient reluctance to accept a diagnosis of depression or enter treatment continue to be a problem [IIC\*].

#### \* Strength of recommendation:

I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

#### Level of evidence supporting a diagnostic method or an intervention:

A = randomized controlled trials; B = controlled trials, no randomization; C = observational trials; D = opinion of expert panel

## Clinical Background

### Clinical Problem and Management Issues

Depression is a common disease with substantial morbidity and mortality. Approximately 5% of the population has major depression at any given time, with men experiencing a lifetime risk of 7-12%; and women 20-25%. The direct and indirect costs associated with major depressive disorder are significant, with an estimated cost of \$59 billion in 2006, including direct patient care, time lost from work and potential income loss due to suicide. Mortality rates by suicide are estimated to be as high as 15% among patients hospitalized for severe depression.

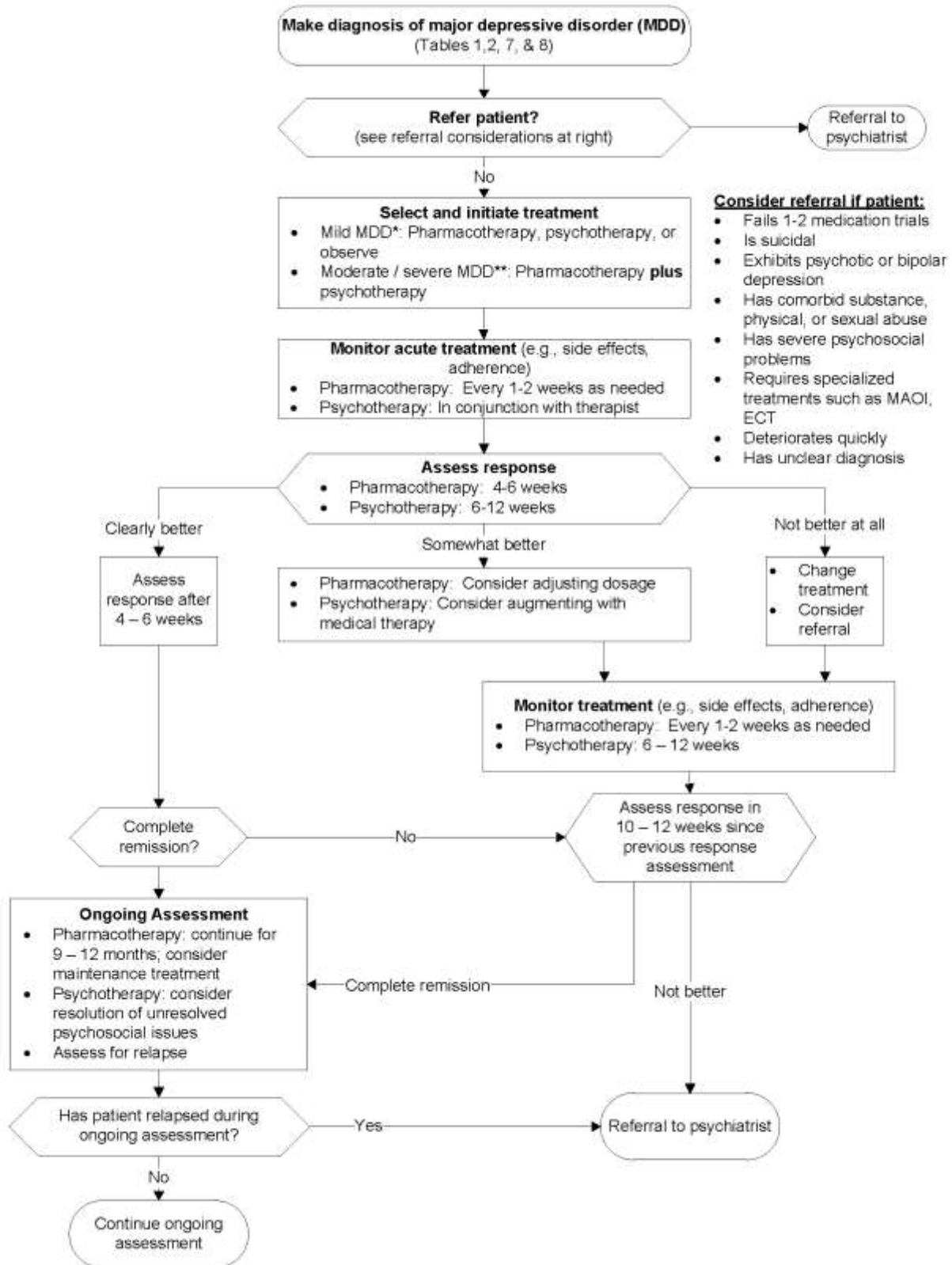
Most patients receive much or all of their care for major depression from their primary care physician.

However, depression is under-diagnosed and under treated because of competing priorities in primary care with the care of other chronic medical conditions, patient stigma, and variability in physician skills and interest.

Diagnosing and treating depression in the primary care setting has many obstacles. The physician-patient encounter time is brief, making it difficult for the physician to fully assess the patient for depressive signs and symptoms. Depressed primary care patients typically present with physical complaints, often not admitting to a depressed mood and are reluctant to discuss depression. In one study, about two-thirds of patients with depression presented only with somatic

(Continued on page 9)

**Figure 1. Overview of Treatment for Depression**



\* **Mild depression:** Depression that meets criteria for MDD but without prominent vegetative symptoms, suicidal ideation, or significant functional impairment.

\*\***Moderate to severe depression:** Depression with significant vegetative symptoms, hopelessness, or suicidal ideation.

\* **Levels of evidence for the most significant recommendations:**

A = randomized controlled trials; B = controlled trials, no randomization; C = observational trials; D = opinion of expert panel.

**Table 1. Common Presentations of or Factors Associated with Depression in Primary Care**

**Multiple organ systems.** Symptoms from multiple organ systems (particularly neurologic, gastrointestinal, and cardiac) that are difficult if not impossible to ascribe to a single medical condition

**Emotions.** Patients who are emotionally flat, verbally withdrawn or tearful, or who are worried or are upset out of proportion to the apparent severity of the problem

**Sleep.** Sleep disturbance, either with initiation or maintenance of sleep

**Medical visits.** Frequent, often unscheduled, patient-initiated visits to the physician or the emergency room for unclear reasons

**"Difficult".** Patients labeled by the physician as “difficult” or a “problem”, as well as a sense of dysphoria by the physician when seeing the patient

**Dysfunction.** Patients who have cognitive or emotional dysfunction i.e., forgetfulness, irritability and loss of motivation or energy

**Recurrence.** Past history of similar depressive or anxious episodes, unspecified “breakdowns” or suicide attempts.

**Family history.** A family history of psychiatric disease, suicide, or abuse of any kind (sexual, physical, or substance)

**Chronic pain syndromes.** Irritable bowel syndrome, fibromyalgia, pelvic pain, migraines, etc.

**Comorbid medical conditions.** Diabetes, coronary artery disease, recent stroke, COPD, asthma, sickle cell disease, parents of children with chronic medical conditions

**Special conditions in women.** Post-partum, post-induced or spontaneous abortion, or emotional, physical, or sexual abuse

**Table 2. Depressive Symptoms and Diagnostic Criteria for Depressive Disorders**

Core Depressive Symptoms		
<ul style="list-style-type: none"> <li>Depressed mood</li> <li>Anhedonia or markedly diminished interest or pleasure in all, or almost all, activities</li> <li>Significant unintentional weight loss or gain</li> <li>Insomnia or hypersomnia</li> <li>Psychomotor agitation or retardation</li> <li>Fatigue or loss of energy</li> <li>Feelings of worthlessness or excessive or inappropriate guilt</li> </ul>	<ul style="list-style-type: none"> <li>Diminished ability to concentrate, or indecisiveness</li> <li>Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a suicide attempt or a specific plan for committing suicide</li> </ul>	<p>Additional Dysthymic Symptoms (qualifying symptoms for Dysthymic Disorder)</p> <ul style="list-style-type: none"> <li>Poor appetite without weight change</li> <li>Low self esteem</li> <li>Feelings of hopelessness</li> </ul>
Diagnostic Category by Symptom Grouping		
Diagnostic Category	Number of Symptoms	Duration
Major Depression	> 5 depressive symptoms, one of which is depressed mood or anhedonia	≥ 2 weeks
Minor Depression <sup>1</sup>	2-4 depressive symptoms, one of which is depressed mood or anhedonia	≥ 2 weeks
Bipolar Disorder	Periods of meeting criteria for MDD plus either periods with > 4 manic symptoms <sup>2</sup> if patient has elevated mood, or > 5 manic symptoms if patient has irritable mood	≥ 2 weeks for depressive symptoms ≥ 7days for manic symptoms, shorter duration required if hospitalized
Dysthymic Disorder	3-4 depressive or dysthymic symptoms	≥ 2 years

Source: DSM-IV-TR American Psychiatric Association, 2000

<sup>1</sup> Minor depression is not yet a full categorical diagnosis in the DSM-IV but is included as a research diagnostic category.

<sup>2</sup> Manic symptoms include elevated or irritable mood, inflated self-esteem or grandiosity, decreased need for sleep, increased talking or pressured speech, flight of ideas or subjective experience that thoughts are racing, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in pleasurable activities that may have a high potential for adverse consequences.

**Table 3. Screening for Depression**

**Quick Screen**

A quick way of screening patients for depression is to ask patients these two questions:

During the past month, have you often been bothered by:

1. Little interest or pleasure in doing things?
2. Feeling down, depressed or hopeless?

Yes  
 Yes

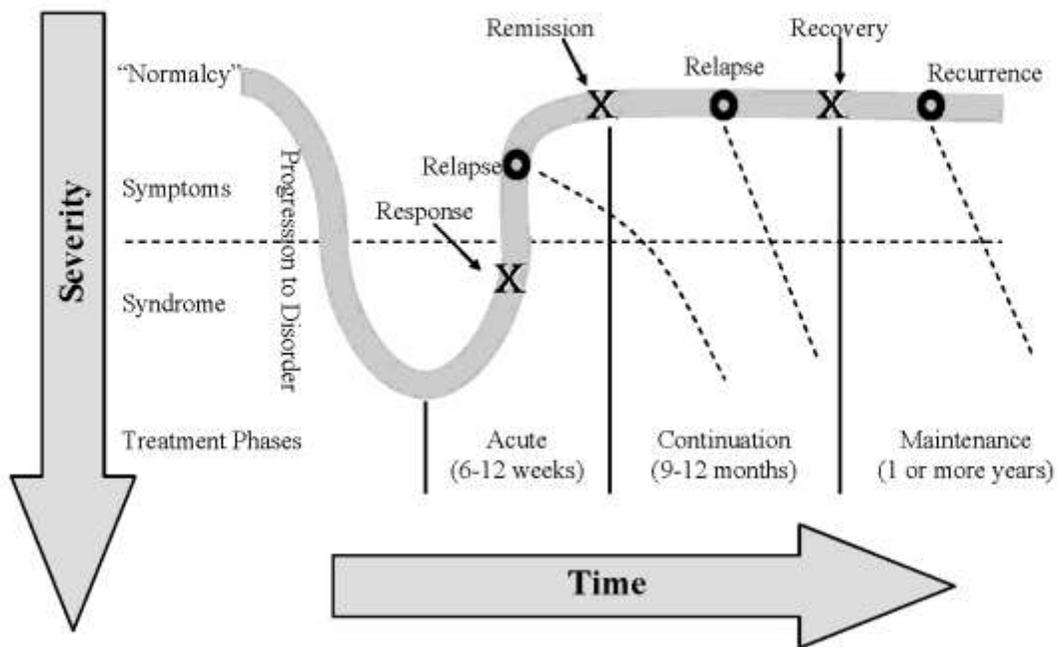
No  
 No

If the patient's response to *both* questions is "no", the screen is negative.

If the patient responded "yes" to *either* question, consider asking more detailed questions or using PHQ-9 patient questionnaire, Appendix A.

Note: These two items are the PHQ-2. The PHQ-9 is described in more detail at the Pfizer website: <http://www.phqscreeners.com/>  
Link to PHQ-9: [http://www.phqscreeners.com/pdfs/02\\_PHQ-9/English.pdf](http://www.phqscreeners.com/pdfs/02_PHQ-9/English.pdf)

**Figure 2. Phases of Treatment for Major Depression**



Adapted from: Kupfer DJ: Long-term treatment of depression. J Clin Psychiatry 1991; 52(Suppl):28-34.

**Table 4. Information the Patient Needs to Know**

Clearly communicate the following with patients:

**Common.** Depression is one of the most common illnesses treated by doctors and mid-level providers and as common as many other chronic diseases, such as diabetes, asthma and arthritis.

**Risk factors.** Several factors in the family or past history are associated with depression, including:

- Gender (female)
- First degree relative with depression
- Drug or alcohol abuse
- Anxiety disorder
- Eating disorder
- Major medical conditions, e.g., coronary artery disease, stroke, diabetes, COPD, chronic pain (back, abdomen, head, etc.).

**Responsive.** Depression is as responsive to treatment as are other major chronic diseases, but several visits and medication adjustments / or psychotherapy trials may be required before full remission is achieved.

**Delayed response.** All antidepressant medications require several weeks to produce their full effects.

**"Not tranquilizers."** Antidepressant medications are neither "tranquilizers" nor addicting, although withdrawal syndromes may exist, especially for agents with shorter half-lives.

**Recurrence.** Depression is frequently a recurrent condition.

**Table 5. Matching Antidepressants to Patients: Selection Dosing & Cost (page 1 of 4)**

<b>Mechanisms of action</b>	<b>Serotonin Selective Reuptake Inhibitors<sup>a</sup></b>		
<b>Generic name</b> <b>(Brand Name)</b>	citalopram ( <i>Celexa</i> )	escitalopram ( <i>Lexapro</i> ) <i>[No benefit over citalopram but significantly higher cost]</i>	fluoxetine ( <i>Prozac &amp; Sarafem</i> )
Side effects and other attributes used in patient selection	May be initially sedating or initially increase alertness. Mild initial sedation is dose-dependent. May be least stimulating SSRI. Negligible drug-drug interactions. Dose-dependently linked to prolonged QT interval	Negligible drug-drug interactions.	Tends to produce more initial nervousness and arousal than other SSRIs. Very long half-life (7-15 days), so less likely to cause withdrawal on abrupt discontinuation.
Sexual dysfunction Pregnancy <sup>b</sup> /Lactation <sup>c</sup>	Common C, L3	Common C, L1 – may be safer than citalopram	Common C, L2 – may be SSRI with greatest risk
Selected important drug-drug interactions <sup>d,e</sup>	Minimal inhibitor of CYP 2D6 isoenzymes. Good choice for medical /surgical patients <i>without</i> severe renal impairment.	Comparable to citalopram.	Potent inhibitor of CYP 2D6 isoenzymes; decreases tamoxifen efficacy
Patient profile <i>most</i> likely to benefit	Patient with limited financial resources, elderly patient, patient with an agitated depression, or patient with GI distress / sensitivity.	Elderly patient, patient with an agitated depression, or patient with GI distress /sensitivity. Claims of more rapid efficacy may be exaggerated.	Patient with limited financial resources, nonadherent or “forgetful” patient (i.e., used as a “depot” oral antidepressant); excessive fatigue.
Patient profile <i>least</i> likely to benefit	Elderly patient with excessive sleep and apathy.	Patients who have failed citalopram. Elderly patient with excessive sleep and apathy.	Patient on several medications and/or frequent medication changes anticipated.
Available preparations & doses	10, 20, 40 mg tablets; 10 mg/5ml solution	5 (unscored), 10, 20 mg scored tablets.	10,20,40 mg capsules; 10, 20 mg tabs; 20 mg/5ml solution
Usual dose, cost/mo. <sup>f</sup> ; Max dose, cost/mo <sup>f</sup>	20-40 mg/d \$6 generic \$105-\$112 brand	15-20mg/d \$106-\$199 40 mg/d \$213	20-40 mg/d \$4-\$15 generic \$191-\$382 brand 80 mg/d \$91 generic \$765 brand
Dosing for youthful, reasonable health	20 mg P.O. Qam (or QHS if sedating.) Titrate upward to 40 mg if no response after 6 weeks.	10 mg/d P.O. Qam (or QHS if sedating). May titrate to 20 mg/d if no response in 6 weeks. 20 mg/d failed to demonstrate benefit over 10 mg/d.	20 mg P.O. Qam; increased doses may be given a.m. and noon, if excessive arousal. Titrate upward if no response in 6 weeks.
Dosing for frail, elderly (>60 years old), medically ill	5-10 mg P.O. Qam x 3 d, 10-20 mg P.O. Qam x 3 d, etc. until desired initial dose. Max recommended dose 20 mg/d. Use with caution in severe renal impairment.	5-10mg/d P.O. Qam (or Qpm if sedating). Use with caution in severe renal impairment.	10 mg P.O. every other a.m. for 3-4 days (i.e., two doses) then similarly titrate upward to 20 mg P.O. Qam.

Adapted by Jolene R Bostwick, PharmD from tables developed by David J. Knesper, M.D., University of Michigan, Department of Psychiatry. Note: It is the responsibility of the treating physician to stay current with the psychopharmacology of antidepressants and to determine dosages and drug interactions. All antidepressant medication labeling includes a black box warning for increased suicidality. Patients treated with antidepressants should be closely observed for possible worsening of depression and suicidality, or unusual behavior, especially at the beginning of therapy or with dosage changes.

(Footnotes continue)

**Table 5. Matching Antidepressants to Patients: Selection Dosing and Cost (page 2 of 4)**

Mechanisms of action Generic name (Brand Name)	Serotonin Selective Reuptake Inhibitors <sup>a</sup>		
	paroxetine (generic available) (Paxil)	paroxetine controlled release (Paxil CR)	sertraline (Zoloft)
Side effects and other attributes used in patient selection	Tends to cause less agitation/insomnia (common with SSRIs); possesses some anticholinergic effects. Somnolence and nausea is dose-related. Short half-life, withdrawal effects common.	Initial nausea rate is less than immediate release; otherwise side-effect profiles nearly identical. Somnolence and nausea are dose-related. Short half-life, withdrawal effects common. Similar response rate compared to immediate release.	Tends to initially increase alertness; patients with psychomotor retardation may benefit. Patients experience more GI distress (diarrhea) compared to other SSRIs.
Sexual dysfunction	Common, may be higher than other SSRIs.	Common	Common
Pregnancy <sup>b</sup> /Lactation <sup>c</sup>	D, L1 – Considered safe in breastfeeding	D, L1 – Considered safe in breastfeeding	C, L1 – A preferred SSRIs in breastfeeding
Selected important drug-drug interactions <sup>d,e</sup>	Potent inhibitor of CYP 2D6 isoenzymes; decreases tamoxifen efficacy	Same as paroxetine immediate release.	Moderate inhibitor of CYP 2D6 isoenzymes. Good choice for medical /surgical patients.
Patient profile most likely to benefit	Less likely to produce initial anxiety and/or insomnia.	Less likely to produce initial nausea than immediate release. Nausea rate at 25 mg/d comparable to escitalopram at 20 mg/d.	Initial activation and increased alertness desired.
Patient profile least likely to benefit	Patients who may require high doses or elderly (who are more susceptible) are more prone to anticholinergic effects (e.g. delirium). Half-life increased by 170% in elderly.	Same as paroxetine immediate release.	Patient sensitive to any of the typical SSRI side-effects (e.g. increased arousal, GI distress).
Available preparations & doses	10,20,30,40 mg tabs; 10mg/5ml suspension	12.5,25, 37.5 mg enteric-coated tabs.	25, 50, 100 mg tabs, 20 mg/ml solution (12% alcohol)
Usual dose, cost/mo. <sup>f</sup> ; Max dose, cost/mo <sup>f</sup>	20-40 mg/d \$15-\$20 <sup>g</sup> generic \$116-\$232 brand 60 mg/d \$120 generic \$348 brand	25-50 mg/d \$120-239 62.5 mg/d \$243	75-150 mg/d \$10-17 generic \$ 228-341 brand 200 mg/d \$187 generic \$ 228 brand
Dosing for youthful, reasonable health	20 mg P.O. Qam; titrate by 10 mg/week. Give QHS if sedating.	25 mg/d P.O. Qam ; may titrate dose by 12.5 mg increments weekly up to 62.5 mg/d if no response in 6 weeks.	50 mg P.O. Qam; titrate weekly based on response up to 200 mg/d.
Dosing for frail, elderly, medically ill	10 mg P.O. Qam Upon titration, dosage should not exceed 40 mg/d.	12.5 mg/d P.O. Qam. May increase dose up to 50 mg/d.	12.5-25 mg P.O. Qam. Titrate to desired effect. Lower doses generally required.

<sup>a</sup> If a patient fails one SSRI class of antidepressants, another SSRI may be tried (don't try a third SSRI). During the initial phase of treatment all SSRIs may produce one or all of the following: Increased arousal (agitation), insomnia, nausea, diarrhea (due to increased GI motility), initial weight loss and subsequent weight gain after about 6 months, sexual dysfunction. Uncommon adverse events include: akathisia (restlessness), psychomotor slowing, mild parkinsonism; apathy.

<sup>b</sup> Pregnancy Risk Category:

- A: Controlled studies show that the possibility of fetal harm is remote
- B: No controlled studies in pregnant women, but no fetal risk has been shown
- C. Drugs should be given only if the patient benefit justifies the potential risk to the fetus
- D. Positive evidence of human fetal risk, but benefits may be acceptable sometimes
- X. Contraindicated in women who are or may become pregnant.

<sup>c</sup> Lactation Risk:

- L1: Low levels detected in milk
  - L2: Higher levels detected in milk
  - L3: Low levels of drug detected in infants
- From LactMed Database, U.S. National Library of Medicine. Bethesda, MD.

<sup>d</sup> Do not combine any of the listed antidepressants with monoamine oxidase inhibitors (MAOIs) (ex. selegiline, tranylcypromine, phenelzine).

<sup>e</sup> The following drug interaction databases are recommended: hanstendandhorn.com, <http://medicine.iupui.edu/clinpharm/ddis/>

<sup>f</sup> Cost = Average wholesale price based -10% for brand products and Maximum Allowable Cost (MAC) + \$3 for generics on 30-day supply, Amerisource Bergen item Catalog 12/10 & Blue Cross Blue Shield of Michigan Mac List, 11/10.

**Table 5. Matching Antidepressants to Patients: Selection Dosing and Cost (page 3 of 4)**

Mechanisms of Action Generic name (Brand Name)	Serotonin/Norepinephrine Reuptake Inhibitor		
	venlafaxine extended release (Effexor XR)	desvenlafaxine extended release (Pristiq) <i>[No benefit over venlafaxine but significantly higher cost]</i>	duloxetine (Cymbalta)
Side effects and other attributes used in patient selection	Similar to those common to all SSRIs with more nausea. BP increases, including sustained hypertension, are dose-dependent, with a linear dose-response. Primarily functions as an SSRI at doses below 225 mg. Should not be combined with other SSRIs. High rates of withdrawal. Side effect profile similar to immediate release.	Major metabolite of venlafaxine with similar side effect profile. Side effects are similar to those common to all SSRIs with more nausea. Can increase blood pressure as well as triglycerides and LDL cholesterol.	Similar to SSRIs and venlafaxine; nausea (dose-dependent) and constipation most troublesome, but, unlike venlafaxine, does not appear to produce sustained hypertension. NOT TO BE PRESCRIBED if concurrent heavy alcohol use and/or evidence of chronic liver disease.
Sexual dysfunction Pregnancy <sup>b</sup> /Lactation <sup>c</sup> Selected important drug-drug interactions <sup>d,e</sup>	Less common C, L3 Usually clinically insignificant due to low protein binding and weak inhibition of P450 enzymes.	Less common C, L3 Usually clinically insignificant. Metabolized via conjugation and to a minor extent by CYP3A4. Strong CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin, nefazodone) may increase levels.	Less common C, L1 Major substrate of CYP1A2 & CYP2D6 – inhibitors (quinolones, fluvoxamine/fluoxetine, paroxetine, quinidine) may increase levels. Also, CYP1A2 inducers may decrease effect (modafinil, omeprazole). Duloxetine is a moderate inhibitor of CYP2D6.
Patient profile <i>most</i> likely to benefit	Patients who fail an SSRI or with menopausal symptoms or comorbid anxiety. At higher doses (e.g., at least 225 mg), patients with chronic pain.	Same as venlafaxine.	Patient with depression and chronic pain (effects on pain are dose-dependent). Patient failing an SSRI trial.
Patient profile <i>least</i> likely to benefit	Patients with unstable BP and perhaps, those who are GI sensitive. A clinically significant withdrawal syndrome requires slow taper.	Same as venlafaxine. Since desvenlafaxine and venlafaxine are equally active and potent, patients who fail venlafaxine would not likely respond to desvenlafaxine.	Patient with preexisting liver disease and/or heavy alcohol use; preexisting or treatment-related anorexia, constipation, and/or other GI symptoms.
Available preparations & doses	37.5, 75, 150, 225 mg capsules (immediate release tablets also available)	50, 100 mg tablets No additional benefit in doses > 50mg.	20, 30, 60 mg capsules.
Usual dose, cost/mo. <sup>f</sup> ; Max dose, cost/mo <sup>f</sup>	150-225 mg/day, \$68-89 generic \$153-\$292 brand 375-450 mg/day \$161-204 generic \$381-\$390 brand	50 mg/day \$135	40 mg/day \$277 60 mg/day \$503
Dosing for youthful, reasonable health	Every 3-7 day titrate upward, starting at 37.5 mg to reduce risk of nausea; dose may be titrated to 225 mg/d. Reduce dose 50% for hepatic impairment; 25-50% for renal.	50 mg/d; higher doses do not increase efficacy and are associated with higher discontinuation rates and adverse effects. In patients with ESRD or severe renal impairment, use 50 mg every other day.	Starting dose 20 mg BID, may increase to 30 mg BID (or 60 mg QHS). If nausea is problematic, start with 20 or 30 mg once daily. Usual dose for pain is 60 mg/day. Doses of 120 mg/day appear safe but efficacy data fail to justify this dose.
Dosing for frail, elderly, medically ill	Every 7 day titrate upward, starting at 37.5 mg; initial trial at 150 mg/d. Reduce dose 50% for hepatic impairment; 25% for renal.	50 mg/d unless severe renal impairment is present, then reduce dose to 50 mg every other day.	Start at 20 mg with breakfast; titrate upward every 3-7 days until 40-60 mg/d in divided doses. If tolerated, may administer in a single dose. Do not administer in hepatic insufficiency or severe renal impairment (CrCl < 30 mL/min)

**Table 5. Matching Antidepressants to Patients: Selection Dosing and Cost (page 4 of 4)**

Mechanisms of action	Serotonin & alpha-2 receptor blocker (increases release of serotonin & norepinephrine)	Norepinephrine/Dopamine Reuptake Inhibitor
<b>Generic name (Brand Name)</b>	mirtazapine (Remeron)	bupropion (Wellbutrin SR, Wellbutrin XL, Wellbutrin IR, Aplenzin, Budeprion)
Side effects and other attributes used in patient selection	Produces sleep; <i>lower</i> doses produce more sleep than higher doses. Weight gain may be ≥ 10 lbs. and is greater than with other newer antidepressants. Has antiemetic properties (blocks 5HT3 receptor as does ondansetron/Zofran). Rare neutropenia and agranulocytosis. Onset of action within 1-2 weeks may be faster than some SSRIs, but response rates are comparable at week 4.	Least likely to switch patient to mania. Most activating antidepressant available. DO NOT USE if history of seizure, head trauma, bulimia (especially if current), anorexia or electrolyte disturbance. Use with caution in patients with a history of substance abuse.
Sexual dysfunction	Unlikely	Rare
Pregnancy <sup>b</sup> /Lactation <sup>c</sup>	C, L1	C, L1
Selected important drug-drug interactions <sup>d,e</sup>	Usually clinically insignificant due to extensive metabolism via CYP1A2 and 2D6. Does not appear to interfere with the metabolism of other drugs.	Metabolized primarily by CYP2B6. Drugs inhibiting CYP2B6 are not currently identified. Strong inhibitor of CYP2D6.
Patient profile <i>most</i> likely to benefit	The medically ill patient with weight loss, insomnia and nausea.	Depressed patients who are actually or potentially bipolar. The apathetic, low energy patient. Patients motivated to stop smoking. Helpful for ADHD <sup>i</sup> .
Patient profile <i>least</i> likely to benefit	The obese patient with fatigue and hypersomnia. Patients with neutropenia.	Patients who are agitated, very anxious and/or panicky. Patients at risk for seizures and/or with history of head trauma, substance abuse, eating disorder, or electrolyte disturbance.
Available preparations & doses	7.5, 15, 30, 45 mg tablets; 15, 30, 45 mg unscored orally disintegrating tablets ( <i>Remeron SolTab</i> ).	For SR: 100, 150, 200 mg coated tablet For XL: 150, 300 mg coated tablet For IR: 75, 100 mg tablets
Usual dose, cost/mo. <sup>f</sup> ; Max dose, cost/mo <sup>f</sup>	30-45 mg/d \$9-\$12 generic \$108-\$128 brand 60 mg/d \$18 generic \$255 brand	For SR: 300-400 mg/d \$113-\$120 generic (max 450 mg/d) \$212-393 brand For XL: 300-450 mg/d \$194-\$450 brand (max dose 450 mg/d) For IR: 200-450 mg/d \$105-212 generic (max dose 450 mg/d) \$192-335 brand
Dosing for youthful, reasonable health	7.5 (more sleep) to 15 mg (less sleep). May titrate up to 45 mg QHS. Dose increases should not be made more frequently than every 1-2 weeks.	For SR: 150 mg with breakfast and before 5 pm; increase to 150 mg BID after 1 week. <u>Maximum</u> dose: 200 mg BID. For XL: 150 mg with breakfast for 3 days, increase as tolerated to 300-450 mg/d. For IR: 100 mg BID, increase to TID after 3 days, max dose 450 mg/d in 3-4 divided doses. DO NOT DOUBLE-UP MISSED DOSES.
Dosing for frail, elderly, medically ill	7.5 to 15 mg at night; increase to 30mg or 45 mg if no improvement. Reduce dose by 25-50% for hepatic or renal impairment.	For SR: Every 3-4 day titrate upward, starting at 100 mg; initial trial at 150 mg BID; last dose before 5 pm. For XL: Every 5-7 days titrate upward, starting at 150 mg; plateau at 300 mg for 2-3 weeks before advance to 450 mg. For IR: Every 3-4 days titrate upward, starting at 50-100 mg/d, increasing by 50-100 mg, up to max of 300 mg/d. DO NOT DOUBLE-UP MISSED DOSES.

<sup>i</sup> “ADHD” means attention deficit hyperactivity disorder.

complaints. Reimbursement restrictions can interfere with comprehensive treatment. Other medical co-morbidities compete for time and attention by both physician and patient.

## Rationale for Recommendations

### Definitions

Specific criteria for diagnoses of depressive disorders are presented in Table 2.

**Major depressive disorder (MDD).** A severe form of depression that is often accompanied by significant functional impairment and increased health services use. Major depressive disorder is the primary focus of these treatment guidelines, as this disorder is common and has the largest evidence-base for treatment. Both psychotherapy and pharmacotherapy have been shown to be effective treatments for major depression, and may be used together.

**Dysthymia.** A chronic, "smoldering" form of depression with fewer, less severe depressive symptoms than MDD but with functional impairment that can sometimes equal the impairment seen among patients with MDD. Although antidepressants are somewhat less efficacious in dysthymic disorder than in MDD, a substantial proportion of patients will respond to antidepressants or structured psychotherapies. Patients with dysthymic disorder may have periods of time when they also meet criteria of MDD, often called "double depression".

**Minor depression.** Minor forms of depression (less than 5 depressive symptoms or duration of symptoms of less than 2 weeks) are common. Although minor depression produces less functional impairment in affected individuals than MDD or dysthymic disorder, because of its frequency, most work days that are missed in the US are attributable to this milder disorder. Specific treatments such as antidepressants or psychotherapy may not be indicated as there are high rates of improvement among these individuals with watchful waiting.

**Seasonal affective disorder (SAD).** A seasonal form of major depression with features similar to MDD but occurring on a cyclical basis related to ambient light deprivation during winter months. Both phototherapy and medications are frequently used.

**Mood disorder associated with a general medical condition.** A form of depression with features similar to MDD but is part of the physiological sequelae of a major medical condition such as cancer, stroke, myocardial infarction, major trauma, or neurodegenerative disorders such as Alzheimer's disease. Perimenopausal mood disorder is addressed in Table 8 (following guideline text). Mood disorders may infrequently arise from the use of certain medications and, more frequently, from substance abuse.

Treating primary disorders such as hypothyroidism is important. Minimizing functional limitations from comorbid medical conditions is also important. However, in general, depression occurring with comorbid conditions should be treated according to its diagnostic criteria and functional impact, irrespective of the presence of the associated medical illness.

**Bereavement.** Grieving is a "normal" reaction to a major loss, such as the death of a close relative or friend. Patients may exhibit many symptoms of MDD following such a loss. However, individuals suffering from bereavement are usually not preoccupied with ideas of worthlessness or guilt and do not experience suicidal ideation. The duration of symptoms varies, but generally symptoms remit or lessen within a few months. Supportive counseling and education usually suffices for treatment, with occasional use of short-term medications for symptom control. Grief may be prolonged beyond 6 months and more severe, and distinguishing it from major depressive disorder may be difficult.

### Diagnosis of Depression

**Common presentations of depression in primary care.** Depression is commonly found in patients who may present to primary care or subspecialty physicians with irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, or chronic pain such as headache, low back pain, and pelvic pain. Patients with anxiety or depression may deny mood or psychiatric symptoms because of social stigma or because they truly do not experience mood symptoms. Overall, symptom-sign mismatch (many seemingly severe symptoms, a negative physical examination, and an increasingly long list of normal laboratory tests) should alert the clinician to a high likelihood of depression or anxiety. However, the clinician should maintain the usual vigilance for undiagnosed medical disease. Intimate partner violence is associated with depression in pregnancy and should be considered in all women with depression.

Assessing patients for clues that a psychiatric diagnosis may be present can be helpful (Tables 1-3). The DSM-IV criteria for the diagnosis of major depression are presented in Table 2. In addition, consider the following:

**History.** Establish the duration of illness, history of prior episodes, family history, history of prior manic or hypomanic episodes, substance abuse, and other comorbid disorders. Patients will sometimes initially deny a prior personal or family history of depression. On further questioning they will often admit to having a relative who was 'moody' or had to 'take a rest' for several weeks. They may relate having to drop out of school for a time because of difficulty coping. It is important to screen for bipolar disorder in any patient presenting with depression. Traditional teaching has suggested that as many as 30-50% of patients with underlying bipolar disorder will develop acute mania when started on antidepressant pharmacotherapy. However, switching to mania is more among patients who have been hospitalized for depression, rather than the typical depressed patient seen by most primary care physicians. A focus on symptoms of

---

hypomania characteristic of Bipolar II disorder may be helpful. Screen for concomitant anxiety disorders which may occur in more than 50% of patients with depression.

**Evaluation.** Evaluate severity, suicidal tendencies and psychotic features. If asked directly, patients are usually very honest regarding suicidal thoughts, plans and intentions. Table 3 presents some quick screening questions for depression. Consider using a self-rating scale or direct questions to measure initial and subsequent severity as the patient is treated. Several self-rating scales are available. As an example, the Patient Health Questionnaire (PHQ-9) and its scoring key are included at the end of this guideline. Once a clinician thinks that the likelihood of depression is sufficient to warrant the use of a structured questionnaire, a questionnaire may not be necessary for determining whether depression diagnostic criteria are met; however, these questionnaires may be helpful in establishing a baseline for ongoing monitoring and determining response to treatment.

**Physical examination.** Look for clues to chronic illnesses, hypothyroidism, and other comorbid illness as described previously. Fatigue is a common presenting complaint in depressed patients in primary care. Consider screening for anemia, liver/renal dysfunction and thyroid disease if other findings suggest possible risk. Many physicians will obtain routine screening tests for chronic disease if the patient has not been seen previously or not had recent routine care. It is often helpful to introduce the diagnosis of depression to the patient as part of the differential diagnosis at the initial visit. One can then see the patient back within 1-2 weeks to further discuss the diagnosis and treatment of depression.

**Laboratory testing.** Laboratory tests have no routine value in the diagnosis of depression, beyond judicious use to rule out medical conditions that might cause the same symptoms.

**General medical illnesses associated with depression.** Depression commonly coexists with certain medical conditions, including myocardial infarction, stroke, cancer, major trauma, multiple sclerosis, Parkinson's Disease, or any major new diagnosis, particularly if hospitalization is involved. Depression can interfere with effective treatment of the other conditions, delaying recovery and significantly increasing morbidity. Depressed patients are three times more likely to be non-adherent with medical recommendations. Depression is a more powerful predictor of mortality from myocardial infarction than physiological measures such as cardiac ejection fraction. Depression is prevalent in patients with heart failure and is associated with a poorer short-term prognosis. Major depressive disorder may occur in greater than 50% of patients after CVA and has been associated with impaired recovery and worsened mortality. Conversely, depression itself may be an independent risk factor for stroke and coronary heart disease. Certain medications may be implicated in the cause of depression as well, such as retinoids and interferon.

## Treatment of Depression

Figure 1 and Tables 4–8 summarize operational information regarding treatment. Figure 1 outlines the overall process for monitoring, assessing, and possibly augmenting treatment. Principles concerning five general components of treatment are discussed below.

- Supportive care
- Pharmacotherapy
- Psychotherapy
- Ongoing clinical assessment
- Treatments for severe or refractory depression

**Comorbid psychiatric illnesses and other special situations.** Patients with a Major Depressive Disorder frequently suffer from other psychiatric disorders and their treatment is influenced by the presence of these comorbid conditions.

Table 7 describes common psychiatric comorbidities and special treatment considerations. In addition, Table 8 presents diagnostic and treatment considerations for patients in complicating circumstances, e.g., partner violence, pregnancy. (Tables 7 and 8 are placed after the guideline text.)

**Supportive care principles.** The treatment of all patients diagnosed with major depression should include patient education and exercise.

**Patient education.** Depression remains poorly understood by the general public. Patients are often reluctant to accept a diagnosis of depression due to stigma, an underestimation of its severity, or a view that depression is an expected response to a life situation. Many patients attempt to deal with the symptoms alone, or seek care only from lay counselors, pastoral counselors, friends or relatives. Adherence with treatment recommendations is often poor because of the above factors. These attitudes and beliefs need to be countered by the physician who emphasizes the severity of the disease, and the importance of its treatment (see Table 4).

**Exercise.** Several small controlled clinical trials show that regular physical exercise (2-3 times/week; either aerobic or anaerobic) is more effective than no treatment in relieving symptoms of depression. In at least two trials the outcome in the exercise group was comparable to that of psychotherapy at 12 weeks, at least for patients with mild depression.

**Pharmacotherapy and psychotherapy comparisons.** In patients with mild to moderate depression, initial treatment may be with medication, psychotherapy or both as guided by the patient's and physician's preferences. Medication is frequently the first-line treatment for patients with more severe depression. In Level 2 of the STAR\*D trial (see "Drug trials" below), cognitive therapy and medication had similar remission rates although time to remission was shorter in the medication group.

**Pharmacotherapy principles.** Table 5 provides practical guidelines for matching first-line antidepressants to patients

---

as well as information on dosing and cost. The following issues should also be taken into account when considering pharmacotherapy.

Choice of agent. In selecting an agent, consider the following.

- No superior agent. Several systematic reviews have not shown a clear cut difference amongst the second-generation antidepressants in efficacy or tolerability.
- Previous success. Use what has worked for the patient in the past.
- First choice. SSRIs and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) are the agents of first choice due to ease of use, usually tolerable side effects and safety in overdose. Paroxetine might not be a first choice, given potential teratogenic effects and issues with withdrawal symptoms. Tricyclic antidepressants and MAOIs are considered second or third line treatment. MAOIs are usually prescribed by specialists.
- Cost. Drugs within a class can vary appreciably in cost. Several medications are now available generically.
- Response to specific medication not predictable. No reliable predictor exists for response to a particular medication.
- Explain potential side effects. Side effects are common and should be explained in detail to the patient at initiation of medication. The most common side effects include constipation, diarrhea, nausea, dizziness, headache, insomnia, somnolence. Sexual side effects are particularly common (up to 60%) and are probably less frequent with bupropion or mirtazapine. However, mirtazapine (Remeron) is more likely to cause weight gain.
- History of seizure. Use SSRIs in patient with a history of seizure disorder. Bupropion lowers the seizure threshold.
- Chronic pain. Despite theoretical pharmacologic properties of some of the second generation agents, for the evidence regarding the superiority of one agent over another for the treatment of chronic pain is mixed. In general, SSRIs may be less helpful for pain, and a mixed agent such as mirtazapine, venlafaxine or duloxetine or a tricyclic agent may be considered.
- Drug interactions. A theoretical concern exists for using antidepressants with CYP2D6 inhibiting properties together with SERMS (selective estrogen receptor modulators). Some oncologists recommend against using tamoxifen with fluoxetine, paroxetine, bupropion, duloxetine. SSRIs and SNRIs which are not potent inhibitors of this enzyme, include venlafaxine, citalopram, escitalopram and sertraline.
- Side effects. Some evidence suggests that SSRIs may increase bone loss and increase the risk for fragility fractures in older patients. In addition, risk may increase for upper gastrointestinal bleeding, especially in patients who are also on NSAIDs. These data are preliminary, with more research required to clarify the absolute risk.

Rare case reports suggest the potential for a patient taking serotonergic antidepressants to develop a serotonin syndrome (altered mental status, agitation, myoclonus, hyperreflexia) with the concomitant use of buspirone, dextromethorphan, tramadol, St. John's Wort, and the triptan class of drugs (used for migraine headache). However, the clinical significance of this risk is unclear and probably extremely low with these combinations. There are combinations, however, that do pose a greater threat. Specifically, when monoamine oxidase inhibitors (MAOIs), like phenelzine, selegiline, or tranylcypromine, are used. Other medications with MAOI activity, including linezolid and methylene blue, also increase the risk of serotonin syndrome when used in combination with any serotonergic medication, including SSRIs and SNRIs.

Trials of drugs. Trials of drugs should consider the following:

- Response rate. Rates of 50% response and 30% remission have been demonstrated with an *adequate trial* (4-6 weeks) of first agent, compared to a 20-40% response rate for placebo. The most common cause of treatment failure is an inadequate medication trial.
- Change. If the patient shows no response to an antidepressant trial at 6-8 weeks, consider switching the antidepressant or augmenting with another agent.

Measuring response to treatment at each follow-up visit with serial measurement tools may be helpful. Tools include the PHQ9, ECS-D, and the Hamilton Rating Scale for Depression.

The Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) Trial was a landmark NIH sponsored study designed to evaluate the best next-step for depressed patients who failed to respond to an initial trial of an SSRI. As opposed to many industry-sponsored short-term efficacy trials of antidepressants, the patients in the STAR\*D study were drawn from real world primary and specialty care clinical practices, had moderate to severe depression, chronic difficulties, and multiple psychiatric and medical comorbidities.

The detailed design of the STAR\*D study and remission rates at each level are presented in Figure 3 (located after the text, following Table 8). The end point of the study was full remission (defined as the absence of symptoms) rather than response to medication (>50% reduction in depression measurement scores). All patients were treated with citalopram at Level 1 for 12 weeks. Those whose depression failed to fully remit progressed to Level 2 where they were switched from citalopram to a medication either within or outside class (bupropion SR, venlafaxine XR or sertraline), were switched from citalopram to cognitive therapy, or had citalopram *augmented* with bupropion SR, buspirone or cognitive therapy. Those who were intolerant or failed to remit advanced to Level 3 where they were again either switched to mirtazapine or nortriptyline or augmented with lithium or triiodothyronine (T3). Those who failed to remit at Level 3 advanced to Level 4 where all medications were discontinued and they were switched

---

to tranylcypromine (an MAOI) or a combination of mirtazapine and venlafaxine XR.

Important findings include the following:

- After an initial treatment failure, it is reasonable to: switch to antidepressant medications within or outside of class; switch to cognitive therapy; or augment with bupropion, buspirone, or cognitive therapy.
- No medication is a clear 'winner.' Switching within or outside a drug class does not seem to matter.
- There was little difference in tolerability or side effects between medications.
- As patients progressed through subsequent levels due to failed treatments, remission rates were low and the chance of remission diminished.
- Many patients will require multiple steps to achieve remission.
- Patients who achieve full remission have a lower risk of relapse than patients who achieve only diminished symptoms.
- There was no difference in the severity of depression or psychiatric comorbidities between the primary and specialty care practices although the primary care patients tended to have more medical comorbidities.
- Remission rates did not differ for patients receiving primary care or specialty care.
- Attrition rates were very high at all levels.

**Referral.** Consider referral after 1-2 failed drug trials or in patients with concomitant substance abuse, personality disorder or suicidality.

**Pregnancy.** The risks of taking medications during pregnancy or lactation should be weighed against the risk of a woman being severely depressed during pregnancy or in the early stages of newborn parenting. When counseling the patient who has depression and wishes to conceive, potential risks and benefits of pharmacotherapy must be weighted. Women considering pregnancy may want to pursue psychotherapy instead of medication.

Maternal depression plays a significant role in child development both ante-partum (e.g., behavior affecting maternal health) and post-partum (e.g, interactions with child). Treatment goals are to maintain mood stability during pregnancy and to prevent post partum decompensation. Prophylaxis to prevent recurrent post-partum depression should be considered, initiating medication in the third trimester (at least 4 to 6 weeks prior to birth).

SSRIs should be the first line drug of choice. Animal studies have shown no risk of fetal anomalies with these drugs. Consider Sertraline due to its shorter half-life compared to Fluoxetine. Paroxetine should be avoided due to evidence of fetal cardiac malformations (although recent studies question this finding). SNRIs should also be considered. Patients already on these medications prior to pregnancy with good response should remain on them.

Limited information exists regarding fetal risks of medications for depression. One recent prospective study of

women on paroxetine, sertraline, and fluvoxamine during pregnancy also failed to reveal an increased teratogenic risk. However, another study found that infants exposed to SSRIs during late pregnancy are at increased risk for serotonergic central nervous system adverse effects in the days after delivery, with the severity of these symptoms being significantly related to cord blood 5-HIAA levels.

A small risk for persistent pulmonary hypertension may occur in newborns of mothers taking SSRIs at the time of delivery, most likely due to vascular effects of serotonin, but the risk is extremely small, if it exists at all, and should be balanced with the consequences of untreated depression in the mother.

For mild to moderate depression, psychotherapy (e.g., cognitive behavioral therapy, interpersonal therapy) may be the initial approach. Medication should be included for moderate to severe depression or for suicidal ideation. Antidepressant use in pregnancy/lactation should follow the same guidelines as any drug in pregnancy: older drugs have more data on fetal risk and should be selected over newer drugs when possible. The American Psychiatric Association and the American College of Obstetrics and Gynecology have jointly developed a clinical practice guideline addressing the specific issues of diagnosing and treating pregnant women.

**Psychotherapy principles.** Table 6 (placed after guideline text) outlines several psychotherapeutic treatments for depression. Psychotherapy alone is as efficacious as antidepressant medication in patients with mild to moderate major depression and may be efficacious even among patients with more severe depression. However, most clinicians recommend combining psychotherapy with pharmacotherapy for patients with severe or chronic depression. Patients treated with psychotherapy alone should be monitored. Patients having an insufficient response after 12-16 weeks should be considered for antidepressant medication.

Physicians should also consider initiating treatment with a combination of psychotherapy and antidepressants if patients have:

- a history of only partial response to previous trials of medication or psychotherapy.
- a history of two or more episodes of major depression with poor interval functioning.
- a depressive episode of 2 or more years.
- psychosocial difficulties that interfere with treatment adherence.

Many different forms of psychotherapy exist. However, only a few short-term psychotherapies that lend themselves to codification in manuals have been tested in randomized controlled trials. Psychotherapy practiced in the community may or may not resemble the standardized psychotherapies proven effective in RCTs.

**Ongoing clinical assessment.** Patients should initially be seen relatively frequently (weekly to biweekly) to assess the patient's response to the treatment intervention,

assess/reassure the patient regarding side effects, evaluate suicidal tendencies, and rule out comorbid disorders. Expert opinion varies regarding visit frequency but 3-7 visits in the first 12 weeks of treatment have been suggested. Some patients treated with antidepressants may experience increased agitation, anxiety, and hostility, particularly in the early stages of treatment, potentially placing them at increased risk of suicidal behavior, and there is now a Black Box warning regarding potential increased suicidal risks among adolescents and young adults. Many patients are also non-adherent with treatment and more frequent visits have been associated with increases in adherence.

Approximately 40%–50% of treated patients will show a good response to pharmacotherapy within about 8-12 weeks, although a smaller percentage (approximately 30%) will meet criteria for complete remission. When remission is achieved, medication should then be continued for an additional 9-12 months. Discontinuing medication too soon, or decreasing dosage below that required for treatment response, is associated with a higher rate of relapse. Office visits during the continuation phase of treatment are conducted on an as-needed basis. Remember to assess patients for risk factors for recurrence or relapse and to consider lifetime maintenance on antidepressants for those with a high risk of relapse.

Conceptualize treatment as occurring in three phases (see Figure 2), with many/most patients requiring only acute and continuation therapy:

1. **Acute:** Aim for remission of all depressive symptoms. The mean time to remission when it occurs, is 6 to 12 weeks after starting antidepressant medications, although the STAR\*D study also indicated that many patients may need more than 12 weeks to remit.
2. **Continuation:** For 9-12 months after symptom relief in order to prevent relapse.
3. **Maintenance:** Recommended for patients with 3 or more episodes of major depression, history of psychotic depression, or first onset of depression at age 55 years or older.

**Managing side effects.** Insomnia, akathisia (a syndrome characterized by motor restlessness), weight gain, and sexual dysfunction are commonly associated with the use of antidepressant agents. Consider the following strategies for managing related side effects:

- **Insomnia:** Add a small dose of trazodone (25-50mg QHS) to an SSRI.
- **Akathisia:** This side effect has been associated with newer antidepressants. Consider adding a small dose of clonazepam (0.5 mg QHS).
- **Weight gain:** No proven remedies exist. Patients should be warned about this potential side effect and regular exercise encouraged both for its weight maintenance effect and for its potential to further help with depressive symptoms. Bupropion may be less likely to result in weight gain.

- **Sexual dysfunction:** While sexual dysfunction with antidepressants is common in both men and women, distinguishing between side effects of a drug and symptoms of the disease can be difficult. Bupropion is least likely to produce this side effect and can be used concomitantly with SSRIs or SNRIs. Other less well-proven or studied strategies include the use of sildenafil, cyproheptadine, and ginkgo biloba.

**Treatment of refractory depression.** Although no single definition of treatment refractory depression exists, patients have often been considered to be treatment refractory if they have been treated with two successive trials of antidepressants in adequate doses for adequate periods of time (6 to 12 weeks). Approximately 40% of patients with MDD will not respond to two trials of antidepressant medication. If symptoms are moderate to severe, patients might be referred to a psychiatrist at this time for further evaluation and treatment.

Psychiatrists will usually re-evaluate the diagnoses of these patients, looking for complicating factors that might explain the lack of treatment response, e.g., concomitant alcohol or substance abuse, accompanying psychiatric disorders, or continuing adverse psychosocial circumstances. Additional treatment strategies may include more intensive or specific psychotherapies such as intensive outpatient treatment of alcohol abuse, alternative environmental supports such as social work case management, or augmentation of antidepressant medication with a variety of pharmacologic agents.

Some primary care physicians will feel comfortable using pharmacologic augmentation strategies with their patients who do not respond to standard antidepressant regimens. Primary care physicians might consider the following strategies, which are commonly used by experts in depression care.

- Combination of antidepressant medication, particularly those with different neurotransmitter actions [B-C\*].
- Lithium in addition to an antidepressant [A\*] – titrated by blood level, with a goal of 0.6-1.0 mEq/l
- Thyroid hormone supplementation in addition to an antidepressant in euthyroid patients [A\*].
- Antipsychotic medication (aripiprazole, risperidone or olanzapine) augmentation of antidepressant medication [A\*].
- Electroconvulsive therapy – a highly efficacious treatment, which may be the treatment of choice for the frail elderly or acutely suicidal patients but requires referral
- Stimulant medication in addition to an antidepressant.
- Monoamine Oxidase Inhibitors (MAOIs).
- Mood stabilizers.

Many of the above augmentation strategies have limited evidence of efficacy and studies supporting their effectiveness often have methodological limitations. The exceptions to this are ECT, MAOIs and lithium

supplementation, and perhaps antipsychotic augmentation, although, to date, most studies examining the effectiveness of the latter strategy have been drug company supported.

**Referral.** Consider referral for patients:

- who fail 2 or more medication trials
- are suicidal
- with psychotic or bipolar depression
- with comorbid substance abuse
- who have severe psychosocial problems
- who require specialized treatments such as ECT
- who have quickly increasing depressive symptoms
- with unclear diagnosis or patients with suspected personality disorders

## **Special Considerations: Adolescents and Older Patients**

### **Adolescents**

In adolescence, presentation of a major depressive disorder (MDD) may include substance abuse, antisocial behavior, social withdrawal and academic failure, with suicide attempts and ideation common. Few long-term studies have been performed on adolescents. Information is limited for this age group on prevalence, treatment, and impact on long term prognosis.

Guidelines for Adolescent Depression in Primary Care (GLAD-PC) offers recommendations for treatment of the adolescent in a primary care setting, that are consistent with those for all depressed patients. The guidelines and supporting toolkit are available at: [www.thereachinstitute.org/guidelines-for-adolescent-depression-primary-care.html](http://www.thereachinstitute.org/guidelines-for-adolescent-depression-primary-care.html) .

In 2003 concerns were raised regarding suicide ideation and behavior in adolescents on SSRIs. The FDA issued a “black box” warning in 2004 for use of SSRIs in adolescence. Since then the use of antidepressants in this group has decreased by 58%. A paralleling increase in suicide completion has occurred. While meta analysis have shown consistent but modest increase in suicidal risks, the American Association of Child and Adolescent Psychiatry has expressed concern that the major depressive disorders themselves carry considerable risk of other morbidity and of mortality.

### **Late Life Depression**

Depression is not a normal consequence of aging. Healthy independent elders have a lower prevalence of major depression than the general population. Rates increase with medical illness such as cancer, heart attack, stroke and Parkinsons disease.

Patients who experience their first episode of depression later in life are less likely to have familial or genetic predisposition as a cause. Other risk factors include:

- Female sex
- Social isolation, widowed, divorced or separated
- Lower socioeconomic status
- Comorbid medical diagnosis, pain, insomnia, functional and cognitive impairment

Depression is a major risk factor in suicide in the elderly. They attempt suicide less often than younger people, but are more successful at completion. Risk factors for suicide include: medical comorbidities, poorly treated chronic pain, terminal or worsening illness, social isolation, personality disorders, previous attempt of suicide, and family history of suicide.

The diagnosis and assessment of depression in older adults is similar to that for all depressed patients as described previously.

Successful treatment of depression is similar to that for all depressed patients. Psychotherapy, medical therapy, and electroconvulsive therapy have all been found effective in older patients. Medication response generally takes longer (up to 4-6 weeks). and up to 3 trials may be necessary to determine whether a therapy is appropriate. Monotherapy is recommended to minimize side effects and drug interactions. Starting doses for medications should be half the dose for younger adults. Evaluation of response should occur every 2-4 weeks. SSRIs are first line therapy. Second line agents include dual action drugs (Venlafaxine, duloxetine), with merazapine also used as a second line drug.

Patients with failure of 3 medical trials, suicidality, depression complicated by other psychiatric diagnoses, and preference for non pharmacologic treatment should be referred to psychiatry.

## **Controversial Areas**

### **St. John’s Wort (*Hypericum Perforatum*)**

St John’s Wort (*Hypericum Perforatum*) is claimed to improve depressive symptoms particularly in patients with mild-moderate depression. (900 mg daily may be effective in mild to moderate depression.) Studies have produced conflicting results, making recommendations regarding St. John’s Wort difficult. Early studies carried out in Europe suggested reported rates of improvement at 4-6 weeks comparable with antidepressants (40%-50% response) with 20-30% placebo response. Side effect frequency was notably lower than with standard antidepressants and included gastrointestinal side effects, allergic reactions, tiredness and restlessness. More recent, larger, and rigorous studies conducted in the United States have been less positive. The more recent studies suggest the benefit may only apply to patients with relatively mild depression. Determining the bioavailability of the active ingredient is a problem in evaluating either the results of a clinical trial or the clinical benefit in an individual patient.

Ascertaining use of St. John's Wort before prescribing usual antidepressants is critical, because of the possible serotonergic effects of Hypericum. In addition, St. John's Wort induces CYP3A4. Consequently, numerous drug interactions can be expected with chronic use of St. John's Wort in patients taking drugs dependent on metabolism via CYP3A4, e.g., statins.

## Withdrawal Syndrome

Several reports and semi-controlled studies suggest that many patients, possibly a majority, experience withdrawal symptoms, especially when agents with short half-lives are stopped suddenly after a long period of use. The syndrome consists of agitation, sudden flashes of light, edginess and disquiet. Some investigators believe these are merely the symptoms for which treatment was originally started, while others believe these agents can cause a withdrawal, although not a physiological addiction. The symptoms only last for a matter of days to weeks, and can be avoided through a slow taper of medication over several weeks or even months when a patient has been treated for a year or more.

## Strategy for Evidence Search

The literature search for this update began with results of the literature search performed in 1997 to develop the initial guideline released in 1998 and the search performed in 2002 for the update released in 2004. The literature search for this update used keywords that were very similar to those used in the previous searches. However, instead of beginning the search with literature in 2002, the guideline team accepted the search strategy and results for the search performed through 12/31/06 for the VA/DoD clinical Practice Guideline for Management of Major Depressive Disorder (MDD).

The search for this update was conducted prospectively on Medline using the major keywords of: depression, depressive disorders; clinical guidelines, controlled clinical trials, cohort studies; adults; English language, and published 1/1/07 – 1/31/10. Terms used for specific topic searches within the major key words included: epidemiology, national cost of treatment (economics); spectrum of depression, seasonal affective disorder, dysthymia; screening for depression; screening for bipolar disorder; diagnosis; suicide risk assessment; patient education; exercise; pharmacotherapy and psychotherapy – comparison and in combination; combinations of more than one pharmacologic agent; serotonin selective reuptake inhibition (citalopram, escitalopram, fluoxetine, paroxetine, sertraline); serotonin/norepinephrine reuptake inhibition (desvenlafaxine, duloxetine, mirtazapine, tricyclic antidepressants, venlafaxine); norepinephrine/dopamine reuptake inhibition (bupropion); serotonin-2 antagonist/reuptake inhibition (nefazodone, trazodone); St. John's Wort (*Hypericum Perforatum*); maintenance on pharmacotherapy, continuation duration; withdrawal syndrome (paroxetine/Paxil, desvenlafaxine, venlafaxine); medication adherence; managing sexual side effects of

pharmacologic agents; pregnancy and pharmacologic agents, breast feeding and pharmacologic agents; pharmacotherapy not included above; mindfulness based therapy; problem solving therapy; interpersonal psychotherapy, cognitive behavioral therapy, short-term or focal psychodynamic psychotherapy, marital therapy, psychotherapy, not included above; other treatment not included above; ongoing clinical assessment; medical comorbidity; alcohol abuse; panic (including generalized anxiety disorder or phobia); obsessive compulsive disorder; post-traumatic stress disorder; eating disorders and anorexia nervosa; partner violence; sexual assault; pregnancy (not included above), postpartum (not included above); and depression not included above. Specific search strategy available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized controlled trials if available, to the exclusion of other data; if randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

## Related National Guidelines

The UMHS Clinical Guideline on Depression is consistent with:

APA Practice Guideline for the treatment of patients with major depressive disorder (2010)

The management of depression during pregnancy a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists (2009)

Guidelines for Adolescent Depression – Primary Care (2007)

United States Preventive Services Task Force. Screening for depression in adults (2009)

Using second-generation antidepressants to treat depressive disorders: A clinical practice guideline from the American College of Physicians (2008)

VA/DoD clinical Practice guideline for Management of Major Depressive Disorder (MDD) (2008)

See full references below.

## Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who

present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

Team Member	Relationship	Company
Jolene R Bostwick, PharmD	None	
R Van Harrison, PhD	None	
Thomas L Schwenk, MD	None	
Linda B Terrell, MD	None	
Amy L Tremper, MD	None	
Marcia A Valenstein, MD	None	

## Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, General Obstetrics & Gynecology, and Psychiatry. The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

## Acknowledgments

The following individuals are acknowledged for their contributions to previous major versions of this guideline:

1998: Thomas L. Schwenk, MD, Family Medicine, Linda B. Terrell, MD, General Internal Medicine, Elizabeth M. Shadigian, MD, Obstetrics & Gynecology, Christopher G. Wise, PhD, Clinical Affairs, Marcia A. Valenstein, MD, Psychiatry. Consultant, David J. Knesper, MD, Psychiatry

2004: Thomas L. Schwenk, MD, Family Medicine, Linda B. Terrell, MD, General Internal Medicine, R. Van Harrison, PhD, Medical Education, Elizabeth M. Shadigian, MD, Obstetrics & Gynecology, Marcia Valenstein, MD, Psychiatry. Consultant, David J. Knesper, MD, Psychiatry

## General References

American Psychiatric Association Work Group on Major Depressive Disorder (Gelenberg AJ, Freeman MP, Markowitz JC, et al). Practice guideline for the treatment of patients with major depressive disorder, third edition. American Journal of Psychiatry, 2010; 167(10 supplement). Also available at [www.psychiatryonline.com/pracGuide/pracGuideTopic\\_7.aspx](http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx) (accessed 11/18/10).

The Management of MDD Working Group. VA/DoD clinical Practice guideline for Management of Major Depressive Disorder (MDD). Washington, DC: U.S.

Departments of Veterans Affairs and of Defense, 2008. Available at:

[www.healthquality.va.gov/Major\\_Depressive\\_Disorder\\_MDD\\_Clinical\\_Practice\\_Guideline.asp](http://www.healthquality.va.gov/Major_Depressive_Disorder_MDD_Clinical_Practice_Guideline.asp) (accessed 10/4/10).

Qaseem A, Snow V, Denberg TD et al. Using second-generation antidepressants to treat depressive disorders: A clinical practice guideline from the American College of Physicians. Annals of Internal Medicine, 2008; 149(10):725-233. Available at:

[www.annals.org/content/149/10/725.full.pdf+html](http://www.annals.org/content/149/10/725.full.pdf+html) (accessed 10/4/10).

United States Preventive Services Task Force. Screening for depression in adults. Annals of Internal Medicine, 2009; 151:784-792. Available at:

[www.uspreventiveservicestaskforce.org/uspstf09/adultdepression/addeprss.htm](http://www.uspreventiveservicestaskforce.org/uspstf09/adultdepression/addeprss.htm) (accessed 10/4/10).

Yonkers KA, Wisner KL, Stewart DE, et al. The management of depression during pregnancy: a report of the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Obstetrics & Gynecology, 2009; 114(3):703-713.

Zuckerbrot RA, Cheung AH, Jensen PS, Stein REC, Laraque D, and the GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary CARE (GLAD-PC): I. Identification, Assessment, and Initial management. Pediatrics, 2007; 120(5):1299-1312.

Cheung AH, Zuckerbrot RA, Jensen PS, Ghalib K, Laraque D, Stein REK, and the GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and Ongoing Management. Pediatrics, 2007; 120(5):1313-1326.

Full report and supporting toolkit available at: [www.thereachinstitute.org/guidelines-for-adolescent-depression-primary-care.html](http://www.thereachinstitute.org/guidelines-for-adolescent-depression-primary-care.html) (accessed 1/25/11).

**Table 6. General Principles of Psychotherapy**

<b>Psychotherapy Modality</b>	<b>Brief Description</b>	<b>Evidence of Effectiveness</b>
Any Psychotherapy	Most psychotherapies have many commonalities, such as a socially sanctioned therapist, emphasis on developing a treatment alliance, a theory that offers a plausible explanation for symptoms, expectations of change, and a structured series of contacts between therapist and patient to bring about change.	Many forms of psychotherapy are more effective than "wait list" controls [A*]. A few short term structured psychotherapies have been shown to be effective in the treatment of MDD [A*]. .
Interpersonal Psychotherapy (IPT)	Focuses on clarification and resolution of interpersonal difficulties. Explores interpersonal losses, role disputes, role transitions, and social skill deficits.	Effective in reducing symptoms as the sole agent in mild to moderate depression [A*].
Cognitive Behavioral Therapy (CBT)	Identifies and attempts to modify negatively-biased cognitions. Behavioral component includes activity scheduling and social skills training.	Effective in reducing symptoms as the sole agent in mild to moderate depression [A*]. Possibly lower relapse rates after treatment discontinuation compared to medication [A*]. Can be successfully delivered in a computer based format [A*]
Marital Therapy	Focuses on improving the marital relationship of patients with depression.	Evidence for increased efficacy in combination with pharmacotherapy for chronic depression [A*].  Marital therapy appears to be effective for depressed women in discordant marital relationships [A*]. Marital therapy should only be considered if violence is screened for and absent in the relationship.

**\* Levels of evidence for the most significant recommendations:**

A = randomized controlled trials; B = controlled trials, no randomization; C = observational trials; D = opinion of expert panel.

**Table 7. Prevalence and Treatment of Co-Morbid Depression**

Co-Morbid Depression	Epidemiology	Diagnosing Co-Morbid Conditions	Special Rx Considerations
Depression accompanied by Alcohol Abuse or Hazardous Alcohol misuse	<ul style="list-style-type: none"> <li>Approximately 15-30% of patients with MDD have an alcohol use disorder</li> <li>10-30% of patients with an alcohol use disorder have concurrent depression</li> </ul>	Consider asking the <u>AUDIT-C</u> -questions (see below).*	<ul style="list-style-type: none"> <li>If there is concurrent alcohol abuse and depression, address the alcohol use to attempt to achieve a period of sobriety. Depressive symptoms may resolve [C*].</li> <li>If unable to achieve sobriety, patients with concurrent depression and alcohol abuse may be treated with an SSRI [A*].</li> <li>Suicide rates are higher among depressed patients with alcohol abuse. Be vigilant in assessing suicidal risk [C*].</li> </ul>
Depression accompanied by Anxiety	<ul style="list-style-type: none"> <li>45% of patients with MDD have significant anxiety symptoms</li> <li>Approximately 40-60% of patients with anxiety disorders have MDD during their lifetime</li> </ul>	Consider asking : <ul style="list-style-type: none"> <li>Are you troubled by repeated, unexpected "attacks" where you suddenly feel very afraid for no apparent reason?</li> <li>Do you often experience periods with rapid heart rate; sweating; dizziness; trembling; feelings of unreality; shortness of breath or choking; fear of going crazy or dying; chest pain; numbness or tingling; chills or hot flashes?</li> </ul>	<ul style="list-style-type: none"> <li>MDD accompanied by anxiety disorders has a relatively poorer prognosis than MDD alone [A*, C*].</li> <li>Patients with MDD and anxiety may need their antidepressants started at lower doses and increased more slowly than individuals with depression alone [C*].</li> <li>SRI's are effective in panic disorder. Bupropion is less effective [B*].</li> </ul>
Depression accompanied by Eating Disorders	<ul style="list-style-type: none"> <li>Perhaps as many as 5-6% of young women with MDD may have an eating disorder</li> <li>30-50% of patients with eating disorders have concurrent MDD</li> </ul>	Be alert for eating disorders among depressed women who are dieting when not "over" weight, have frequent weight fluctuations, or are amenorrheic.	<ul style="list-style-type: none"> <li>MDD in patients with anorexia may be refractory to treatment until normal weight is re-established [C*].</li> <li>If using antidepressants, consider use of an SSRI [A*]. If considering psychotherapy, consider formal cognitive behavioral therapy.</li> </ul>
Depression accompanied by Dementia	<ul style="list-style-type: none"> <li>Approximately 20-30% of patients with dementia may have significant depressive symptoms and 10-20% may have MDD</li> </ul>	Be alert for expressions of worthlessness, crying, decreased interest and pleasure in activities	<ul style="list-style-type: none"> <li>One RCT suggests benefit with treating depression among patients with Alzheimers, a small RCT suggests no benefit. Overall the literature is sparse in this area.</li> </ul>

**\* AUDIT-C Questions and Scoring**

**Q#1:** How often did you have a drink containing alcohol in the past year?

Never	0 points
Monthly or less	1 point
Two to four times a month	2 points
Two to three times per week	3 points
Four or more times a week	4 points

**Q#2:** How many drinks did you have on a typical day when you were drinking in the past year?

1 or 2	0 points
3 or 4	1 point
5 or 6	2 points
7 to 9	3 points
10 or more	4 points

**Q#3:** How often did you have six or more drinks on one occasion in the past year?

Never	0 points
Less than monthly	1 point
Monthly	2 points
Weekly	3 points
Daily or almost daily	4 points

The AUDIT-C is scored on a scale of 0-12 (scores of 0 reflect no alcohol use). In men, a score of 4 or more is considered positive; in women, a score of 3 or more is considered positive. Generally, the higher the AUDIT-C score, the more likely it is that the patient's drinking is affecting his/her health and safety.

**Table 8. Special Issues for Women**

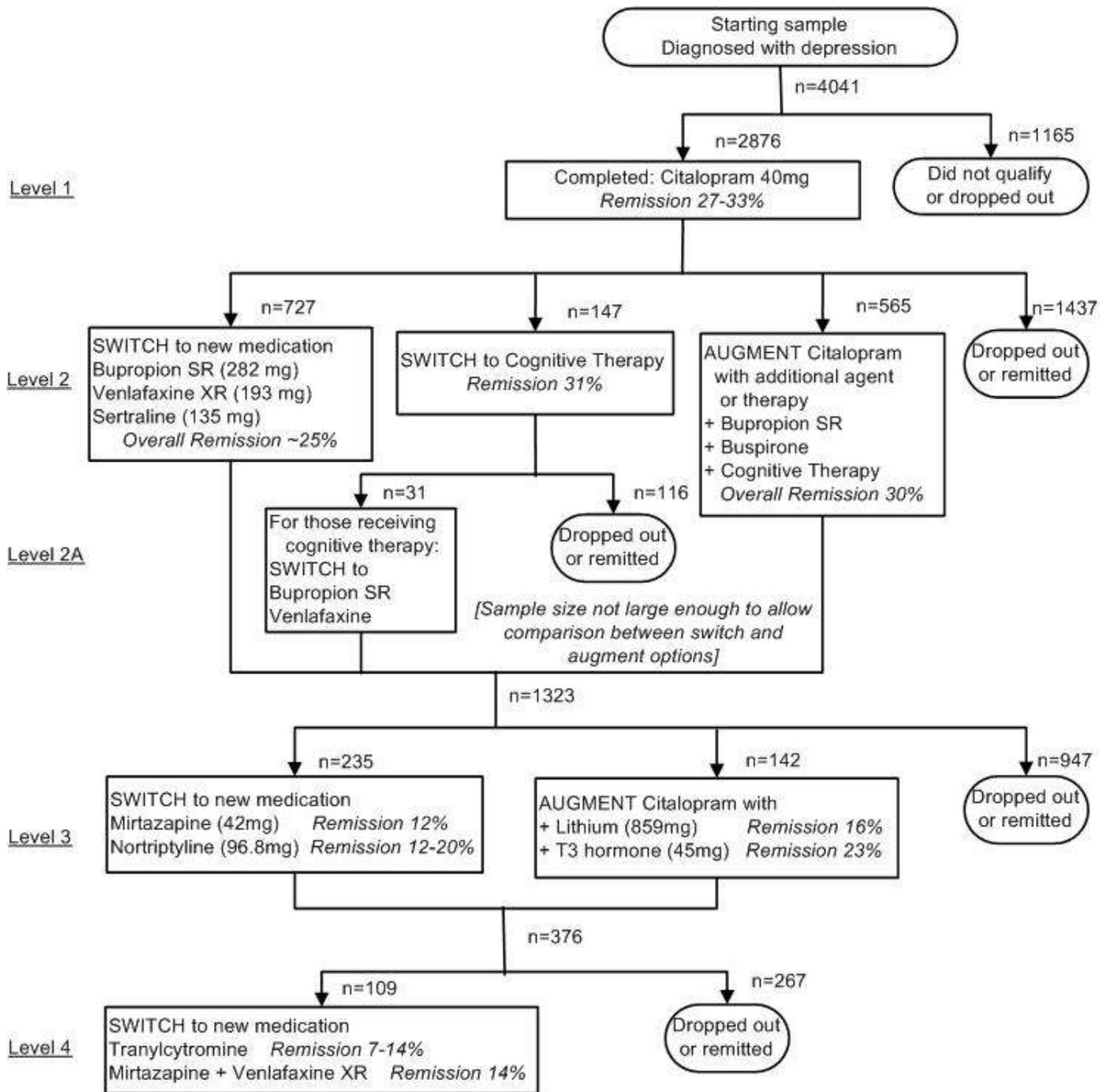
Issues	Epidemiology	Diagnostic Considerations	Treatment considerations
Partner Violence	<ul style="list-style-type: none"> <li>• One quarter of women are victims of partner violence in their lifetimes and 1 in 10 women report violence in the last 12 months.</li> </ul>	<p>Ask in the history:</p> <ul style="list-style-type: none"> <li>• Have you ever been in a relationship where you have been beaten, punched, choked or hurt in any way?</li> <li>• Screen for stalking, homicide risk, sexual assault</li> </ul>	<ul style="list-style-type: none"> <li>• Getting out of the relationship is recommended, but homicide rates increase after separation.</li> <li>• Couples therapy is not recommended.</li> <li>• The “battered women syndrome” (a form of post-traumatic stress disorder [PTSD]) is very common.</li> </ul>
Sexual Assault	<ul style="list-style-type: none"> <li>• 1/3 of all sexual assault victims are depressed.</li> <li>• 1/3 have attempted suicide.</li> <li>• 1/3 have post-traumatic stress disorder.</li> <li>• 1/8 adult women are sexually assaulted in their lifetime; 60% of these assaults occur before age 18.</li> </ul>	<p>Ask in the history:</p> <ul style="list-style-type: none"> <li>• Have you ever been forced to have sex against your will?</li> <li>• As a child or as an adult, did anyone touch you inappropriately sexually?</li> </ul>	<ul style="list-style-type: none"> <li>• Therapists with expertise with sexual assault survivors and PTSD are best.</li> <li>• Pelvic exams will need to be conducted more carefully or avoided. Refer for gynecological care as well as care for depression.</li> </ul>
Pre-Conceptual Counseling	<ul style="list-style-type: none"> <li>• Depression is common. Discuss prior/current mental health issues.</li> <li>• Women are twice as likely to experience depression as men.</li> <li>• Highest rate is in women ages 22 to 44.</li> </ul>	<ul style="list-style-type: none"> <li>• Severity of depression</li> <li>• Number/frequency of episodes</li> </ul> <p>Response history (relapses tend to become progressively harder to treat)</p>	<ul style="list-style-type: none"> <li>• Discontinuing or decreasing meds prior to or early in pregnancy may increase risk of relapse</li> <li>• If you do decrease meds, taper (i.e. 25% every 1-2 weeks)</li> <li>• If patient is getting a good response from current meds, best to continue same (unless contraindicated in pregnancy)</li> </ul>
Pregnancy	<ul style="list-style-type: none"> <li>• Women currently on medications have a 43% chance of relapse during pregnancy:</li> <li>• 68% when meds discontinued</li> <li>• 25% when continued</li> <li>• intermediate risk for dose change</li> </ul>	<ul style="list-style-type: none"> <li>• History of depression ante-or post-partum; family history</li> <li>• Decreasing or discontinuing medications</li> <li>• Psychosocial factors: ETOH, drugs,</li> <li>• Poor social support, marital instability</li> <li>• Previous pregnancy loss, sleep deprivation</li> <li>• Pain</li> <li>• Depression in the year prior to and the year after delivery</li> </ul>	<ul style="list-style-type: none"> <li>• Initiate systematic screening in 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> trimester and postpartum, *as many symptoms of pregnancy are similar to those of depression</li> <li>• For mild to moderate depression, consider psychotherapy</li> <li>• For moderate to severe or suicidal ideation, consider antidepressants               <ul style="list-style-type: none"> <li>- See medication chart for pregnancy classification</li> <li>- SSRIs first line choice</li> <li>- Decision to use an anti depressant at any point in pregnancy depends more on the severity of the depression and response to meds than the specific pharmacological risks.</li> <li>- A single agent at a higher dose is preferable to multiple agents to reduce exposure risk</li> </ul> </li> <li>• Consider non pharmacological treatments such as exercise, light therapy and ECT (with appropriate fetal monitoring)</li> </ul>

(Table 8 continues on next page)

**Table 8. Special Issues for Women (continued)**

Postpartum	Depression is about 15% post partum but increases about 3x in women w/ prior history of PP depression	<ul style="list-style-type: none"> <li>• Mood episodes similar to depressive episodes prior to pregnancy, but onset is within 4 weeks of birth</li> <li>• Increase risk with history of major depressive disorder, alcohol / drug dependence, or mania, which can cause depressive symptoms</li> <li>• greatest period of risk for major depression is first 9 weeks after delivery</li> </ul>	<ul style="list-style-type: none"> <li>• Specific screens for PP period recommended</li> <li>• Post partum” blues” are transient, occur in the first few weeks, but remit spontaneously</li> <li>• Breast feeding may disrupt sleep and increase depression</li> <li>• If patient is breast feeding, may be on a mini-pill (progesterone only), which may increase depression</li> <li>• Consider IUD or barrier method</li> </ul>
Hormonal Contraceptives	<ul style="list-style-type: none"> <li>• May be associated with depression.</li> </ul>	<ul style="list-style-type: none"> <li>• More common in progesterone contraception: depo provera, mini-pill (progesterone only)</li> </ul>	<ul style="list-style-type: none"> <li>• Mini-pill used frequently in breast-feeding mother. Consider IUD or barrier method</li> <li>• Mirena IUD (progesterone implanted, but little systemic effect)</li> <li>• Paraguard copper T IUD</li> <li>• Consider trial of mini pill prior to long term contraception (Depoprovera shots)</li> <li>• Symptoms of hormonal contraception (lower mood, libido) may be confused with depression</li> </ul>
Post and Peri-menopausal Exogenous Hormone Replacement Therapy	<ul style="list-style-type: none"> <li>• Hot flashes/sweats may disrupt sleep and trigger depression</li> </ul>	<ul style="list-style-type: none"> <li>• Insomnia, fatigue, worries associated with health, dependence of old age</li> </ul>	<ul style="list-style-type: none"> <li>• Screen for depression separately.</li> <li>• Consider Rx with hormone replacement, Effexor, clonidine for autonomic symptoms</li> <li>• See Late-life Depression section</li> </ul>

**Figure 3. STAR\*D  
Study Design and Remission Results at Each Level**



**References:**

<http://www.nimh.nih.gov/trials/practical/stard/index.shtml>

<http://ajp.psychiatryonline.org/cgi/content/full/164/2/201>

<http://ajp.psychiatryonline.org/cgi/reprint/163/11/1905>

<http://content.karqer.com/ProdukteDB/produkte.asp?Aktion=ShowPDF&ArtikelNr=318293&Ausgabe=254424&ProduktNr=223864&filename=318293.pdf>

## Patient Health Questionnaire (PHQ-9)

**Patient Name:** \_\_\_\_\_

**Date:** \_\_\_\_\_

	Not at all	Several days	More than half the days	Nearly every day
1. Over the <i>last 2 weeks</i> , how often have you been bothered by any of the following problems?				
a. Little interest or pleasure in doing things	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. Feeling down, depressed, or hopeless	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. Trouble falling/staying asleep, sleeping too much	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d. Feeling tired or having little energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e. Poor appetite or overeating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f. Feeling bad about yourself or that you are a failure or have let yourself or your family down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g. Trouble concentrating on things, such as reading the newspaper or watching television.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
h. Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around a lot more than usual.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
i. Thoughts that you would be better off dead or of hurting yourself in some way.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. If you checked off any problem on this questionnaire so far, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?				
	Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## PHQ-9\* Questionnaire for Depression Scoring and Interpretation Guide

### For physician use only

#### Scoring:

Count the number (#) of boxes checked in a column. Multiply that number by the value indicated below, then add the subtotal to produce a total score. The possible range is 0-27. Use the table below to interpret the PHQ-9 score.

Not at all (#) \_\_\_\_\_ x 0 = \_\_\_\_\_  
Several days (#) \_\_\_\_\_ x 1 = \_\_\_\_\_  
More than half the days (#) \_\_\_\_\_ x 2 = \_\_\_\_\_  
Nearly every day (#) \_\_\_\_\_ x 3 = \_\_\_\_\_

**Total score:** \_\_\_\_\_

Interpreting PHQ-9 Scores			
Diagnosis	Total Score	For Score	Action
Minimal depression	0-4	≤ 4	The score suggests the patient may not need depression treatment
Mild depression	5-9	5 - 14	Physician uses clinical judgment about treatment, based on patient's duration of symptoms and functional impairment
Moderate depression	10-14		
Moderately severe depression	15-19	> 14	Warrants treatment for depression, using antidepressant, psychotherapy and/or a combination of treatment.
Severe depression	20-27		

\* The PHQ-9 is described in more detail at the Pfizer website: <http://www.phqscreeners.com/>