

Depression

Depression Guideline Team

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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.

UMHS Preferred Drugs version

Patient population. Adults with depressive disorders

Objectives. (1) Improve the early recognition and treatment of depression in the primary care setting.
(2) Familiarize clinicians with appropriate treatment options, drug side effects and interactions.
(3) Improve patient's understanding of depression as a treatable illness.
(4) Identify when referral is indicated.

Key points

Epidemiology

- **Common.** Depression is common, underdiagnosed and undertreated.
- **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 [evidence: C*].

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

- **Drug treatment.** 50-65% of patients respond to the first antidepressant [A*]. No particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patients' symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response [A*]. Relative costs can also be considered (e.g., generics). UMHS preferred agents are Fluoxetine (generic) and citalapram (Celexa®). 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 [C*].
- **Frequent initial visits.** Patients require frequent visits early in treatment to assess response to intervention, suicidal ideation, side effects, and psychosocial support systems [D*].
- **Continuation therapy.** Continuation therapy (9-12 months after acute symptoms resolve) decreases the incidence of relapse of major depression [A*]. Long term maintenance or life-time drug therapy should be considered for selected patients based on their history of relapse and other clinical features [B*].
- **Education/support.** Patient education and support are essential. Social stigma and patient resistance to the diagnosis of depression continue to be a problem [D*].

* 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.

Clinical Background

Clinical Problem and Management Issues

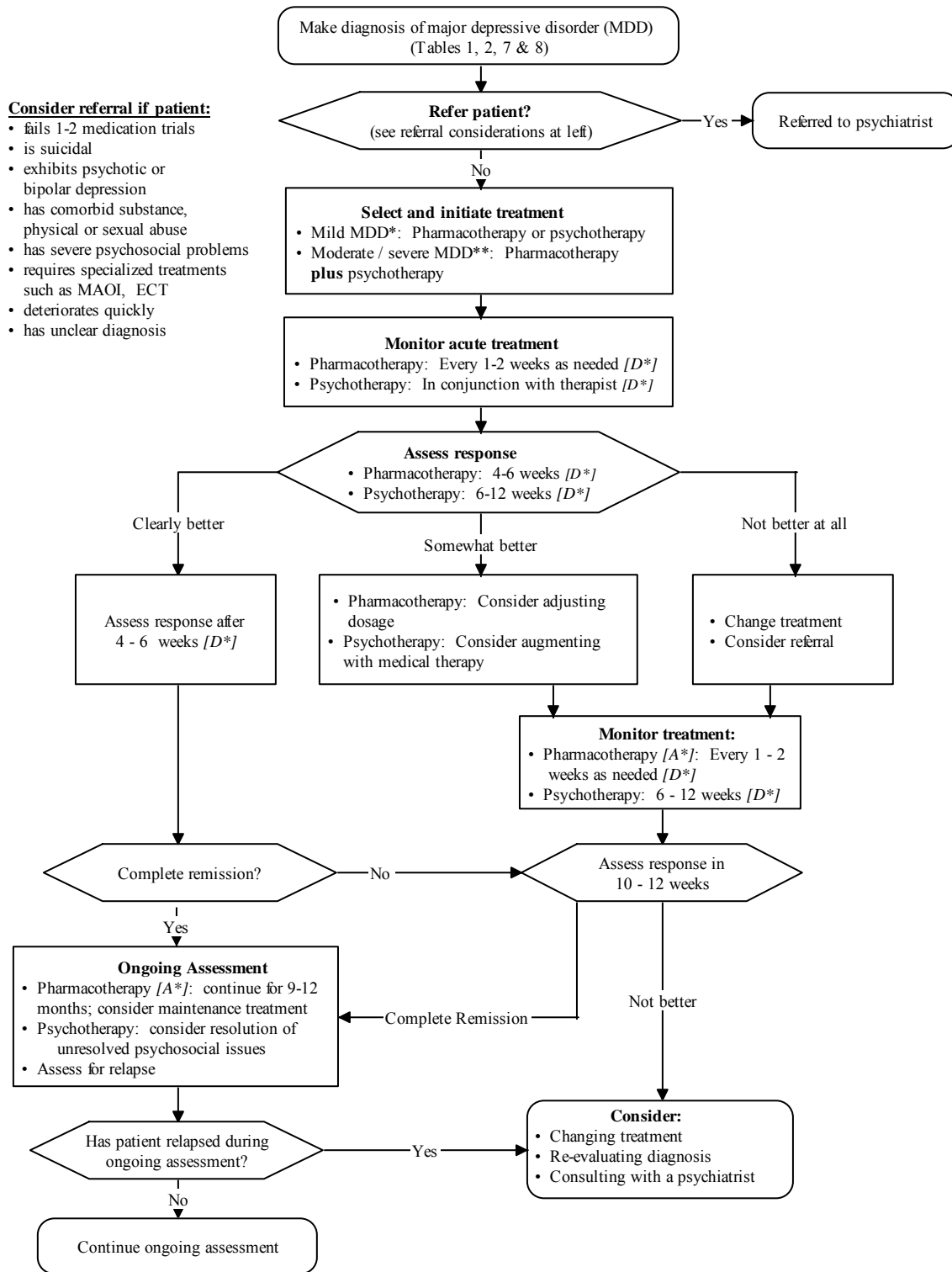
Depression is a common disease with substantial morbidity and mortality. Approximately 5% of the population has major depression at any given time, with men experiencing a lifetime risk of 7-12%; and women 20-25%. The direct and indirect costs associated with major depressive disorder are significant, with an estimated cost in 1990 of \$43 billion 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 doctor, yet depression is underdiagnosed and undertreated.

In a recent epidemiologic study of more than 25,000 primary care patients only 54% of patients who screened positive for depression were recognized as having psychological problems by their primary caregiver and only 15% were given a diagnosis of depression. 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 the same study, an average of 69% of patients presented only with somatic complaints. Reimbursement restrictions can interfere with comprehensive treatment. Competing medical co-morbidities compete for time and attention by both physician and patient.

(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

<p>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</p> <p>Emotions. Patients who are emotionally flat, verbally unproductive or tearful, or who are worried or are upset out of proportion to the apparent severity of the problem</p> <p>Sleep. Sleep disturbance, either with initiation or maintenance of sleep</p> <p>Medical visits. Frequent, often unscheduled, patient-initiated visits to the physician or the emergency room for unclear reasons</p> <p>"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</p> <p>Dysfunction. Patients who have cognitive or emotional dysfunction i.e., forgetfulness, irritability and loss of motivation or energy</p> <p>Recurrence. Past history of similar episodes, unspecified “breakdowns” or suicide attempts.</p> <p>Family history. A family history of psychiatric disease, suicide, or abuse of any kind (sexual, physical, or substance)</p> <p>Chronic pain syndromes. Gastrointestinal, fibromyalgia, pelvic pain, migraines, etc.</p> <p>Comorbid medical conditions. Diabetes, coronary artery disease, recent stroke, COPD and many chronic medical conditions</p> <p>Special conditions in women. Post-partum, post-induced or spontaneous abortion, or emotional, physical, or sexual abuse</p>

Table 2. Depressive Symptoms and Diagnostic Criteria for Depressive Disorders

Core Depressive Symptoms		
<ul style="list-style-type: none"> • Depressed mood • Anhedonia or markedly diminished interest or pleasure in all, or almost all, activities • Significant unintentional weight loss or gain • Insomnia or hypersomnia • Psychomotor agitation or retardation • Fatigue or loss of energy • Feelings of worthlessness or excessive or inappropriate guilt 	<ul style="list-style-type: none"> • Diminished ability to concentrate, or indecisiveness • Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, a suicide attempt or a specific plan for committing suicide <p>Additional Dysthymic Symptoms (qualifying symptoms for Dysthymic Disorder)</p> <ul style="list-style-type: none"> • Poor appetite without weight change • Low self esteem • Feelings of hopelessness 	
Diagnostic Category by Symptom Grouping		
Diagnostic Category	Number of Symptoms	Duration
Major Depression	> 5 depressive symptoms, one of which is ...	≥ 2 weeks
Minor Depression ¹	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 ² 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

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

² 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 painful 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

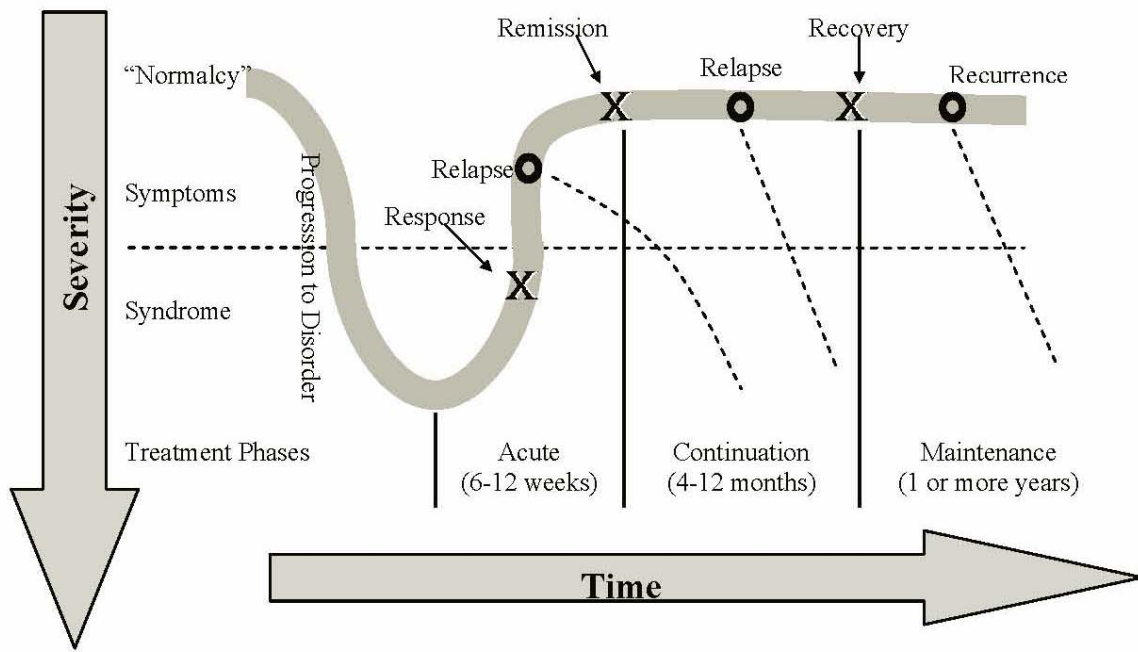
No
 No

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.

* PHQ-9 is described in more detail at the McArthur Institute on Depression & Primary Care website www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/

Figure 2. Phases of Treatment for Major Depression



Source: Kupfer DJ: Long-term treatment of depression. J Clin Psychiatry 1991; 52(Suppl):28-34. Copyright 1991. Physicians Postgraduate Press. Adapted and reprinted with permission.

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.

Risk factors for depression include:

- Being female
- Anxiety disorder
- Major medical conditions, including coronary artery disease, stroke, diabetes, COPD, chronic back pain.
- First degree relative with depression
- Eating disorder
- Drug or alcohol abuse

Responsive. Depression is as responsive to treatment as are other major chronic diseases, but several visits, and medication and dosage adjustments 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 (see above).

Recurrence. Depression is frequently a recurrent condition.

Table 5. Matching Antidepressants to Patients: Selection Dosing & Cost (page 1 of 4) [UMHS Preferred Agents in **Bold**]

Mechanisms of action	Serotonin Selective Reuptake Inhibitors			
Generic name (Brand Name)	citalopram (<i>Celexa</i>)	escitalopram (<i>Lexapro</i>)	fluoxetine (generic available) (<i>Prozac & Sarafem</i>)	fluoxetine weekly (<i>Prozac Weekly</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.	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.	Tends to produce more initial nervousness and arousal than other SSRIs. Very long half-life: 7-15 days.
Sexual dysfunction	Common	Common	Common	Common
Pregnancy^b /Lactation^c	C, L3	C, L3	C, L2 (older) L3(infant)	C, L2 (older) L3(infant)
Selected important drug-drug interactions^{d,e}	Minimal inhibitor of CYP 2D6 isoenzymes. Good choice for medical /surgical patients <i>without</i> renal impairment.	Comparable to citalopram.	Potent inhibitor of CYP 2D6 isoenzymes; increases risk of phenytoin (Dilantin) toxicity.	Potent inhibitor of CYP 2D6 isoenzymes; increases risk of phenytoin (Dilantin) toxicity.
Patient profile most likely to benefit	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.	Noncompliant or “forgetful” patient (i.e., used as a “depot” oral antidepressant); excessive fatigue.	Identical to fluoxetine; also, once weekly may reduce personnel costs in institutional settings.
Patient profile least likely to benefit	Elderly patient with excessive sleep and apathy. Note: 20% excreted by kidney.	Elderly patient with excessive sleep and apathy. Note: 20% excreted by kidney.	Patient on several medications and/or frequent medication changes anticipated.	Identical to fluoxetine.
Available preparations & doses	20, 40 mg scored, coated tablets.	5 (unscored), 10, 20 mg scored tablets.	10,20,40 mg capsules; 10 mg scored tabs; 20 mg/5ml concentrate	90 mg capsule containing enteric-coated pellets
Usual dose, cost/mo.^f ; Max dose, cost/mo^f	20-40 mg/d \$21-\$22 generic \$77-\$80 brand 60 mg/d \$39 generic \$158 brand	15-20mg/d \$70-\$128 40 mg/d \$140	20-40 mg/d \$9-\$59 generic \$133-\$239 brand 80 mg/d \$114 generic \$478 brand	90 mg/week \$95 90 mg 2x wk \$180
Dosing for youthful, reasonable health	20 mg P.O. Oam (or QHS if sedating.) Titrate upward if no response after 6 weeks.	10-20 mg/d P.O. Qam (or QHS if sedating);15-20 mg/d thereafter. Titrate upward if no response in 6 weeks.	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.	20 mg/d fluoxetine x 7d; thereafter, 90 mg/wk. Titrate upward if no response in 6 weeks.
Dosing for frail, elderly, 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.	5 mg/d P.O. Qam (or Qpm if sedating); titrate upward weekly to 15 mg/d initial dose.	5-10 mg P.O. Q every other a.m. For 3-4 days (i.e., two doses) then similarly titrate upward to 20 mg P.O. Qam initial dose.	Identical to fluoxetine; slowly titrate upward to 40-60 mg/d before switching to 90 mg/ weekly.

Adapted 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. **Patients treated with antidepressants should be closely observed for possible worsening of depression and suicidality, especially at the beginning of therapy or when the dose increases or decreases.**

(Footnotes continue)

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

Mechanisms of action	Serotonin Selective Reuptake Inhibitors					
Generic name (Brand Name)	paroxetine (generic available) (Paxil)	paroxetine controlled release (Paxil CR)	sertraline (Zoloft)			
Side effects and other attributes used in patient selection	Tends to cause fewer arousal and insomnia effects common with SSRIs; possesses some anti-cholinergic effects.	Initial nausea rate is 14% vs 23% for immediate release; otherwise side-effect profiles nearly identical.	Tends to initially increase alertness; patients with psychomotor retardation may benefit.			
Sexual dysfunction	Common	Common	Common			
Pregnancy^b /Lactation^c	D, L2	D, L2	C, L2			
Selected important drug-drug interactions^{d,e}	Potent inhibitor of CYP 2D6 isoenzymes.	Potent inhibitor of CYP 2D6 isoenzymes.	Weak inhibitor of CYP 2D6 isoenzymes. Good choice for medical /surgical patients. Contraindicated with pimozide (Orap).			
Patient profile most likely to benefit	Less likely to produce initial anxiety and/or insomnia.	Less likely to produce initial nausea. Nausea rate at 25 mg/d comparable to escitalopram at 20 mg/d.	The medical/surgical patient on one or more medical drugs. 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.	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.	Patient sensitive to any of the typical SSRI side-effects (e.g. increased arousal).			
Available preparations & doses	10,20,30,40 mg tabs; 10mg/5ml concentrate	12.5 and 25 mg enteric-coated tabs.	25, 50, 100 mg scored, coated tabs, 20 mg/ml concentrate			
Usual dose, cost/mo.^f; Max dose, cost/mo^f	20-40 mg/d \$33-\$39 ^g generic \$86-\$94 brand 60 mg/d \$72 ^g generic \$178 brand	25-50 mg/d \$85-\$169 62.5 mg/d \$250	75-150 mg/d \$122 200 mg/d \$163			
Dosing for youthful, reasonable health	20 mg P.O. Qam; increased doses may be given a.m. and noon; if excessive arousal. Give QHS if sedating.	25 mg/d P.O. Qam x 7d; 50 mg/d thereafter; increase to 62.5 mg/d if no response in 6 weeks.	50 mg P.O. Qam x 1 week; 75 mg P.O. Qam thereafter; increased doses may be given a.m & noon, if excessive arousal.			
Dosing for frail, elderly, medically ill	5-10 mg P.O. Qam x 3-4 d, 10-20 mg P.O. Qam x 3-4 d, etc. until desired initial dose.	12.5 mg/d P.O. Qam x 7d; 25 mg/d P.O. Qam, etc., until desired initial dose.	12.5-25 mg P.O. Qam x 3 d; 25-50 mg P.O. Qam x 3 d, etc., until desired initial dose.			

^a 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. Dosage should be decreased 50% in patients with hepatic impairment as a 3-fold increase in plasma levels is possible.

^b 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.

^c Lactation Risk Category:

- L1: Safest
 - L2: Safer
 - L3: Moderately Safe
 - L4: Possibly Hazardous
 - L5: Contraindicated
- From Hale, T. Medications and mothers' milk. Amarillo, TX. Pharmasoft Medical Publishing, 2000

^d Do not combine any of the listed antidepressants with monoamine oxidase inhibitors (MAOIs).

^e The following drug interaction data bases are recommended: drug-interaction.com, hanstenandhorn.com, medicine.iupui.edu/flockhart/

^f 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 4/05 & Blue Cross Blue Shield of Michigan Mac List, 10/7/05.

^g Generic version recently available. Cost expected to drop appreciably below this amount.

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

Mechanisms of Action	Serotonin-2 Antagonist/ Reuptake Inhibitor	Serotonin/Norepinephrine Reuptake Inhibitor	Serotonin/Norepinephrine Reuptake Inhibitor
Generic name <i>(Brand Name)</i>	nefazodone (Serzone)	venlafaxine extended release (<i>Effexor XR</i>)	duloxetine (<i>Cymbalta</i>)
Side effects and other attributes used in patient selection	BLACK-BOX WARNING: Liver damage and/or liver failure in 1/250,000 patients. Corrects sleep disturbances and reduces anxiety in about a week. Side effects somewhat opposite to SSRIs. Fatigue and dizziness common complaints.	Identical to those common to all SSRIs with more nausea. Sustained hypertension risk is 3% at ≥ 300 mg. BP increases are dose-dependent, with a linear dose-response. Constipation is unusual but may cause discontinuation.	Similar to SSRIs and venlafaxine; nausea and constipation most troublesome, but, unlike venlafaxine, does not appear to produce sustained hypertension. NOT TO BE PRESCRIBED ordinarily if concurrent heavy alcohol use and/or evidence of chronic liver disease.
Sexual dysfunction	Unlikely	Less common	Less common
Pregnancy^b /Lactation^c	C, L4	C, L3	C, Lactation – still no data
Selected important drug-drug interactions^{d,e}	Moderate inhibitor of CYP3A3/4 and p-glycoprotein. Causes 15% reduction in oral clearance of digoxin. Contraindicated with cyclosporine, simvastatin (Zocor).and many other statins, pimozide (Orap), and sildenafil (Viagra).	Usually clinically insignificant due to low protein binding and weak inhibition of P450 enzymes.	Major substrate of CYP1A2 & CYP2D6 – inhibitors (quinolones, fluvoxamine/fluoxetine, paroxetine, quinidine) may increase levels. Also, CYP1A2 inducers may decrease effect.
Patient profile most likely to benefit	The depressed, over-anxious patient with marked difficulty sleeping.	Patients with menopausal symptoms or failing an SSRI trial. At higher doses (e.g., 225 mg or higher), patients with chronic pain.	Patient with depression and chronic pain (effects on pain are dose-dependent). Patient failing an SSRI trial.
Patient profile least likely to benefit	Patients who sleep excessively with life-long underachievement and excessive contentment. Patients with severe depression tend to require maximum dose.	Patients with unstable BP and perhaps, those who are GI sensitive. A clinically significant withdrawal syndrome requires slow downtaper.	Patient with preexisting liver disease and/or heavy alcohol use; preexisting or treatment-related anorexia, constipation, and/or other GI symptoms.
Available preparations & doses	100, 150 mg scored; 50, 200, 250 mg unscored tablets.	37.5, 75, 150 mg capsules (immediate release tablets available)	20 mg, 30 mg and 60 mg capsules.
Usual dose, cost/mo.^f; Max dose, cost/mo^f	300-400 mg/d \$31-50 generic 600 mg/d \$60 generic	150-225 mg/d \$104 -\$157 375-450 mg/d \$310 -\$322	40 mg/day \$183 60 mg/day \$102
Dosing for youthful, reasonable health	Use 150 mg tablets: ½ tab at HS x 4 nights; 1 tab x 4 nights; ½ tab in am and 1 tab at HS x 4 nights; ½ tab in am and 1½ tabs HS x 4 nights; ½ tab in am and 2 tabs HS x 4 nights; 1 tab am and 2 tabs HS thereafter.	Every 3-7 day titrate upward, starting at 37.5 mg reduces risk of nausea; initial trial at 225 mg/d. Reduce dose 50% for hepatic impairment; 25% for renal.	Starting dose 20 mg BID, may increase to 30 mg BID (or 60 mg QHS). 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 3-4 days titrate upward, starting at 25-50 mg BID; 150 mg BID initial trial.	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.	Start at 20 mg with breakfast; titrate upward every 3-7 days until 40-60 mg/d in divided doses. mg/day in single or divided doses.

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
Generic name (Brand Name)	mirtazapine (<i>Remeron</i>)	bupropion sustained-release (<i>Wellbutrin SR, Wellbutrin XL, Wellbutrin IR</i>)
Side effects and other attributes used in patient selection	Produces sleep; <i>lower</i> doses produce more sleep than do higher doses. Weight gain may be \geq 10 lbs. Has antiemetic properties (blocks 5HT3 receptor as does ondansetron/Zofran). Risk of neutropenia = 1.5%; risk agranulocytosis = 0.1%.	Least likely to switch patient to mania. Most activating antidepressant available. DO NOT USE if history of seizure, head trauma, substance abuse, bulimia, anorexia or electrolyte disturbance.
Sexual dysfunction	Unlikely	Rare
Pregnancy^b /Lactation^c	C, L3	B, L3
Selected important drug-drug interactions^{d, e}	Usually clinically insignificant due to extensive metabolism via CYP1A2, 2D6, 3A4. Does not appear to interfere with the metabolism of other drugs.	Metabolized primarily by CYP2B6. Drugs inhibiting CYP2B6 are not currently identified. Recent report finds that bupropion may cause clinically significant inhibition of CYP2D6.
Patient profile most likely to benefit	The medically ill patient with weight loss, insomnia and nausea.	The now depressed, actually or potentially, bipolar patient. The apathetic, low energy patient. Patients motivated to stop smoking. Helpful for ADHD ⁱ .
Patient profile least 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	15, 30 mg scored tablets; 45 mg unscored tablet; 15, 30, 45 mg unscored orally disintegrating (<i>not</i> orally dissolving) tablet (<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.^f; Max dose, cost/mo^f	30-45 mg/d 60 mg/d	\$33-35 generic \$92-\$94 brand \$60 generic \$184 brand
		For SR: 300-400 mg/d (max 450 mg/d) For XL: 300-450 mg/d (max dose 450 mg/d) For IR: 200-450 mg/d (max dose 450 mg/d)
		\$90-\$175 generic \$122-\$227 brand \$114-\$201 \$26-\$55 generic \$94-\$211 brand
Dosing for youthful, reasonable health	7.5 (more sleep) to 15 mg (less sleep) night one; 30 mg night two; increase to 45 mg if no improvement in two weeks. Reduce dose by 50% for hepatic impairment; 25% for renal.	For SR: 100-150 mg with breakfast and before 7 pm; increase to <u>minimum</u> dose: 150 mg BID. For XL: 150 mg with breakfast, increase as tolerated to 300-400 mg/d. For IR: 100 mg BID, increase to TID after 3 days, max dose 450 mg/d. DO NOT DOUBLE-UP MISSED DOSES.
Dosing for frail, elderly, medically ill	15 mg at night x 3; 30 mg thereafter; increase to 45 mg if no improvement in two weeks. Reduce dose by 50% for hepatic impairment; 25% for renal.	For SR: Every 3-4 day titrate upward, starting at 100 mg; initial trial at 150 mg BID; last dose before 7 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 450 mg/d. DO NOT DOUBLE-UP MISSED DOSES.

ⁱ “ADHD” means attention deficit hyperactivity disorder.

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 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 the physiological sequelae of a major medical condition such as cancer, stroke, myocardial infarction, major trauma, or neurodegenerative disorders such as Huntington's or Alzheimer's Disorders. Mood disorders may arise from the use of certain medications such as oral contraceptives, antihypertensives, and alcohol. Distinguishing depression that occurs with medical comorbid conditions from depression that occurs secondary to co-morbid conditions is difficult and probably not of clinical significance. The depression 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 vary, 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.

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.

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 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. As many as 30-50% of patients with underlying bipolar disorder will develop acute mania when started on antidepressant pharmacotherapy. Screen for concomitant anxiety disorders which may occur in more than 50% of patients with depression [C].

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.

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. 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 a week 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, 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 noncompliant with medical recommendations. Depression is a more powerful predictor of mortality from myocardial infarction than physiological measures such as cardiac ejection fraction, although it is not yet known whether treatment of the depression changes this risk. Conversely, depression itself may be an independent risk factor for stroke and coronary heart disease [C]. Medications may be implicated in the cause of depression as well. Consider especially when using tretinoids 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

Treatment is influenced by comorbid illnesses and other special situations. Patients with a Major Depressive Disorder frequently suffer from other psychiatric disorders. 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 resistant to the diagnosis of depression due to stigmatization, 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.

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.

Pregnancy. The risks of taking medication 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 weighed. Women considering pregnancy may want to pursue psychotherapy instead of medication. Animal studies of Selective Serotonin Reuptake Inhibitor (SSRIs) have not shown an increased risk of major fetal anomalies. One recent prospective study of women on paroxetine, sertraline, and fluvoxamine during pregnancy also failed to reveal an increased teratogenic risk. However, another study has recently 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. Data on breastfeeding and the newer antidepressants are limited.

Prophylaxis to prevent recurrent post-partum depression should be considered after discussing risks and benefits with the patient. Prophylactically initiate medication in the third trimester (at least 4 to 6 weeks prior to birth).

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

- **No superior agent.** No agent has been proven to be superior to another in efficacy or time to response.
- **Previous success.** Use what has worked for the patient in the past.
- **First choice.** SSRIs and Serotonin Noradrenaline Reuptake Inhibitors (SNRIs) are the agents of first

choice due to ease of use, usually tolerable side effects and safety in overdose.

- **Seizure.** Use SSRIs in patient with a history of seizure disorder. Bupropion lowers the seizure threshold.
- **Pain.** Mirtazapine (Remeron) and venlafaxine (Effexor) are agents which affect both noradrenergic and serotonergic transmission and may have a theoretical role in the treatment of chronic pain, as does a soon-to-be-available mixed receptor agent duloxetine. They are as effective as SSRIs in the treatment of major depression. The most common side effects are similar to those of SSRIs.
- **Cost.** Drugs within a class can vary appreciably in cost. Several medications are now available generically.

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.

Drug trials. Trials of drugs should consider the following:

- **Response rate.** A 50-65% response rate has been demonstrated with an *adequate trial* of first agent, compared with 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 4-6 weeks, consider switching the antidepressant. Many patients will respond when switched to another antidepressant either in the same or in a different class. If patients fail to respond to two antidepressant trials, consider referral to specialty services. Pharmacological augmentation or concurrent psychotherapy may be needed.
- **Referral.** Consider referral after 1-2 failed drug trials.

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 depression. Patients treated with psychotherapy should be monitored, and patients having no response to therapy after 6 weeks or only a partial response after 12 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 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.

There are many different forms of psychotherapy. However, only a few short-term psychotherapies that easily 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 frequently (weekly to biweekly) to assess the patient's response to the intervention, assess/reassure the patient regarding side effects, evaluate suicidal tendencies, and rule out comorbid disorders. 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 for suicidality [C*]. 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 [C*].

Fifty to sixty-five percent of treated patients will show good response to pharmacotherapy within about 4-8 weeks. Medication should then be continued *at the same dosage* for an additional 9-12 months. Discontinuing medication too soon, or decreasing dosage below that required for treatment, is associated with a high 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:** Relieve all depressive symptoms.
2. **Continuation:** For 4-12 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, although recent studies of antiepileptics with serotonergic and dopaminergic properties such as topiramate and zonisamide are encouraging.
- **Sexual dysfunction:** Common with all antidepressants. 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. Patients are commonly considered to have treatment refractory depression if they have been treated with two successive trials of antidepressants with different pharmacologic mechanisms in adequate doses for adequate periods of time (4 to 6 weeks). Approximately 10-15 % of patients with MDD will not respond to two trials of antidepressant medication. Generally, patients meeting the criteria for treatment refractory depression should be referred to a psychiatrist for further evaluation and treatment.

Psychiatrists will usually re-evaluate the diagnoses of these patients, looking for complicating factors that might explain their lack of treatment response -- such as concomitant general medical disorders, 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.

Relatively few primary care physicians will feel comfortable using pharmacologic augmentation regimens or alternative somatic treatment with their patients who do not respond to standard antidepressant regimens. Primary care physicians should be familiar with the following strategies, which are commonly used by experts in depression care.

- Electroconvulsive therapy [A*] – a highly efficacious treatment, which may be the treatment of choice for the frail elderly or acutely suicidal patients
- Monoamine Oxidase Inhibitors (MAOIs) [A*].
- Lithium in addition to an antidepressant [A*] – titrated by blood level, with a goal of 0.6-1.0 m Eq/l
- Thyroid hormone supplementation in addition to an antidepressant in euthyroid patients [A*].
- Valproic acid, other mood stabilizers, or an atypical antipsychotic in addition to an antidepressant [C*].
- Higher than usual doses of antidepressants [C*].
- Multiple antidepressants, particularly those with different neurotransmitter actions [C*].
- Stimulant medication in addition to an antidepressant [C*].

Of note is the fact that many augmentation strategies have limited evidence of efficacy and that studies supporting

their effectiveness often have methodological limitations. Thus, these strategies are generally reserved for patients who have failed to respond to the well-supported treatments. The exceptions to this are ECT, MAOIs and lithium supplementation for which good evidence exists for effectiveness. There is reasonable evidence for thyroid supplementation of antidepressants and less evidence for other augmentation strategies.

Referral. Consider referral for patients:

- who fail 1-2 medication trials
- are suicidal
- with psychotic or bipolar depression
- with comorbid substance abuse
- who have severe psychosocial problems
- who requires specialized treatments such as MAOI, ECT
- who have quickly increasing depressive symptoms
- with unclear diagnosis or patients with suspected personality disorders

Controversial Areas

St. John's Wort (*Hypericum Perforatum*)

St John's Wort (*Hypericum Perforatum*) is claimed to improve depression symptoms particularly in patients with mild-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 (50-70% 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.

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 recent reports and semi-controlled studies suggest that some patients, probably a minority, 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.

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. The literature search conducted in 2002 for this project was conducted prospectively on Medline using the major keywords of: depression, depressive disorders; consensus development conferences, practice guidelines, guidelines, outcomes and process assessment (health care); clinical trials, controlled clinical trials, multicenter studies, randomized controlled trials, cohort studies; adults; English language; and published between 1/1/97-9/30/02. Terms used for specific topic searches within the major key words included: epidemiology; national cost of treatment (economics); screening (for depression, bipolar disorder; alcohol abuse); diagnosis; suicide risk assessment; patient education; exercise; serotonin selective reuptake inhibition (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), serotonin/norepinephrine reuptake inhibition (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), medication adherence, managing sexual side effects of pharmacologic agents, pregnancy and pharmacologic agents, breast feeding and pharmacologic agents, pharmacotherapy not included above; 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, 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 clinical 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

Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. American Journal of Psychiatry 2000; 157(4, suppl). Available at: www.psych.org/psych_pract/treatg/pg/Depression2e.book.cfm

Some Internet Resources

Agency for Healthcare Research and Quality (AHRQ)
www.ahrq.gov/

American Medical Association:
www.ama-assn.org

Depression and Bipolar Support Alliance
www.dbsalliance.org

National Institute of Mental Health
www.nimh.nih.gov

National Mental Health Association
www.nmha.org/ccd

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.

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Annotated References

Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. American Journal of Psychiatry 2000; 157(4, suppl). Available at: www.psych.org/psych_pract/treatg/pg/Depression2e.book.cfm

This practice guideline from the American Psychiatric Association is an authoritative review of evidence-based approaches to diagnosis and treatment of major depressive disorder, last updated in 2000.

Diagnosis and treatment of depression in late life: consensus statement update. *JAMA* 1997;278:1186-1190.

This consensus statement sponsored by the National Institute of Mental Health is an update of an earlier statement, and is an excellent resource for the more specific issue of diagnosing and treating major depressive disorder in elderly patients.

Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry*. 2003;60:720-726.

Table 6. General Principles of Psychotherapy

Psychotherapy Modality	Brief Description	Evidence of Effectiveness
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*]. Evidence for increased efficacy in combination with pharmacotherapy for chronic depression [A*].
Marital Therapy	Focuses on improving the marital relationship of patients with depression.	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	<ul style="list-style-type: none"> • Approximately 15-30% of patients with MDD have an alcohol use disorder • 10-30% of patients with an alcohol use disorder have concurrent depression 	<p>Consider asking the <u>CAGE</u> questions:</p> <p>C Have you ever felt that you should cut down on your drinking?</p> <p>A Have people annoyed you by criticizing your drinking?</p> <p>G Have you ever felt bad or guilty about your drinking?</p> <p>E Eye opener: Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?</p> <p>If the patient answers yes to two or more of these questions, the provider should complete a more thorough assessment.</p>	<ul style="list-style-type: none"> • 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*]. • If unable to achieve sobriety, patients with concurrent depression and alcohol abuse may be treated with an SSRI [A*]. • There are higher suicide rates among depressed patients with alcohol abuse. Be vigilant in assessing suicidal risk [C*].
Depression accompanied by Anxiety	<ul style="list-style-type: none"> • 45% of patients with MDD have significant anxiety symptoms • Approximately 40-60% of patients with anxiety disorders have MDD during their lifetime 	<p>Consider asking :</p> <ul style="list-style-type: none"> • Are you troubled by repeated, unexpected "attacks" where you suddenly feel very afraid for no apparent reason? • 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? 	<ul style="list-style-type: none"> • MDD accompanied by anxiety disorders has a relatively poorer prognosis than MDD alone [A*, C*]. • Patients with MDD and anxiety may need their antidepressants started at lower doses and increased more slowly than individuals with depression alone [C*]. • SRIs are effective in panic disorder. Bupropion is less effective [B*].
Depression accompanied by Obsessive Compulsive Disorder	<ul style="list-style-type: none"> • 10% of patients with MDD have a lifetime history of OCD • 10-30% of patients with OCD will have MDD 	<p>Consider asking:</p> <ul style="list-style-type: none"> • Do you have unwanted ideas, images, or impulses that keep recurring? Must you repeatedly complete specific actions in order to feel comfortable? 	<ul style="list-style-type: none"> • Patients with depression and OCD should be treated with a SSRI [A*] and often require higher doses of SSRIs than patients with depression alone. • Cognitive behavioral therapy is effective in patients with OCD and referral should be considered [A*].
Depression accompanied by Eating Disorders	<ul style="list-style-type: none"> • Perhaps as many as 5-6% of young women with MDD may have an eating disorder • 30-50% of patients with eating disorders have concurrent MDD 	<p>Be alert for eating disorders among depressed women who are dieting when not “over” weight, have frequent weight fluctuations, or are amenorrheic.</p>	<ul style="list-style-type: none"> • MDD in patients with anorexia may be refractory to treatment until normal weight is re-established [C*]. • If using antidepressants, consider use of an SSRI [A*]. If considering psychotherapy, consider formal cognitive behavioral therapy.
Depression accompanied by Dementia	<ul style="list-style-type: none"> • Approximately 20-30% of patients with dementia may have significant depressive symptoms and 10-20% may have MDD 	<p>Be alert for expressions of worthlessness, crying, decreased interest and pleasure in activities</p>	<ul style="list-style-type: none"> • 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.

Table 8. Special Issues for Women

Issues	Epidemiology	Diagnostic Considerations	Treatment considerations
Partner Violence	<ul style="list-style-type: none"> • One quarter of women are victims of partner violence in their lifetimes and 1 in 10 women report violence in the last 12 months. • Women are victims 95% of the time, men 5% of the time. • Victims can be in a heterosexual or homosexual relationship and can come from any socioeconomic, racial or educational class. 	<p>Ask in the history:</p> <ul style="list-style-type: none"> • Have you ever been in a relationship where you have been beaten, punched, choked or hurt in any way? • If yes, but separated, screen for stalking. • If yes, also screen for increased homicide. Risk/dangerousness assessment. • If yes, screen for sexual assault in the relationship (occurs in 1/3 of partner violence relationships). 	<ul style="list-style-type: none"> • Getting out of the relationship is recommended, but homicide rates increase after separation. • Couples therapy is not recommended. • Therapists with expertise with partner violence victims are best. • The “battered women syndrome” (a form of post-traumatic stress disorder [PTSD]) is very common. • Repeated face to face questions give higher prevalence rates.
Sexual Assault	<ul style="list-style-type: none"> • 1/3 of all sexual assault victims are depressed. • 1/3 have attempted suicide. • 1/3 have post-traumatic stress disorder. • 1/8 adult women are sexually assaulted in their lifetime; 60% of these assaults occur before age 18. 	<p>Ask in the history:</p> <ul style="list-style-type: none"> • Have you ever been forced to have sex against your will? • As a child or as an adult, did anyone touch you inappropriately sexually? 	<ul style="list-style-type: none"> • Therapists with expertise with sexual assault survivors and PTSD are best. • Pelvic exams will need to be conducted more carefully or avoided. Refer for gynecological care as well as care for depression.
Pregnancy	<ul style="list-style-type: none"> • Lifetime prevalence of depression in U.S. is 9-20% for women. • Pregnancy does not protect against depression. Instead, the incidence of depression mirrors the general female population. • If abused during pregnancy, 3X greater risk for attempted or completed homicide, as compared to non-pregnant abused women. 	<p>Complicating the diagnosis of depression is the fact that many signs and symptoms of pregnancy are those of depression: trouble sleeping, fatigue, change in appetite, nausea and vomiting, and irritability.</p> <ul style="list-style-type: none"> • Ask about previous lifetime or post-partum depression, family history of depression, and multiple life changes. • Explore potential co-morbid psychiatric diagnosis. • Other risks for depression in pregnancy include: development of a “high risk” pregnancy, detection of a fetal anomaly, and prior pregnancy loss. 	<ul style="list-style-type: none"> • Risks and benefits of therapy should be weighed including the risk to the fetus and benefits to the mother of treatment vs. the significant risks of untreated major depression. Psychotherapy, exercise, light therapy and sleep deprivation pose no risks to the fetus. Older SSRI’s (such as fluoxetine) show no evidence of increased congenital anomalies and no behavioral or long-term cognitive effects. Tricyclic antidepressants show no teratogenicity, but side effects are multiple. MAO inhibitors are not recommended. ECT can be safely used in pregnancy, even in the first trimester.

Postpartum	<ul style="list-style-type: none"> • Mood episodes are similar to those of non-postpartum mood episodes, but onset is within 4 weeks of childbirth, a time of major psychosocial adjustment. • Risk of postpartum depression is about 15%. Women with a history of previous depression may be at 3 times greater risk than women with no prior history. • Term pregnancy / delivery reduces suicide rate by 50% while induced abortion may increase suicide by 2-3 times the general population risk. 	<ul style="list-style-type: none"> • Previous major depressive disorder, alcohol dependency and mania are risk factors for postpartum depression. • Postpartum “blues” are transient and may occur in the first few weeks but usually remit spontaneously. • The period of greatest risk for major depression is during the first 9 weeks after delivery. • Breastfeeding may interrupt sleep and increase depression for some women. 	<ul style="list-style-type: none"> • Assess the amount and frequency of lactation first. • Offer the woman psychotherapy or non-drug alternatives first, then drugs second. Anti-depressant half life may influence newborn exposure but clinical significance is unclear. The baby should also be monitored for side effects. • ECT can be safely used in lactation. • Screen for postpartum violence at regular maternal visits and well-child visits.
Hormonal Contraceptives	<ul style="list-style-type: none"> • Hormonal contraceptives may be associated with depression. • Some women report a lower mood and libido on hormones, especially progesterone. 	<ul style="list-style-type: none"> • Depression may worsen or appear in some women on hormonal contraceptives. 	<ul style="list-style-type: none"> • Consider a trial of progesterone-only oral contraceptive pills before long-acting progesterones (Depo-Provera, Mirena IUD). • For women already on hormonal contraceptives, try discontinuing for one month before initiating antidepressants.
Post and Peri-menopausal Exogenous Hormone Replacement Therapy	<ul style="list-style-type: none"> • Hormones, especially progesterone, may lower mood and libido. • Hot flashes and night sweats may disrupt sleep, worsening or triggering depression. 	<ul style="list-style-type: none"> • Check thyroid studies. • Sleeping difficulties are common in menopause. • Screen for depression separately. 	<ul style="list-style-type: none"> • Hormone replacement therapy may help with sleeping difficulties for some women. • Effexor and clonidine patches modulate autonomic symptoms of menopause for some women.

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		

* PHQ-9 is described in more detail at the McArthur Institute on Depression & Primary Care website
www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/