Clinical Guidelines And Primary Care

Alfred O. Berg, MD, MPH, Series Editor

Guidelines For The Diagnosis And Treatment Of Major Depression

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One of the mandates of the Agency for Health Care Policy and Research (AHCPR) is to develop clinical guidelines for common problems. AHCPR convened a panel of experts, the Depression Guideline Panel, from mental health professions and primary care specialties to conduct an evidence-based review of the diagnosis and treatment of depression. The resulting clinical practice guideline documents released in April 1993[1-4] provide a comprehensive look at what is and is not known about the diagnosis and treatment of major depression in primary care. The report promises to be useful both to practicing physicians and to researchers. A complete set of figures and tables from the *Quick Reference Guide for Clinicians*[1] is reproduced in the Appendix. The entire set of guideline documents is available from AHCPR.*

Need for Depression Guidelines

One in 8 individuals might require treatment for depression in his or her lifetime.[3] The direct and indirect costs of the disorder are high. Evidence suggests only one-third to one-half of those with major depressive disorder have their conditions detected by primary care and other physicians. Evidence also suggests that, once detected, depression is frequently undertreated. Guidelines were developed to assist primary care physicians in the diagnosis and treatment of this disorder.

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Depression Guideline Panel

The Depression Guideline Panel was convened by the Agency for Health Care Policy and Research and was chaired by an academic psychiatrist. The other members of the panel included 1 academic psychiatrist who is a research methodologist, 5 other professors of psychiatry, 1 professor of social work, 1 professor of psychology, 1 professor of general internal medicine and 1 of internal medicine and psychiatry, 2 practicing family physicians, and 1 consumer representative. Biographical sketches of the panel members are available in the guideline documents. Primary care, though represented, was in the minority. An academic family physician who could combine the perspective of family practice with research expertise would have been an excellent addition to this panel.

Guideline Development

The panel first defined the issues and narrowed the scope of the study. Scientific reviews of the available literature were commissioned from the National Library of Medicine. Using the method described by Eddy,[5] abstracts were used to establish whether the study met the standards set by the panel, i.e., whether the study was a randomized controlled trial and whether the definitions of disease and outcome were sufficiently standardized to be comparable with other studies. Acceptable articles were reviewed and evidence tables generated. When possible, studies were combined using meta-analysis to improve their usefulness in generalizing to a wider population. The panel also commissioned a new analysis of a large population-based study to answer questions not addressed in the current literature. Once the guidelines were developed, the documents were sent to more than 100 peer, scientific, organizational, and consumer reviewers. In addition, an independent group representing primary care

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providers — the intended users — was asked to review the documents. The members of this group are not named or further described. Final documents were revised based on information provided during the review process.

The panel's methods are well described within the documents. Of particular merit is the panel's use of intent-to-treat as the denominator in the meta-analysis. Many studies are reported as success rates for those who completed treatment or who were exposed to an adequate trial of treatment. This approach always makes success rates look better, but it is neither scientifically correct nor clinically useful. The rationale for intent-to-treat analysis is well presented. All guidelines are designated by a grade reflecting the quality of the scientific evidence supporting the recommendation: A — good research-based support, B — fair research-based support, and C — expert opinion or clinical experience.

Guideline Presentation

Four guideline documents are now available and are reviewed here. The first is a patient education pamphlet, *Depression Is a Treatable Illness: A Patient's Guide*.[2] The second is a summary document for practitioners, *Quick Reference Guide for Clinicians*.[1] This reference guide summarizes the recommendations contained in two longer documents — *Detection and Diagnosis*[3] and *Treatment of Major Depression*.[4] These latter two documents in turn summarize the relevant sections of the 1500-page *Guideline Report*[6] (not reviewed). The evidence tables on which the guidelines are based are available in the final report.

Patient Guide

The patient guide is well written and organized. Inside the front cover is detailed information on finding help for depression. The first suggestion is "Call your family physician or other health care provider." The first section is simply written and focuses specifically on who gets depressed, how to know whether you are depressed, and how to get help. It comes with the positive message that help is available for this treatable disease. The second section begins with a symptom checklist for depression and for mania. The checklists are followed by more detailed information about depression. Three patient aids are contained in this document: (1) a health questionnaire relevant to depression, (2) a form for patients to record answers to their questions about medication, and (3) a weekly activity log to record medication compliance and treatment response. The explanatory models and knowledge provided to patients in this guide are parallel to those presented to practitioners in the rest of the documents. As a result, patients will not feel the frustration of conflicting information, and the physician's teaching will be reinforced. The absence of proprietary support for any one treatment adds usefulness to the guide.

Clinicians' Quick Reference Guide

The reference guide for clinicians might be useful as a reminder or as an easily located source for the many diagrams and tables it contains (Appendix), but it does not stand alone, nor is it intended to do so.

Perhaps one reason so many clinical guidelines are frustrating to the primary care physician is that they contain only the conclusions with insufficient rationale to be believable. In this case, the careful reader is rewarded with the two longer documents that support the reference guide and present what is known and at what level of certainty. Both longer volumes are complemented by an excellent index and table of contents, a glossary of terms, and extensive references. Both documents are excellent references for the specific questions that arise in practice.

Detection and Diagnosis

Volume 1 focuses on diagnosis and detection. It gives a complete but concise overview of the mood disorders and other conditions associated with mood symptoms. Depression is discussed in relation to other psychiatric disorders and as it occurs with other medical disorders. Diabetes, heart disease, chronic fatigue syndrome, and fibromyalgia are discussed individually. Medications that can cause depression are described. The final section is devoted to the detection of depression.

Treatment of Major Depression

Volume 2 focuses on treatment of major depression. The first section describes the aims of treatment, promoting a model proposed by Kupfer[7] that divides treatment into acute, continuation, and maintenance phases. The guidelines specifically address choice of treatment, treatment adherence, and measuring outcome. Separate sections

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address acute phase treatment with medication, psychotherapy, and the combination of the two. Excellent tables detail medication side effects, pitfalls, dosage, and therapeutic range. Finally, continuation and maintenance treatment options are discussed. Flow diagrams that summarize recommendations are presented throughout. A synopsis of panel recommendations is found in the Appendix.

Guideline Limitations

The Depression Guideline Panel presents concerns about these guidelines, which I share. Most importantly, "The panel found a very small number of studies of high scientific quality conducted specifically in primary care settings." Most of the randomized controlled trials were done in academic centers on psychiatric patients in or out of the hospital, undoubtedly a more psychiatrically ill population with more severe disease and more combined disorders than seen in primary care. For example, the guidelines state that 15 percent of major depressions have psychotic features, a figure that seems quite high for primary care practice. For research purposes, most studies exclude medically ill patients; but medically ill patients are at much higher risk for depression than is the general population.

Panel members chose to focus their evaluation of treatment on major depression that meets criteria described in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised *(DSM III-R)*[8] and to exclude children, adolescents, bipolar illness, and depression not otherwise specified. Physicians who work in primary care will find themselves again wondering about the utility of *DSM III-R* diagnoses in their practices. For example, in primary care practice depression not otherwise specified or depression that does not meet criteria for major depression is the more common presenting complaint. Whether the treatment guidelines apply to this diagnosis is unknown.

The panel reports a study justifying concern about generalizing findings from other settings to primary care. Blackburn, et al.[9] reported that cognitive psychotherapy alone was more efficacious than medication or medication combined with psychotherapy in a primary care setting. The reverse was true in the hospital; combined therapy was most effective. If these results are replicated in other studies, further investigation of the differences will be needed. Perhaps there are differences in severity of disease and its chronicity (treatment early in the disease is known to be more effective), or depression might be a heterogeneous illness with some patients actually having different disorders.

As the panel frequently points out, the absence of scientific study of a treatment does not mean it is ineffective, just that it is not known to be effective. Many of the studies available for analysis were sponsored by pharmaceutical firms to achieve approval by the Food and Drug Administration. Thus much more is known about treatment with medication than with other modalities. The studies of various psychotherapies were done by proponents of whichever types they studied. The panel also points out that standardizing psychotherapies is extremely difficult, and there are few comparisons between types of psychotherapy. Because the response rates to all the types of psychotherapy studied are quite similar, I wonder whether it is regular contact with a caring individual that produces the beneficial effect.

Reliance on the randomized controlled trial as the reference standard means that certain modalities, such as the effect of longer term therapy in the prevention of depression relapse, will likely never be adequately studied. The panel policy recommends that physicians "choose tested over untested therapies." Because medication has been heavily studied and is known to be efficacious, it is recommended. The case is persuasive, but I wonder what the results would be if other modalities had been better studied. No doubt these guidelines will stir controversy among the proponents of various treatment modalities. Primary care physicians, however, should focus their attention on ensuring that patients get some form of affordable and effective treatment for this disabling disease.

Finally, two omissions deserve comment. First, information on costs of treatment is notably absent, which could have resulted from concern about the potential for inappropriate use of this information by insurance companies and other policy makers. For the primary care physician, however, cost is a critical issue both in choosing between medication and psychotherapy and among different medications. Second, cross-cultural issues, both in diagnosis and treatment, are omitted. In some patient populations these issues are critical to the success of treatment.

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Guidelines in Clinical Practice

Family physicians will likely find these guidelines quite useful. The scoring of the scientific evidence to support a guideline is helpful: as new knowledge is reported, the physician can weigh its validity and incorporate changes. Many of the recommended clinical policies provide a clear framework in which to practice. Even in the sections that are based on expert opinion, the guidelines are practical and clinically useful. One detects the input of practicing physicians in their development. The guidelines' descriptive flow diagrams and excellent medication tables are reproduced here as an Appendix.

AHCPR Guidelines versus the APA Depression Guideline

Coincidentally, in April 1993 an expert panel sponsored by the American Psychiatric Association (APA) published *Practice Guideline for Major Depressive Disorder in Adults*.[10] This guideline focuses on treatment of major depression in adults and rather than on detection and diagnosis. The guideline is directed at psychiatrists and therefore emphasizes topics less relevant to primary care, such as treatment-resistant depression, electroconvulsive therapy, and monoamine oxidase inhibitors (MAOIs). For the same reason, however, its tone is collegial and not as condescending as are many expert guidelines intended for primary care physicians. The underlying recommendations for treatment of major depression are largely the same as the AHCPR guidelines. The APA guideline presents a clear, concise description of the major psychotherapeutic options and suggestions for selecting appropriately between them. The authors divide the antidepressant medications into three categories: cyclic, serotonin reuptake inhibitors, and MAOIs. This system is straightforward and useful. The APA recommendations are also coded, using three levels. Unlike the AHCPR guidelines, however, the APA codes are not based on the strength of supporting evidence but rather on the clinical confidence of the expert panel. This system does not help the user decide how to incorporate new information as it arises. As with any expert panel that represents one professional group, in this case psychiatrists, bias is undoubtedly introduced by the accepted practices of that professional group. For example, the APA guideline supports long-term psychotherapy as a treatment for major depression. The evidence-based AHCPR guidelines, on the other hand, conclude the efficacy of this practice is not well supported in the literature. Unfortunately, costs are not addressed in the APA guideline, nor is patient education. The AHCPR guidelines address primary care and the less differentiated cases more effectively and are easier references for specific questions. The APA guideline is 20 pages long, easily readable, and is like having a good psychiatric consultant. Nevertheless, for primary care physicians, the more comprehensive evidence-based guidelines from AHCPR will be more useful.

Further Research

Many important questions remain to be answered in primary care practices. Depression not otherwise specified needs much more extensive study. Many of these guidelines need to be tested in primary care practice for their actual utility. There is evidence that lower doses of medications for depression are frequently used in primary care practice; because these lower doses result in fewer side effects and lower cost, it would be useful to know whether they are effective. The findings of the Depression Guideline Panel should lead to redirection of research efforts toward primary care.

Conclusion

The process of developing these guidelines was costly and time intensive but has resulted in a set of guidelines that provides a framework for rational diagnosis and treatment of patients suffering from major depression. The Depression Guideline Panel is honest about the limitations of knowledge and the assumptions used to generalize studies in psychiatric settings to primary care practice. They are clear about the methodology used; backup documentation, including evidence tables, is available in the complete report. The patient guide is particularly innovative. As in any well-done guideline, many gaps in knowledge are revealed. It is hoped that elucidating these gaps will lead to research that will help to close them. Careful attention should be paid to the response of primary care physicians to these guidelines to ensure they are useful in practice. If the guidelines do prove to be useful, this careful process should be replicated in other areas and more guidelines such as these developed.

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Appendix

Synopsis of the Guidelines' General Recommendations

The established diagnostic criteria for major depressive disorder are presented in Table 1. Physicians are reminded of the importance of questioning patients about suicide thoughts and of assessing suicide risk (Table 2). It is often reassuring to patients to learn that such thoughts are not uncommon. The panel confirms that the diagnosis of depression is made by clinical history and interview. Often a family member or close friend can give a more accurate report than the patient. The panel stresses the importance of asking about previous manic episodes to avoid precipitating a manic episode with antidepressant medication.

Figure 1 outlines the diagnostic decisions needed to differentiate primary mood disorders. Ten to 15 percent of major depressive conditions are caused by general medical illnesses or other conditions (Figure 2). In general, the associated

Table 1. *DSM-III-R* Criteria for Major Depressive Disorder.*

At least five of the following symptoms are present during the same period. At least (1) depressed mood or (2) loss of interest or pleasure must be present. Symptoms are present most of the day, nearly daily for at least 2 weeks.

1. Depressed mood (sometimes irritability in children and adolescents) most of the day, nearly every day
2. Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day (as indicated either by subjective account or observation by others of apathy most of the time)
3. Significant weight loss or gain
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue (loss of energy)
7. Feelings of worthlessness (guilt)
8. Impaired concentration (indecisiveness)
9. Recurrent thoughts of death or suicide

**DSM-III-R. Diagnostic and Statistical Manual of Mental Disorders*, ed. 3, revised. Used with permission from the American Psychiatric Association.

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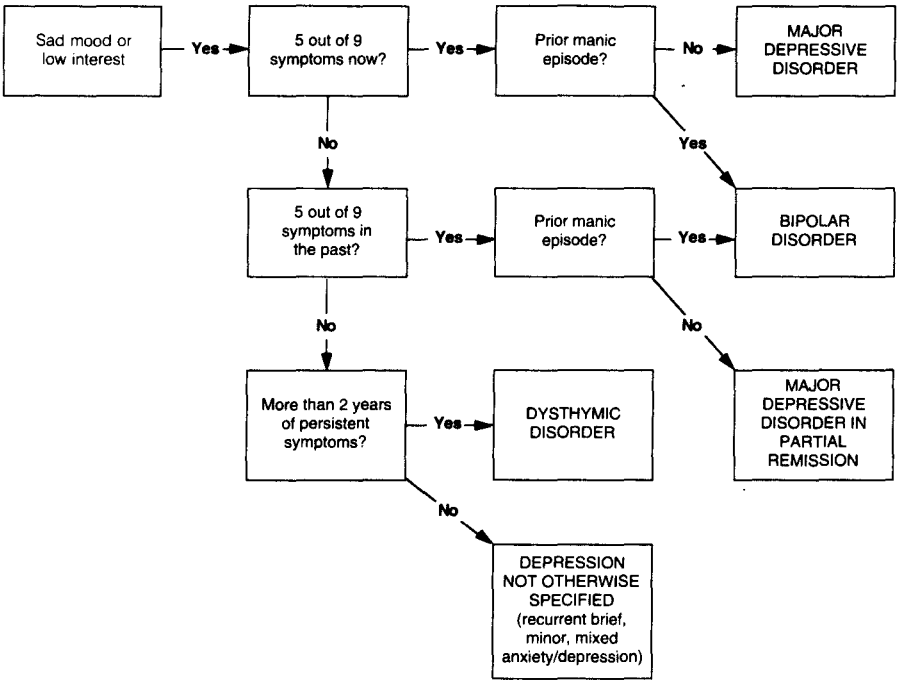

Source: Depression Guideline Panel. *Depression in Primary Care: Volume 1. Detection and Diagnosis. Clinical Practice Guideline, Number 5.* Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication no. 93-0550. April 1993:20.

Figure 1. Differential diagnosis of primary mood disorders.

conditions should be treated first. Depression is also frequently associated with other current psychiatric disorders (Figure 3). When the coexisting condition is anxiety, panic, or a personality disorder, treat the depression first. When there is substance abuse, eating disorder, or obsessive-compulsive disorder, this problem should be treated first, as the depressive symptoms might resolve without specific treatment. In the case of medical disorders, any disease or treatment medication that causes depression should be addressed first. In all other cases depression should be treated as a coexisting illness and treated concurrently (Figure 4).

The treatment of depression is divided into three phases, as illustrated in Figure 5. Figure 6 presents a flow diagram for the treatment of depression. The choice of treatment modality is based on history and severity of the illness. Mild-to-moderate depression can be treated effectively with psychotherapy alone, medication alone, or a combination of both. More severe or recurrent depression is more likely to require medication or medication plus psychotherapy. When medication is chosen, the panel recommends that the primary care physician become familiar with one drug with minimal side effects from each of the major classes of antidepressants (Tables 3 and 4). Many patients will respond to an adequate trial with the first medication chosen (Figure 7). Figure 8 is a flow diagram for managing partial or nonresponders. The panel stresses full remission, not improvement, as the objective of treatment. Long-term maintenance medication should be considered in patients with three previous epi-

Table 2. Suicide Risk Factors.

Category	Risk Factor
Psychosocial and clinical	Hopelessness
	White race
	Male sex
	Advanced age
	Living alone
History	Previous suicide attempts
	Family history of suicide attempts
	Family history of substance abuse
Diagnostic	General medical illnesses
	Psychosis
	Substance abuse

Source: Depression Guideline Panel. *Depression in Primary Care: Detection, Diagnosis, and Treatment. Quick Reference Guide for Clinicians, Number 5.* Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication no. 93-0552. April 1993:3.

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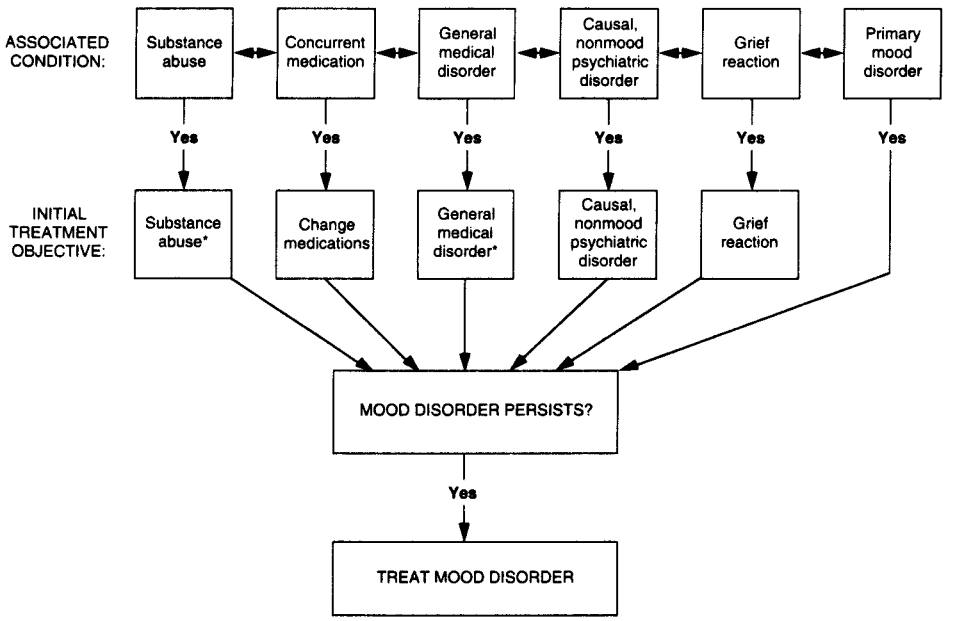
sodes of major depression or with two episodes if the patient has a family history of depression, early age of onset, or early recurrence. The panel recommends that consultation with a mental health professional can be useful when the patient is actively suicidal or psychotic or not responding to one or two medication trials. This synopsis provides a brief sketch of the contents of the guidelines and is not a substitute for obtaining and using the full set of guidelines.



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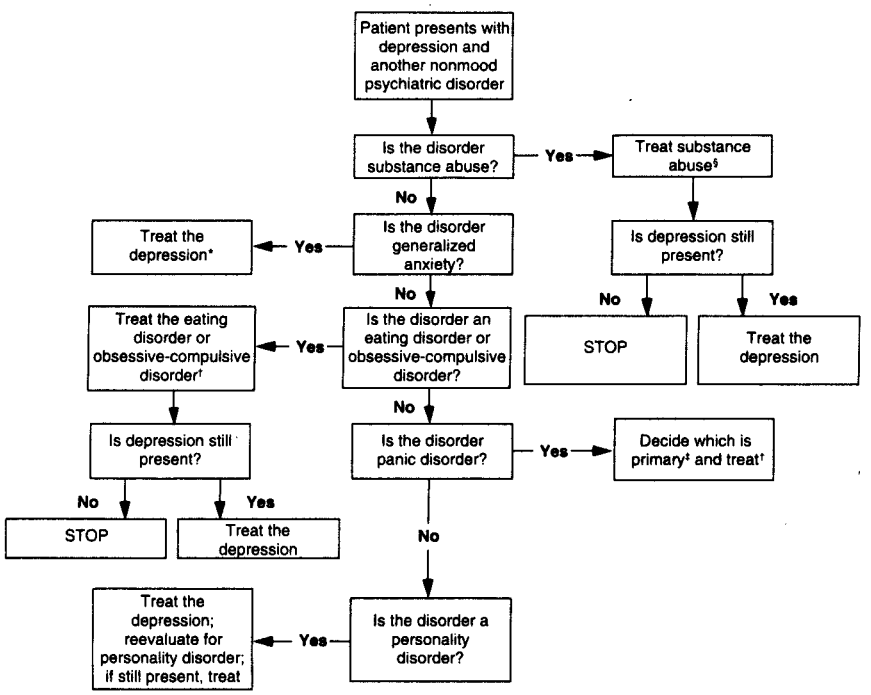
*Depending on the clinical situation and the patient's history, both the mood disorder and the associated condition can be primary treatment objectives.

Figure 2. Conditions associated with mood symptoms or major depressive episodes.



Source: Depression Guideline Panel. *Depression in Primary Care: Volume 1. Detection and Diagnosis. Clinical Practice Guideline, Number 5.* Rockville, MD. US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication no. 93-0550. April 1993:44.

*When the depression is treated, the anxiety disorder should resolve as well.
†Choose medications known to be effective for both the depression and the other psychiatric disorder.
‡In certain cases (based on history), both major depression and substance abuse might require simultaneous treatment.
§Primary is the most severe, the longest standing by history, or the one that runs in the patient's family.

Figure 3. Relation between major depressive and other current psychiatric disorders.

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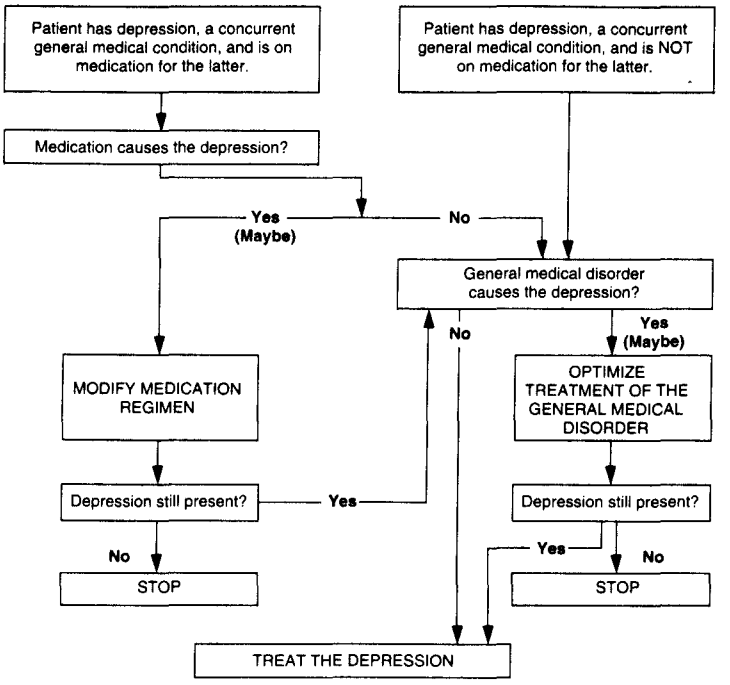

Note: in some clinical situations, treatment of the depression (e.g., if severe, incapacitating, or life-threatening) cannot be delayed until treatment for the general medical disorder has been optimized.

Source: Depression Guideline Panel. *Depression in Primary Care: Volume 1. Detection and Diagnosis. Clinical Practice Guideline, Number 5.* Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research.

Figure 4. Relation between major depressive and other current general medical disorders.

Table 3. Side-Effect Profiles of Antidepressant Medications.

Drug	Side Effect*						
		Central Nervous System		Cardiovascular			Other
	Anticholinergic†	Drowsiness	Insomnia/ Agitation	Orthostatic Hypotension	Cardiac Arrhythmia	Gastrointestinal Distress	Weight Gain (> 6 kg)
Amitriptyline	4+	4+	0	4+	3+	0	4+
Desipramine	1+	1+	1+	2+	2+	0	1+
Doxepin	3+	4+	0	2+	2+	0	3+
Imipramine	3+	3+	1+	4+	3+	1+	3+
Nortriptyline	1+	1+	0	2+	2+	0	1+
Protriptyline	2+	1+	1+	2+	2+	0	0
Trimipramine	1+	4+	0	2+	2+	0	3+
Amoxapine	2+	2+	2+	2+	3+	0	1+
Maprotiline	2+	4+	0	0	1+	0	2+
Trazodone	0	4+	0	1+	1+	1+	1+
Bupropion	0	0	2+	0	1+	1+	0
Fluoxetine	0	0	2+	0	0	3+	0
Paroxetine	0	0	2+	0	0	3+	0
Sertraline	0	0	2+	0	0	3+	0
Monoamine oxidase inhibitors (MAOIs)	1	1+	2+	2+	0	1+	2+

*0 = absent or rare 1+ 2+ = in between 3+ 4+ = relatively common.
†Dry mouth, blurred vision, urinary hesitancy, constipation.

Source: Depression Guideline Panel. *Depression in Primary Care: Detection, Diagnosis, and Treatment. Quick Reference Guide for Clinicians, Number 5.* Rockville, MD. US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication no. 93-0552. April 1993:14.

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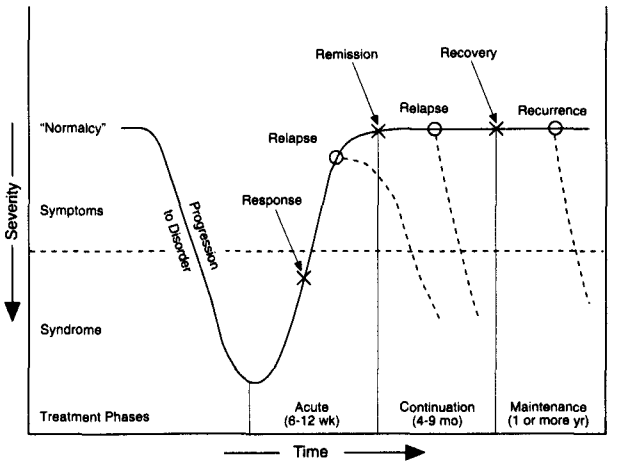

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Figure 5. Phases of treatment for major Depression.

Table 4. Pharmacology of Antidepressant Medications.

Drug	Therapeutic Dosage Range (mg/d)	Average of Elimination Half-lives* h (Range)	Potentially Fatal Drug Interactions
Tricyclics			
Amitriptyline (Elavil, Endep)	75–300	24 (16–46)	Antiarrhythmics, MAOIs
Clomipramine (Anafranil)	75–300	24 (20–40)	Antiarrhythmics, MAOIs
Desipramine (Norpramin, Pertofrane)	75–300	18 (12–50)	Antiarrhythmics, MAOIs
Doxepin (Adapin, Sinequan)	75–300	17 (10–47)	Antiarrhythmics, MAOIs
Imipramine (Janimine, Tofranil)	75–300	22 (12–34)	Antiarrhythmics, MAOIs
Nortriptyline (Aventyl, Pamelor)	40–200	26 (18–88)	Antiarrhythmics, MAOIs
Protriptyline (Vivactil)	20–60	76 (54–124)	Antiarrhythmics, MAOIs
Trimipramine (Surmontil)	75–300	12 (8–30)	Antiarrhythmics, MAOIs
Heterocyclics			
Amoxapine (Asendin)	100–600	10 (8–14)	MAOIs
Bupropion (Wellbutrin)	225–450	14 (8–24)	MAOIs (possibly)
Maprotiline (Ludiomil)	100–225	43 (27–58)	MAOIs
Trazodone (Desyrel)	150–600	8 (4–14)	—
Selective serotonin reuptake inhibitors (SSRIs)			
Fluoxetine (Prozac)	10–40	168 (72–360)†	MAOIs
Paroxetine (Paxil)	20–50	24 (3–65)	MAOIs‡
Sertraline (Zoloft)	50–150	24 (10–30)	MAOIs‡
Monoamine oxidase inhibitors (MAOIs)§			For all 3 MAOIs: Vasoconstrictors,‖ decongestants,‖ meperidine, and possibly other narcotics
Isocarboxazid (Marplan)	30–50	Unknown	
Phenelzine (Nardil)	45–90	2 (1.5–4.0)	
Tranylcypromine (Parnate)	20–60	2 (1.5–3.0)	

*Half-lives are affected by age, sex, race, concurrent medications, and length of drug exposure.
†Includes both fluoxetine and norfluoxetine.
‡By extrapolation from fluoxetine data.
§MAO inhibition lasts longer (7 days) than drug half-life.
‖Including pseudoephedrine, phenylephrine, phenylpropanolamine, epinephrine, norepinephrine, and other.

Source: Depression Guideline Panel. *Depression in Primary Care: Detection, Diagnosis, and Treatment. Quick Reference Guide for Clinicians, Number 5.* Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication no. 93-0552. April 1993:15.

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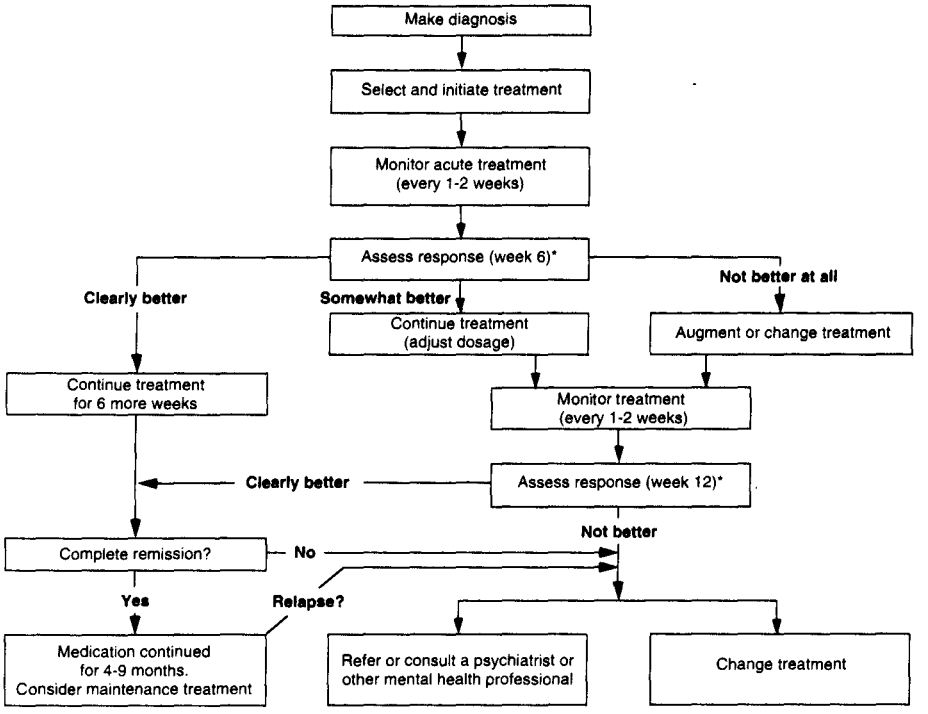
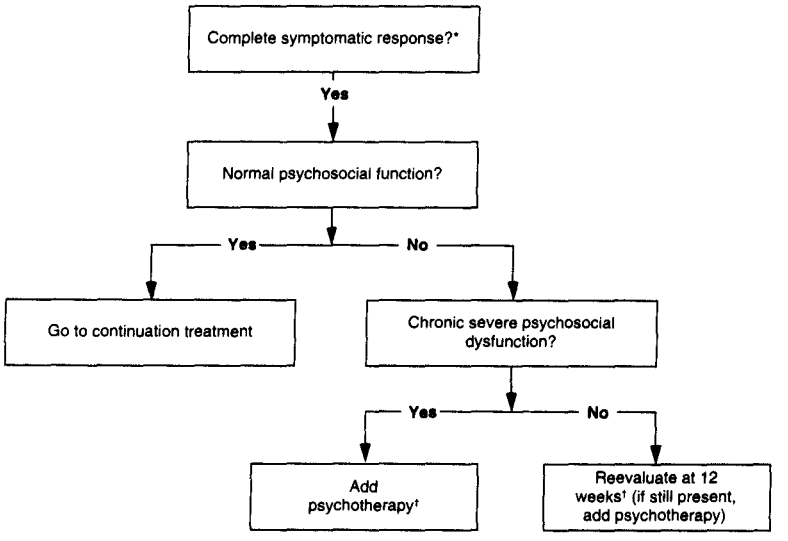


Source: Depression Guideline Panel. *Depression in Primary Care: Volume 2. Treatment of Major Depression. Clinical Practice Guideline, Number 5.* Rockville, MD. US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication no. 93-0550. April 1993:29.

Figure 6. Overview of treatment for depression.

*Times of assessment (weeks 6 and 12) rest on very modest data. It might be necessary to revise the treatment plan earlier for patients who fail to respond.



Source: Depression Guideline Panel. *Depression in Primary Care: Volume 2. Treatment of Major Depression. Clinical Practice Guideline, Number 5.* Rockville, MD. US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication no. 93-0550. April 1993:66.

Figure 7. Six-Week Evaluation: Responders to Medication.*

*Complete response with no or very few symptoms.

†These suggestions are based on indirectly relevant data, logical inference, and clinical experience.

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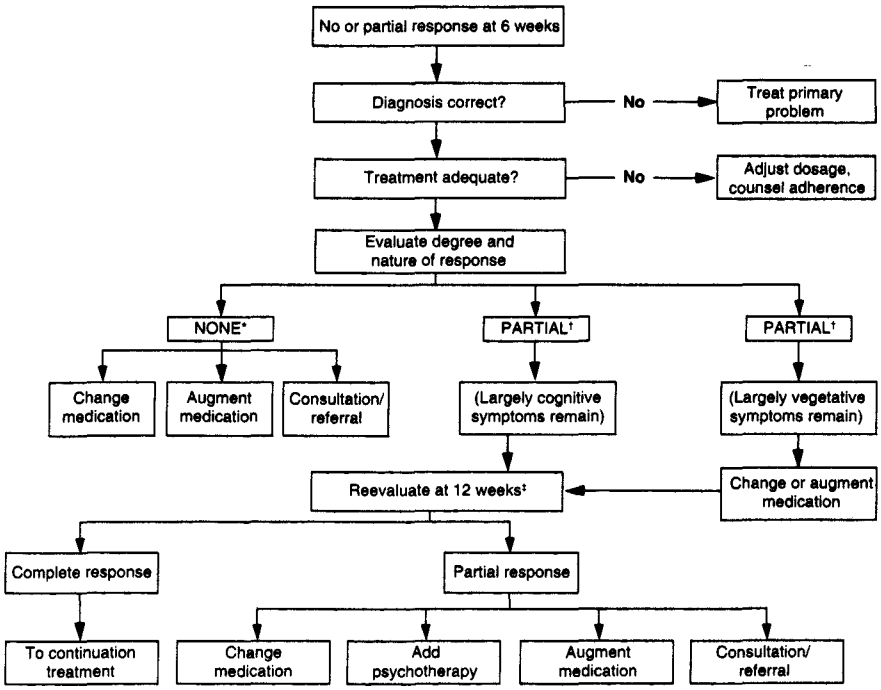

Source: Depression in Guideline Panel. *Depression in Primary Care: Volume 2. Treatment of Major Depression. Clinical Practice Guideline, Number 5.* Rockville, MD. US Department of Health and Human Service, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication no. 93-0550. April 1993:67.

Figure 8. Six-week evaluation: partial responders or nonresponders to medication.

*No response — patient is nearly as symptomatic as at pretreatment.

†Partial response — patient is clearly better than at pretreatment, but still has significant symptoms. Consultation or referral may be valuable before proceeding further.

‡Suggestions for management are based on some indirectly relevant studies, logic, and clinical experience.

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