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The Agency for Health Care Policy and Research (AHCPR) was established in December 1989 under Public Law 101-239 (Omnibus Budget Reconciliation Act of 1989) to enhance the quality, appropriateness, and effectiveness of health care services and access to these services. AHCPR carries out its mission by conducting and supporting general health services research, including medical effectiveness research, facilitating development of clinical practice guidelines, and disseminating research findings and guidelines to health care providers, policymakers, and the public.

The legislation also established within AHCPR the Office of the Forum for Quality and Effectiveness in Health Care (the Forum). The Forum has primary responsibility for facilitating the development, periodic review, and updating of clinical practice guidelines. The guidelines will assist practitioners in the prevention, diagnosis, treatment, and management of clinical conditions.

Other AHCPR components include the following. The Center for Medical Effectiveness Research has principal responsibility for patient outcomes research and studies of variations in clinical practice. The Center for General Health Services Extramural Research supports research on primary care, the cost and financing of health care, and access to care for underserved and rural populations. The Center for General Health Services Intramural Research uses large data sets for policy research on national health care expenditures and utilization, hospital studies, and long-term care. The Center for Research Dissemination and Liaison produces and disseminates findings from AHCPR-supported research, including guidelines, and conducts research on dissemination methods. The Office of Health Technology Assessment responds to requests from Federal health programs for assessment of health care technologies. The Office of Science and Data Development develops specialized data bases for patient outcomes research.

Guidelines are available in formats suitable for health care practitioners, the scientific community, educators, and consumers. AHCPR invites comments and suggestions from users for consideration in development and updating of future guidelines. Please send written comments to Director, Office of the Forum for Quality and Effectiveness in Health Care, AHCPR, Executive Office Center, Suite 401, 2101 East Jefferson Street, Rockville, MD 20852.

Guideline Development and Use

Guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical conditions. This guideline was developed by an independent, multidisciplinary panel of private sector clinicians and other experts convened by the Agency for Health Care Policy and Research (AHCPR). The panel employed an explicit, science-based methodology and expert clinical judgment to develop specific statements on patient assessment and management for the clinical condition selected.

Extensive literature searches were conducted and critical reviews and syntheses were used to evaluate empirical evidence and significant outcomes. Peer review and field review were undertaken to evaluate the validity, reliability, and utility of the guideline in clinical practice. The panel's recommendations are primarily based on the published scientific literature. When the scientific literature was incomplete or inconsistent in a particular area, the recommendations reflect the professional judgment of panel members and consultants.

The guideline reflects the state of knowledge, current at the time of publication, on effective and appropriate care. Given the inevitable changes in the state of scientific information and technology, periodic review, updating, and revision will be done.

We believe that the AHCPR-assisted clinical guideline development process will make positive contributions to the quality of care in the United States. We encourage practitioners and patients to use the information provided in this Clinical Practice Guideline. The recommendations may not be appropriate for use in all circumstances. Decisions to adopt any particular recommendation must be made by the practitioner in light of available resources and circumstances presented by individual patients.

J. Jarrett Clinton, MD
Administrator
Agency for Health Care Policy and Research

Foreword

This Clinical Practice Guideline (Depression in Primary Care: Volume 1. Detection and Diagnosis; and Volume 2. Treatment of Major Depression) was developed with support from the Agency for Health Care Policy and Research (AHCPR) by the Depression Guideline Panel to assist primary care providers (e.g., general practitioners, family practitioners, internists, nurse practitioners, registered nurses, mental health nurse specialists, physician assistants, and others) in the diagnosis of depressive conditions and the treatment of major depressive disorder. The panel hopes that the general principles embodied in these guidelines will also provide a framework for other medical and nonmedical practitioners who assume responsibilities for the recognition and care of depressed persons.

Depression was selected as a topic for guideline development because:

- Depressive disorders are commonly encountered in primary care, as well as in other treatment settings.
- Most depressed patients seek care from primary care practitioners.
- A range of effective treatments are available and commonly provided for these conditions.
- There is a large body of scientific evidence on which to base these guidelines.
- Practice surveys indicate that improvements are needed in primary care practitioners' ability to recognize and treat depressive disorders.
- Depressive disorders result in significant morbidity and mortality.
- Depressive disorders have a high prevalence in the general population.

These guidelines are not aimed at rendering selected procedures reimbursable or not reimbursable; that decision logically falls to third-party payors. Nor do they specify which professionals should conduct which procedures, an issue addressed by licensing/privileging bodies. Should the recommended steps in the diagnosis or treatment of depression fall outside the expertise of the practitioner, he or she should seek a consultation with, or a referral to, someone knowledgeable in these matters.

The Depression Guideline Panel is composed of experts from diverse disciplines, as well as a consumer representative. The guidelines are based on systematic literature reviews commissioned by the panel and conducted by experts in numerous areas relevant to depression, with special attention to the clinical issues most pertinent to the diagnosis and treatment of depression in primary care. Guideline development also included input from a broad range of professional and consumer organizations and individuals. The guidelines have undergone peer review and field review with intended users in clinical sites to evaluate the document both conceptually and operationally. For practitioners, patients, and their families, we hope these guidelines provide a richer understanding of depression. For researchers, we hope we have identified key areas of uncertainty for further investigation.

Research develops knowledge. The synthesis and specification of current knowledge do not mitigate (in fact increase) the need for careful translation and application of this knowledge. Practitioners translate and apply that knowledge. However, in many cases they have to act without sufficient scientifically based data.

The panel's inferences as to what is optimal patient care are not expected to apply to all patients or situations. Knowledge developed through research can only provide a starting point for approaching a particular patient. Algorithms are not applicable in every case, and often provide only coarse road maps for managing patients. Adaptation of guidelines to particular patients requires practitioners to have skill, training, knowledge, and experience, and patients and families to have patience, understanding, trust, and knowledge.

This is the first edition of the Clinical Practice Guideline. We plan to revise the guidelines based on new knowledge, empirical evaluation of their impact on patient outcome, and critiques from users. The panel

welcomes comments and suggestions for use in the next edition. Please send written comments to Director, Office of the Forum for Quality and Effectiveness in Health Care, AHCPR, Executive Office Center, Suite 401, 2101 East Jefferson Street, Rockville, MD 20852.

Abstract

Despite the high prevalence of depressive symptoms and full major depressive episodes in patients of all ages, depression is underdiagnosed and undertreated by primary care and other nonpsychiatric practitioners, who are, paradoxically, the providers most likely to see these patients initially. Primary mood disorders include both depressive (unipolar) and manic-depressive (bipolar) conditions. Major depressive disorder (sometimes called unipolar depression) is characterized by one or more episodes of mild, moderate, or severe clinical depression without episodes of mania or hypomania (i.e., low-level mania).

Depression may co-occur with nonpsychiatric medical disorders or with other psychiatric disorders; it may also be brought on by the use of certain medications. Major risk factors for depression include a personal or family history of depressive disorder, prior suicide attempts, female gender, lack of social supports, stressful life events, and current substance abuse. The social stigma surrounding depression is substantial and often prevents the optimal use of current knowledge and treatments. The cost of the illness in pain, suffering, disability, and death is high. Given the strong evidence that treatments are effective, third-party coverage for the diagnosis and treatment of depression should be equal to that available for other medical disorders.

Depression Guideline Panel. Depression in Primary Care: Volume 1. Detection and Diagnosis. Clinical Practice Guideline, Number 5. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 93-0550. April 1993.

Dedication

Depression in Primary Care is dedicated to the memory of Gerald L. Klerman, MD, who passed away while serving as one of our scientific reviewers. Dr. Klerman, in his lifetime of research, teaching, and clinical work, and in his years of government service as the administrator of the Alcohol, Drug Abuse, and Mental Health Administration, Public Health Service, Washington, DC (1977-80), worked diligently to develop scientifically based information to help clinicians better serve their patients. We remain indebted to him for his contribution to our panel and to the field of psychiatry in general.

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Acknowledgments

These guidelines were developed with the help of many dedicated contributors. The reviewing consultants for treatment issues searched and compiled a vast literature. The scientific reviewers critiqued the reviews and several drafts of the guideline document. A variety of professional organizations, patient groups, and individuals provided peer review and pilot-tested the guidelines. Finally, critical administrative, scientific, technical, and secretarial support made the entire effort feasible. A full listing of all those involved in this effort appears in the lists of contributors at the end of this document.

Special recognition goes to David Schriger, MD, MPH, UCLA School of Medicine, Los Angeles, California, panel methodologist, who critiqued all reviews and drafts of the guidelines and helped to conceptualize the overall approach, specify clinical issues, and organize the relevant data. Extraordinary credit also goes to Madhukar Trivedi, MD, Instructor, Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, scientific assistant to the chair, who helped to conceptualize the overall approach, conduct all meta-analyses, and review most studies of medication efficacy. Without him, this project would not have been possible.

Executive Summary

Up to one in eight individuals may require treatment for depression during their lifetimes. The direct costs of treatment for major depressive disorder combined with the indirect costs from lost productivity are significant, accounting for approximately $16 billion per year in 1980 dollars. Regrettably, only one-third to one-half of those with major depressive disorder are properly recognized by practitioners. Fewer than one-third of patients with bipolar disorder are in treatment.

Despite the high prevalence of depressive symptoms and major depressive episodes in patients of all ages, depression is underdiagnosed and undertreated by primary care and other nonpsychiatric practitioners, who are, paradoxically, the providers most likely to see these patients initially. Depression may occur concurrently with

other nonpsychiatric general medical disorders or with other psychiatric disorders; it may also be brought on by the use of certain medications. Major risk factors for depression include a personal or family history of depressive disorder, prior suicide attempts, female gender, lack of social supports, stressful life events, and current substance abuse. The social stigma surrounding depression is substantial and often prevents the optimal use of current knowledge and treatments. The cost of the illness in pain, suffering, disability, and death is high.

Once identified, depression can almost always be treated successfully, either with medication, psychotherapy, or a combination of both. Not all patients respond to the same therapy, but a patient who fails to respond to the first treatment attempted is highly likely to respond to a different treatment.

This Clinical Practice Guideline focuses on the diagnosis of depressive disorders, particularly in outpatients. Depression is defined according to the current U.S. standard diagnostic system in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), published by the American Psychiatric Association.

Overview

The clinical practice guideline statements contained in Depression in Primary Care were developed to assist patients and primary care practitioners in the detection and diagnosis of depressive conditions and the treatment of major depressive disorder. This guideline is an abbreviated version of a far larger Depression Guideline Report and is divided into two volumes: this one, Volume 1: Detection and Diagnosis, and its companion volume, Volume 2: Treatment of Major Depression. The Depression Guideline Report contains more than 3,500 relevant references.

Detection and Diagnosis systematically reviews the diagnosis of depressive and other mood disorders, according to the current U.S. standard system in Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (American Psychiatric Association, 1987). The disorders reviewed include both unipolar forms of primary mood disorders (e.g., major depressive disorder, dysthymic disorder), depression not otherwise specified (DNOS), and bipolar forms of primary mood disorders (e.g., bipolar I disorder, bipolar disorder not otherwise specified, cyclothymic disorder). The co-occurrence of depression with other nonmood psychiatric disorders and with other nonpsychiatric medical conditions is also considered, as is depression caused by medications. Finally, the guidelines offer a strategy for making a differential diagnosis of depression, including risk factors and clinical clues, use of laboratory and psychological tests, and ongoing clinical reassessment.

A clinical depression or a mood disorder is a syndrome (a constellation of signs and symptoms) that is not a normal reaction to life's difficulties. Mood disorders involve disturbances in emotional, cognitive, behavioral, and somatic regulation. A sad or depressed mood is only one of many signs and symptoms of clinical depression. In fact, the mood disturbance may include apathy, anxiety, or irritability in addition to or instead of sadness; also, the patient's interest or capacity for pleasure or enjoyment may be markedly reduced. Up to one in eight individuals may require treatment for depression during their lifetimes; up to 70 percent of psychiatric hospitalizations are associated with mood disorders. According to data based on a 1980 population base, the total number of cases of major depressive disorder among those 18 or older in a 6-month period is 4.8 million; in addition, over 60 percent of suicides can be attributed to major depressive disorder.

Based on 1980 data, mood disorders account for more than 565,000 hospital admissions, 7.4 million hospital days, and 13 million physicians' visits annually. The total cost of mood disorders to society, including indirect costs that result from lost productivity, is estimated to be $16 billion annually. In addition to economic costs, depression can carry great personal costs because of the social stigma associated with diagnosis and treatment of a mental illness. This stigma likely plays a large role in patients' reluctance to seek, accept, and adhere to treatment. Yet, when identified, depression can almost always be treated successfully, either with medication, psychotherapy, or a combination of the two. The potential savings to be derived from the appropriate treatment of persons suffering from depression are socially and economically significant.

The high prevalence of depression and the success of available treatments prompted the need to develop a guideline to assist primary care providers (general practitioners, family practitioners, internists, nurse

practitioners, registered nurses, mental health nurse specialists, physician assistants, and others) in the diagnosis of depression. The Depression Guideline Panel that prepared these guidelines is composed of experts from various mental health and primary care disciplines and a consumer representative, selected for their range and diversity of expertise. The guidelines are based on systematic literature reviews commissioned by the panel and conducted by experts in numerous areas relevant to depression, with special attention to clinical issues most pertinent to diagnosis and treatment of depression in primary care. Guideline development also included input from a broad range of professional and consumer organizations and individuals. The guidelines have undergone peer review and field review with intended users in clinical sites to evaluate the document both conceptually and operationally.

The panel did not review the material used to develop the taxonomy in DSM-III-R. Rather, the panel reviewed the epidemiology of major depressive disorder in community samples and primary care settings and the course, co-occurrence, and co-morbidity of depressive and other medical conditions. Where summary statistics were lacking, but data sets were available, the panel commissioned reanalyses of available data. The panel also reviewed literature on the role of self-reports and clinician ratings as tools for detecting or differentially diagnosing depression. The role of laboratory tests in the differential diagnosis of medical causes of depression was reviewed by using thyroid function testing as an example.

Because of the current discrimination against those with depressive and other psychiatric conditions, appropriate diagnosis and treatment may carry a far greater personal cost for patients with depression than for those with other medical conditions. Future efforts should address and seek to overcome the consequences of this stigma through the education of health care providers, patients and their families, and the general population to ensure accurate, early diagnosis and effective, early treatment.

1. Guideline Development

Background

At least five reports suggest that primary care practitioners underdiagnose and/or undertreat depressive conditions (Gullick and King, 1979; Johnson, 1974; Ketai, 1976; Magruder-Habib, Zung, Feussner, et al., 1989; Popkin and Callies, 1987). In fact, only one-third to one-half of patients with major depressive disorder are properly recognized by primary care and other practitioners. Only about one-third of patients with bipolar disorder are in treatment. The problem of underrecognition is important enough to warrant special attention.

Other psychiatric disorders are often accompanied by mood symptoms or formal mood syndromes. That is, patients may suffer concurrently from two psychiatric syndromes. In addition, substance abuse or withdrawal may cause mood symptoms/syndromes -- so-called substance-induced mood disorders.

Depressive symptoms or full syndromes commonly accompany a variety of other general medical disorders. For example, diabetes, cancer, heart attacks, and stroke are often accompanied by depressive symptoms of sufficient duration and intensity to meet the criteria for specific mood syndromes. Recognized general medical conditions, such as neurologic, metabolic, oncologic, and other illnesses, can biologically cause mood symptoms or formal mood syndromes (i.e., organic or secondary mood disorders). In other cases, mood syndromes may be psychological reactions to the disability or prognosis associated with nonpsychiatric medical conditions. Some prescription medicines used to treat general medical conditions, such as antihypertensive drugs, may also precipitate or maintain depressive symptoms or syndromes, especially in persons with a personal or family history of mood disorders.

For these reasons, the Depression Guideline Panel has provided Clinical Practice Guideline: Depression in Primary Care to introduce practitioners to the key features of depressive conditions and, thus, to improve early diagnosis. This guideline, an abbreviated version of a far larger document, is divided into two volumes: this one, Volume 1. Detection and Diagnosis, and its companion, Volume 2. Treatment of Major Depression. The nearly 40 literature reviews conducted for these guidelines identified more than 3,500 relevant references, which are cited in the Guideline Report (roughly 1,200 pages). Only recent reviews and highly salient references are cited

here.

Definition of Depression

The panel defined depression according to the current U.S. standard diagnostic system in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (American Psychiatric Association, 1987). Given the need to complete this report in a timely fashion, the panel focused on major depressive disorder with some consideration of DNOS. The DSM-III-R system is closely aligned with and easily translated to the International Classification of Diseases, Ninth Edition (ICD-9) system of the World Health Organization (WHO). Both the DSM-III-R and the ICD-9 are undergoing revisions, which are to be completed by the end of 1993. In choosing to use the DSM-III-R, the panel acknowledges the availability of other clinical taxonomies pertinent to the diagnosis of depression in primary care practice and recognizes that the selection of a particular taxonomy can add bias to the guideline. The panel recognizes this limitation, but believes the DSM-III-R to be the best taxonomy available at this time.

The panel also recognizes that a variety of clinical conditions may be viewed as mood disorder "equivalents." These include masked depression, chronic pain, chronic fatigue syndrome, somatization disorder, fibromyalgia, and others. The panel commissioned reviews of the literature on these conditions to provide a scientific basis for recognizing and differentiating these conditions from mood disorders.

Literature Reviews and Guideline Development

Practitioners often confront clinical situations for which direct research data are limited, but for which indirectly relevant data are available. The translation of what is scientifically confirmed or suspected into what is clinically required or recommended requires training, professional judgment, and experience.

These guidelines are based on systematic literature reviews conducted by experts in diverse substantive areas relevant to depression, with special attention to the clinical issues most pertinent to the diagnosis and treatment of depression in primary care. To develop principles for diagnosis and treatment of mood syndromes in association with other illnesses, the panel also commissioned reviews of the literature on depression and selected general medical conditions. Where evidence is either lacking or incomplete, this is noted; in these cases, either no guideline has been derived or options are provided, based on logical inference, available data, and panel consensus. When the evidence is reasonably clear, though modest in amount, these findings are noted, and a tentative recommendation is offered. Thus, the guidelines that follow are coded according to the strength of the available evidence as interpreted by the panel:

A. Good research-based evidence, with some panel opinion, to support the guideline statement.

B. Fair research-based evidence, with substantial panel opinion, to support the guideline statement.

C. Guideline statement based primarily on panel opinion, with minimal research-based evidence, but significant clinical experience.

This synopsis of diagnostic issues is not based on reviews of the evidence for or against the validity of specific diagnostic entities. (For such reviews, see DSM-IV Sourcebook [Frances and Widiger, in press].) Rather, the panel reviewed the epidemiology of major depressive disorder in community samples and primary care settings and the course, co-occurrence, and co-morbidity of depressive and other medical conditions. The panel also reviewed literature on the role of self-reports and clinician ratings as tools for detecting or differentially diagnosing depression. Therole of laboratory tests in differential diagnosis of the medical causes of depression was illustrated by using the example of thyroid function testing.

This synopsis describes the various forms of depression; their course, epidemiology, and common clinical expression in different age groups; the co-occurrence of depressive symptoms or formal syndromes with other psychiatric or nonpsychiatric medical conditions; the role of medications in causing depression; and the role of clinical and laboratory procedures in the detection and differential diagnosis of depression.

The depression guidelines were drafted in four different formats: (1)the full Depression Guideline Report; (2) the Clinical Practice Guideline, which condenses pertinent information from the report into two volumes for easy use by practitioners; (3) the summary Quick Reference Guide for Clinicians; and (4) A Patient's Guide. The literature reviews, drafts of the full Depression Guideline Report, and all four shorter versions were sent to 14 scientific reviewers, who critiqued them. The guidelines were revised and sent to the original 14 reviewers, plus 14 new scientific reviewers for further critique and subsequent revision.

Peer review was requested for both the diagnosis and treatment volumes, as well as for A Patient's Guide and the Quick Reference Guide for Clinicians, from 73 professional organizations and 3 patient advocacy groups. In addition, independent family, general medical, and nurse practitioners reviewed these guidelines for ease of use, feasibility, and utility. These reviews provided the basis for final guideline revisions (Figure 1).

Additional revisions to these guidelines are anticipated, based on further comments from practitioners, new scientific evidence, studies of the impact of these guidelines on primary care practice, and new reviews to address areas not yet discussed. For example, the panel has not reviewed treatment of certain conditions, such as bipolar disorder; certain treatments, such as use of lithium alone; or certain patient groups, such as children and adolescents. These topics were deferred to subsequent years either because they are less common in primary care or because logistic constraints made deferral necessary. The panel invites correspondence from users to help in these future revisions.

Interpretation of the Scientific Literature

Several limitations to the available scientific literature made the development of guidelines for primary care providers difficult:

- Most studies on diagnosis and treatment of depression come from non-primary care settings (usually psychiatric or psychological practice settings).
- Only modest data are available on the usefulness of DSM-III-R in patients with depression and concurrent medical disorders.
- Only a few randomized controlled treatment trials have been conducted in patients with depression and concurrent significant medical disorders.
- The long-term outcomes of treated and untreated mood disorders seen in primary care settings are relatively unstudied.
- While a moderate number of randomized controlled acute treatment trials using medication and some trials using psychotherapy have been conducted in geriatric patients, only seven trials were conducted in primary care settings, though geriatric patients are common in primary care.
- Even fewer randomized controlled trials with depressed children and adolescents are available, and none have been conducted in primary care settings.
- While many patients with mood disorders seen in primary care settings have DNOS or "minor" forms of depression, very few randomized controlled trials on these patients have been undertaken.

Although several authors have questioned the generalizability of research findings from psychiatric to primary care settings, many difficulties encountered in primary care are also found in psychiatric settings. These include distinguishing depressions from underlying medical disorders, identifying medical disorders that present with depressive symptoms, treating mood disorders in patients with other general medical illnesses, and identifying and treating depressive psychological reactions to nonpsychiatric medical disorders.

The panel believes it essential to highlight the impact of current social and cultural forces, as well as current reimbursement policies, on timely diagnosis and treatment of depressive and other psychiatric conditions.Social stigma contributes to:

- Resistance of patients to seek treatment.
- Reluctance of practitioners to look for and formally diagnose depressions.
- Poor adherence by patients during long-term treatment of more chronic forms of depression.

- Low reimbursement rates by third-party payors for these conditions.
- Inappropriate emphasis on depression and other psychiatric disorders on applications for driver's license,employment, security clearance, and other "routine" purposes (a situation that may be improved with the recent enactment of the Americans with Disabilities Act).

Because of the current discrimination against persons with depressive and other psychiatric conditions, appropriate diagnosis and treatment may carry a far greater personal cost for patients with depression than for those with other medical conditions. In some cases, acknowledgment of diagnosis and treatment of depression can actually worsen an individual's social, occupational, and economic status. The ultimate long-term consequences of this stigma must be addressed to ensure accurate, early diagnosis and effective, early treatment.

The implementation of these guidelines may require one or more of the following:

- Increased reimbursement for those time-intensive tasks recommended in these guidelines.
- Educational efforts aimed at primary care practitioners.
- Patient/family education.

On the other hand, use of these guidelines may reduce overall medical costs, since patients with clinical depression may be identified and treated earlier in the course of the illness, thus reducing the need for multiple physician visits for various somatic symptoms of depression (e.g., tension headaches, abdominal pain, joint pain, insomnia) and the need for eventual, more complex and expensive treatments for more chronic depressions. Indirect cost savings, such as fewer days lost from work, less disability, and less pain and suffering, are additional benefits of effective treatment.

2. Guideline: Overview of Mood Disorders

Guideline: Depressive disorders should not be confused with the depressed or sad mood that normally accompanies specific life experiences particularly losses or disappointments. Mood disorders involve disturbances in emotional, cognitive, behavioral, and somatic regulation. A clinical depression or a mood disorder is a syndrome (a constellation of signs and symptoms) that is not a normal reaction to life's difficulties. A sad or depressed mood is only one of many signs and symptoms of a clinical depression. In fact, the mood disturbance may include apathy, anxiety, or irritability in addition to or instead of sadness; also, the patient's interest or capacity for pleasure or enjoyment may be markedly reduced. Not all clinically depressed patients are sad, and many sad patients are not clinically depressed. **(Strength of Evidence =A.)**

Primary mood disorders include both depressive (unipolar) and manic-depressive (bipolar) conditions. Most mood disorders seen in primary care settings are thought by some to be at an early, poorly organized stage of the illness. These disorders are often mixed with anxiety symptoms and accompanied by vague somatic complaints. Furthermore, they may be less profoundly severe, but more chronic, than those mood disorders encountered primarily by mental health care providers. Patients initially seeking care from primary care providers may be less inclined toward a psychological explanation or conceptualization of their depression.

Guideline: Major depressive disorder (sometimes called unipolar depression) is characterized by one or more episodes of major depression without episodes of mania or hypomania (low-level mania). By definition, major depressive episodes last at least 2 weeks (and typically much longer). **(Strength of Evidence = A.)**

A sad mood or a significant loss of interest is required, along with several associated signs and symptoms (Table 1), to diagnose a major depressive episode.

Guideline: A major depressive episode can occur as part of a primary mood disorder (e.g., major depressive or bipolar disorder), as part of other nonmood psychiatric conditions (e.g., eating, panic, or obsessive-compulsive disorders), in cases of drug or alcohol intoxication or withdrawal, as biologic or psychological consequences of various nonpsychiatric general medical conditions or as consequences of the use of selected prescription

medications. Finally, a grief reaction (bereavement) may initially (within the first 2 months) meet the criteria for a major depressive episode. **(Strength of Evidence = A.)**

Whether general medical conditions or medications simply precipitate mood episodes in vulnerable individuals or whether they cause episodes de novo is unclear (Figure 2).

Unipolar forms of primary mood disorders are divided into three groups:

- Major depressive disorder consists of one or more episodes of major depression with or without full recovery between these episodes.
- Dysthymic disorder features a low-grade, more persistent (less episodic) depressed mood and associated symptoms for at least 2 years, during which a major depressive episode has not occurred. Many patients with dysthymic disorder subsequently suffer superimposed episodes of major depression over the course of their illness. In such cases, both dysthymic and major depressive disorders are diagnosed according to DSM-III-R.
- Depression not otherwise specified is a residual category reserved for patients with symptoms and signs of depression that do not meet the formal diagnostic criteria for either dysthymic or major depressive disorders. If patients have previously met the criteria for major depressive disorder, which then goes into partial remission, major depressive disorder in partial remission (not DNOS) is diagnosed.

Guideline: Bipolar disorders are recurrent, episodic conditions characterized by a history of at least one manic or hypomanic episode. Ninety-five percent of persons with bipolar disorder also have recurrent episodes of major depression. **(Strength of Evidence = A.)**

Bipolar disorders have been grouped into three types:

- Bipolar I disorder requires at least one manic episode, along with (nearly always) major depressive episodes. A manic episode consists of a distinct period of elevated or irritable mood, along with several symptoms such as grandiosity, decreased need for sleep, pressured speech, and poor judgment.
- Bipolar disorder not otherwise specified is a residual category that includes bipolar II disorder, a condition characterized by recurrent episodes of major depression along with hypomanic (but not full-blown manic) episodes, as well as other forms that do not meet formal criteria for bipolar I or cyclothymic disorder.
- Cyclothymic disorder is characterized by numerous hypomanic episodes and numerous periods of mild depressive symptoms insufficient in duration or severity to meet the criteria for major depressive episodes. Cyclothymic disorder is typically chronic, lasting at least 2 years by definition.

Figure 3 summarizes the differential diagnosis of primary mood disorders. The clinically depressed patient must suffer either a sustained sad mood or a significant loss of interest/pleasure, plus associated criterion symptoms. If at least five total symptoms are present for at least 2 weeks, the patient has either a grief reaction or a major depressive episode. The typical bereaved person and nearly all patients with adjustment reactions suffer only two or three associated symptoms. Such patients are rarely suicidal and do not have any significant functional impairment. By definition, these reactions are time-limited (classically lasting less than 6 months) and are not associated with hallucinations or delusions. Some bereaved persons evidence sufficient symptoms to meet the criteria for a major depressive episode within the first month or two following the loss. If these symptoms persist beyond 2 months, the diagnosis should be changed to major depression.

Nearly all patients with major depressive disorder report significant life stresses. The simple presence of a life stress is not a basis for diagnosing either a grief or a situational adjustment reaction, nor is it a basis for excluding the diagnosis of major depressive disorder. Rather, if the patient has only two to three associated symptoms that are mild and present for a short time and if there is no history of major depressive, manic, or hypomanic episodes, an adjustment disorder with depressed mood may be diagnosed. Treatment for this condition and for a classic grief reaction is usually support and reassurance. For some cases of adjustment disorder with depressed mood, a change in lifestyle or relationship patterns may be needed.

If someone has only two or three (but not five or more) symptoms associated with a major depressive episode, it

is essential that the practitioner ask about prior major depressive episodes to see if the patient has only partially recovered from a prior major depressive episode. If so, treatment proceeds as for major depressive disorder.

If prior or current major depressive episodes are diagnosed, a history of manic (or hypomanic) episodes should be sought to evaluate the possibility of the presence of a bipolar disorder. If no such episodes have occurred, a history of prior episodes of major depression is sought to determine whether the major depressive disorder is single episode or recurrent. The number of episodes, including the present one, determines whether maintenance treatment should be a consideration.

Even if the patient has only two or three symptoms of major depression and no prior major depressive episodes, it is still important to elicit a history of manic episodes. The patient may have a full bipolar disorder without yet having sustained a full major depressive episode.

Major Depressive Disorder

Clinical Features and Course

Major depressive disorder may begin at any age, although it usually begins in the mid-20s and 30s. Symptoms develop over days to weeks. Some people have only a single episode, with a full return to premorbid functioning. However, more than 50 percent of those who initially suffer a single major depressive episode eventually develop another. In these cases, the diagnosis is revised to recurrent major depressive disorder. Individuals with recurrent major depressive disorder are at greater risk of developing bipolar disorder than are those with single episodes, and they are more likely to have first-degree biologic relatives with major depressive disorder. Some patients who meet the criteria for major depressive disorder, especially of the recurrent type, have a genotype that groups them more clearly with patients with bipolar disorder, as evidenced by a family history of bipolar disorder, early onset of their major depressive disorder, a higher frequency of depressive episodes, and a greater tendency to show psychomotor retardation and hypersomnia during the episode of major depression (Akiskal, 1983). These patients may have a greater tendency to develop hypomania with standard tricyclic antidepressants (TCAs), and their recurrent depressive episodes may be more responsive to lithium alone (Akiskal, 1983).

The course of recurrent major depressive disorder is variable. In some patients, the episodes are separated by many symptom-free years of normal functioning. For others, the episodes become increasingly frequent with greater age. Major depressive episodes nearly always reduce social, occupational, and interpersonal functioning to some degree, but functioning usually returns to the premorbid level between episodes if the episodes remit completely.

Studies of patients with major depressive disorder have found that most untreated episodes last 6 to 24 months. (For a review of these studies, see Goodwin and Jamison, 1990, and Rush, Cain, Raese, et al., 1991.) For two-thirds of cases, symptoms remit completely and functioning returns to the premorbid level. In the remaining cases, the full episode may persist for more than 2 years (about 5 to 10 percent), or recovery between episodes may be partial (about 20 to 25 percent). Approximately one-fourth of patients develop major depression superimposed on a low-grade chronic depression (dysthymic disorder), which accounts for the majority of those with poor interepisode recovery.

Major depressive episodes may end completely or only partially. If the latter occurs, clinical experience and some research data suggest that:

- The likelihood of a subsequent episode is higher.
- The need for longer term treatment is increased.
- The prognosis is for continuing poor or partial interepisode recovery following subsequent episodes.
- The need for treatment with both medication and psychotherapy may be greater.

According to data from community samples, women are more likely to remain depressed at 1-year followup than are men (Weissman and Myers, 1978). For women, older age, less than a high school education, and an unstable marital history are risk factors. In addition, women with major depressive disorder whose disease was more

severe, more recurrent, or associated with greater prior or current co-morbidity for panic or somatization disorder (but not drug or alcohol abuse) at initial evaluation are more likely to have major depressive disorder 1 year later. Men, but not women, with both dysthymic and major depressive disorders initially are more likely to have major depressive disorder 1 year later. For men, age, education, and marital history are unrelated to outcome. For both sexes, longer lasting episodes of major depressive disorder at initial evaluation are related to the presence of major depressive disorder 1 year later.

The panel commissioned a reanalysis of the data from the large, multisite Epidemiologic Catchment Area (ECA) Study, which involved more than 18,000 interviews in several communities (Eaton, Holzer, von Korff, et al., 1984; Eaton, Regier, Locke, et al., 1981; Regier, Boyd, Burke, et al., 1988; Regier, Myers, Kramer, et al., 1984; Weissman and Klerman, 1978; Weissman, Leaf, Tischler, et al., 1988; Weissman and Myers, 1978) and revealed that at 1-year followup 40.3 percent of those with major depressive disorder still had the same diagnosis, 2.6 percent had developed dysthymic disorder, 16.7 percent had improved somewhat but had not completely recovered, and 40.5 percent had no mood disorder (Johnson and Weissman, unpublished manuscript). Studies also indicate that treatment for major depressive disorder is more effective earlier in the episode, before it becomes chronic (Bielski and Friedel, 1976; Kupfer, Frank, and Perel, 1989; Rush, Hollon, Beck, et al., 1978). Taken together, these findings suggest that early treatment is essential to reduce subsequent morbidity and mortality.

To put these findings into context, it is necessary to recognize that data from epidemiologic community samples include many mood-disordered persons who are neither seeking nor receiving treatment for their psychiatric disorders. Assuming that these people are "less ill" than are those in treatment with mental health care specialists, outcomes based on community samples are likely to provide a more optimistic view than are outcomes in primary care or psychiatric outpatient samples.

Epidemiology

Guideline: The point prevalence for major depressive disorder in the Western industrialized nations is 2.3 to 3.2 percent for men and 4.5 to 9.3 percent for women. The lifetime risk for major depressive disorder is 7 to 12 percent for men and 20 to 25 percent for women. Risk factors for major depressive disorder include female gender (especially during the postpartum period), a history of depressive illness in first-degree relatives, and prior episodes of major depression. **(Strength of Evidence = A.)**

The above gender difference is found in community samples and, thus, is not due to increased female help-seeking behavior. Prevalence rates for major depressive disorder are unrelated to race, education, income, or civil status. Recent epidemiologic data clearly indicate that the age at onset of major depressive disorder has decreased for the more recently born (the "birth cohort" effect) in many westernized cultures.

A recent review of available studies strongly suggests that psychosocial events or stresses may play a significant role in precipitating the first or second episodes of major depressive disorder, but they may play little or no role in the onset of subsequent episodes (Post, 1992). That is, for the recurrent forms of major depressive disorder, new episodes are less likely to involve a specific precipitant as the disorder becomes more firmly established.

Individuals with major depressive disorder, as well as those with dysthymic disorder and DNOS, are high users of medical services and are as functionally impaired as are patients with severe chronic medical disorders (Katon, von Korff, Lin, et al., 1990; von Korff, Ormel, Katon, et al., 1992; Weissman, Leaf, Tischler, et al., 1988; Weissman and Myers, 1978).

The lifetime psychiatric co-morbidity rate for major depressive disorder can be as high as 43 percent (Sargeant, Bruce, Florio, et al., 1990). That is, up to 43 percent of patients with major depressive disorder have histories of one or more nonmood psychiatric disorders. The 1-month point prevalence for concurrent in contrast to lifetime psychiatric co-morbidity is 8 percent.

Depressive conditions are highly prevalent in primary care settings (Johnson and Weissman, unpublished

manuscript). Prevalence rates of depression based on chart notations by primary care physicians vary from 1.5 to 4.5 percent. Structured psychiatric interviews based on standard diagnostic systems (DSM-III-R or ICD-9) provide the best prevalence data because they identify all who have the conditions and differentiate them from those with depressive symptoms from other causes. (However, even many of the studies in which the investigators used structured interviews may not fully exclude patients whose depression was caused by concurrent nonpsychiatric medical disorders, medications, or substances of abuse.) Eleven studies have used structured psychiatric interviews and specific diagnostic criteria to determine the prevalence of major depressive disorder in primary care settings (Table 2). The point prevalence of major depressive disorder in primary care outpatient settings ranged from 4.8 to 8.6 percent; 14.6 percent of adult medical inpatients studied met ICD-9 criteria for major depressive disorder (Feldman, Mayou, Hawton, et al., 1987).

Costs of Untreated Major Depressive Disorder

Guideline: Patients with major depressive disorder have substantial amounts of physical and psychological disability, as well as occupational difficulties. **(Strength of Evidence = A.)**

Untreated major depressive disorder has a substantial effect on health and functioning. Patients in a major depressive episode report substantially poorer intimate relationships and less satisfying social interactions than do members of the general population who have previously suffered from depression or who currently have other psychiatric disorders (Fredman, Weissman, Leaf, et.al.,1988).

Physical complaints are also common during a major depressive episode. Twenty-three percent of patients in one study reported some days in which their health kept them in bed all or most of the day in the previous 2 weeks, compared to 5 percent for the general population (Wells, Golding, and Burnam, 1988a). This finding is supported by reports of the health status of community respondents with major depressive disorder, 48 percent of whom described their health as either fair or poor, compared to only 19 percent of the general population (Wells, Golding, and Burnam, 1988a). Other general population data indicate that patients with major depressive disorder reported 11 disability days per 90-day interval versus 2.2 disability days for the general population (Broadhead, Blazer, George, et al., 1990). Data from community respondents indicate that 38 percent of patients with major depressive disorder have some chronic activity restriction, and 30 percent of those with depression reported decreased activity days in the previous 2 weeks (Wells, Golding, and Burnam, 1988a).

Clinical samples of patients with major depressive disorder also provide evidence of severe impairment in interpersonal and occupational functioning, including loss of work time (Wells, Stewart, Hays, et al., 1989). Patients with major depressive disorder have more physical illnesses than do other patients seen in primary care settings (Coulehan, Schulberg, Block, et al., 1990). Health care utilization is increased in persons in the community with major depressive disorder compared to other patients in the general medical setting (Regier, Hirschfeld, Goodwin, et al., 1988).

Major depressive disorder is associated with increased mortality, which is generally considered to be secondary to suicide and accidents (Wells, 1985). A recent report indicated that patients with major depressive disorder admitted to nursing homes had a 59 percent greater likelihood of death in the first year following admission compared to those without major depressive disorder (Rovner, German, Brant, et al., 1991). Patients with major depressive disorder in the ECA Study aged 55 and over had a mortality rate over the next 15 months that was four times higher than that of nondepressed age-matched controls. Up to 15 percent of patients with major depressive disorder severe enough to require hospitalization eventually die by suicide (Coryell, Noyes, and Clancy, 1982).

Subgroups of Major Depressive Disorder

Studies of major depressive disorder reveal heterogeneity with regard to the biology, family history, pharmacologic response, genetics, and course of illness. Several schemes have been proposed to subdivide major depressive conditions. The common subgroups and possible clinical relevance of each are shown in Table 3. These subtypes are not all-inclusive. For example, a large number of patients who have major depressive disorder without melancholic, psychotic, or atypical features have episodes that are not seasonally related and do not have a postpartum onset.

Three subgroups based on cross-sectional symptom features psychotic, melancholic, and atypical may have implications for treatment selection. Two based on course features seasonal pattern and postpartum onset have prognostic utility; the seasonal type may also suggest the specific therapeutic option of light therapy. However, these subgroups may not be etiologically distinct. Rather, they may represent varying clinical expressions of the same condition over time, in different age groups, or in the context of particular provoking stimuli.

Psychotic Features

Guideline: Psychotic features refer to the presence of delusions or hallucinations. They occur in 15 percent of patients with major depressive disorders. **(Strength of Evidence = A.)**

In psychotic depressions, psychotic features are never present without concurrent mood symptoms. Psychotic depressions must be distinguished from schizoaffective disorder. In the latter only, there are periods of at least 2 weeks during which delusions or hallucinations are present without mood disturbances.

The content of the hallucinations or delusions in psychotic depressions is usually logically consistent with the predominant sad mood (mood-congruent). For example, there may be a delusion that the patient has sinned in an unforgivable way. Less commonly, the hallucinations or delusions have no obvious relationship to sadness (mood-incongruent); for example, there may be persecutory delusions, for which the person has no explanation. Studies to date suggest that mood-incongruent symptoms are associated with a worse prognosis; evolve into schizophreniform or schizo-affective disorders; involve a less episodic, more chronic course; and require more assiduous, longer maintenance treatment(s). (See Lalive-Aubert and Rush, 1992; Lalive-Aubert and Rush, in press, for reviews.)

The psychotic features of psychotic major depressive disorder usually recur in subsequent episodes, should such episodes occur. Some studies suggest that psychotic depressive episodes are familial (Schatzberg and Rothschild, in press; Weissman and Johnson, 1990).

For psychotic depressions, TCAs plus a neuroleptic or electroconvulsive therapy (ECT) are each superior to TCAs alone in treating the illness (Depression Guideline Panel, forthcoming). Given the markedly disabling nature of psychotic depression, maintenance treatments are strongly indicated when the disorder is recurrent. However, the relative efficacy of maintenance treatment compared to placebo; the value of including both a neuroleptic and an antidepressant in maintenance treatment; and the acute and maintenance phase efficacy of non-TCA medications, lithium, or selected anticonvulsants have not been studied in randomized controlled trials (Schatzberg and Rothschild, 1992).

Melancholic Features

Guideline: The key melancholic features of major depressive disorder are:

- Psychomotor retardation or agitation.
- Loss of interest or pleasure.
- Lack of reactivity to usually pleasant stimuli.
- Worse depression in the morning.

- Early morning awakening.

(Strength of Evidence = A.)

Melancholic symptom features appear to repeat from episode to episode in individuals with recurrent, severe major depressive disorder. They are more commonly present in older depressed patients (see Rush and Weissenburger, in press, for a review). Melancholic features are not uniquely associated with a family history of depression. They are associated with reduced rapid eye movement latency and/or dexamethasone nonsuppression (Rush, Cain, Raese, et al., 1991).

Severely symptomatic patients whose depression has melancholic features are likely to respond to treatment with TCAs or to ECT. Melancholic features do not predict which antidepressants will be effective, though their presence indicates that anxiolytics will not be effective (Depression Guideline Panel, forthcoming). The presence of melancholic symptom features, especially in the severely ill, should sharply increase the practitioner's tendency to treat with antidepressants and should provoke a thorough questioning for the presence of psychotic symptom features. If medications fail, ECT should be strongly considered for these patients.

Atypical Features

The groups studying atypical features define the features differently. Two types, vegetative and anxious, have been proposed in the literature. Vegetative features include:

- Overeating.
- Oversleeping.
- Weight gain.
- A mood that still responds to events (reactive mood).
- Extreme sensitivity to interpersonal rejection.
- A feeling of heaviness in the arms and legs.

Anxious features include:

- Marked anxiety.
- Difficulty in falling asleep.
- Phobic symptoms.
- Symptoms of sympathetic arousal.

Atypical features of either type are associated with a younger age at onset of illness. Whether these symptoms run in families, repeat across episodes, or are associated with an identifiable or unique biology is not known. However, rapid eye movement latency is not characteristically reduced in this type of mood disorder. The relationship between atypical and melancholic symptom features remains to be clarified. Some data suggest that atypical symptoms may be more likely earlier in the course of major depressive disorder, while melancholic features are more likely to appear later.

Several randomized controlled trials indicate that, when atypical features (those in the vegetative group above) are present, monoamine oxidase inhibitors (MAOIs) are more effective than TCAs, although the latter are still more effective than placebo. Case reports and clinical experience suggest that those depressions with atypical features may respond better to selective serotonin reuptake inhibitors (SSRIs) than to TCAs.

Seasonal Pattern

Guideline: DSM-III-R indicates that a seasonal pattern for major depressive disorder can be diagnosed only if:

- Episodes are recurrent (at least two episodes by some criteria, three by other criteria).
- There has been a regular temporal relationship between the onset of the major depressive episodes and a particular period of the year (such as regular onset of depression in fall and offset in spring).
- Seasonal episodes substantially outnumber nonseasonal episodes.

Most often, depressive symptoms remit fully between seasonal episodes. **(Strength of Evidence = A.)**

The first systematic evidence of the prevalence of seasonal affective disorder was an estimate of 6 percent from a study in the New York area. Subsequently extended to various east coast latitudes, this study showed less than 2 percent prevalence in Florida and nearly 10 percent prevalence in New Hampshire (Rosenthal, Levendosky, Skwerer, et al., 1990; Terman, 1988). There are two to three times as many people personally troubled by the winter recurrence of seasonal mood symptoms than there are those with manifestations severe enough to warrant clinical diagnosis (Kasper, Wehr, Bartko, et al., 1989; Rosen, Targum, Terman, et al., 1990; Terman, Botticelli, Link, et al., 1989).

Preliminary evidence suggests that light therapy is effective in the short-term treatment of outpatients with mild to moderate seasonal major depressive disorder. Further research is required before such a claim can be made for subsyndromal seasonal affective disorder. To date, no hazard has been encountered with short-term light therapy using standard fluorescent lighting apparatus (designed to produce 2,500 to 10,000 lux stimulation and low levels of ultraviolet emission). Exposure extending beyond 2 weeks has not been fully evaluated. Clinical reports suggest that medications may also be effective for some seasonal mood disorders.

Postpartum Onset

Postpartum mood symptoms are divided into three categories, based on severity: blues, psychosis, and depression (Kendell, 1985; for a review, see Purdy and Frank, in press). Postpartum blues are brief episodes (1 to 4 days) of labile mood/tearfulness that normally occur in 50 to 80 percent of women within 1 to 5 days of delivery. Treatment consists of reassurance and time to resolve this normal response.

Postpartum psychoses can be divided into depressed and manic types. Patients with the depressed type show more psychotic, disoriented, agitated, and emotionally labile features, as well as more psychomotor retardation, than do nonpostpartum matched depressed controls (Dean and Kendell, 1981). Most of these cases are associated with signs of organic impairment. Features of the manic type are similar to features of a classic mania. The incidence of postpartum psychosis is low (0.5 to 2.0 per 1,000 deliveries), as shown in eight studies (Grundy and Roberts, 1975; Hemphill, 1952; Kendell, Rennie, Clarke, et al., 1981; Meltzer and Kumar, 1985; Nott, 1982; Paffenbarger, 1964; Paffenbarger and McCabe, 1966; Paffenbarger, Steinmetz, Pooler, et al., 1961). Many early cases were mistaken for toxic/infectious states.

The symptoms of postpartum psychosis develop rapidly (over 24 to 72 hours), typically beginning 2 to 3 days after delivery. The period of risk for developing postpartum psychosis is within the first month following delivery. For acute postpartum psychosis, the prognosis is generally good. However, many patients have previously had or subsequently develop a bipolar disorder. The risk of postpartum psychosis is higher for those with episodes at prior deliveries. The recurrence rate is from 33 to 51 percent.

Nonpsychotic postpartum depressions (major or minor depressive disorders) have also been identified (O'Hara, Neunaber, and Zekoski, 1984). These conditions may occur from 2 weeks to 12 months postpartum, but typically occur within 6 months. The prevalence of nonpsychotic depressions is 10 to 15 percent within the first 3 to 6 months after childbirth, which is somewhat higher than are the rates (5 to 7 percent) in nonchildbearing matched controls. However, the risk for nonpsychotic postpartum depression is higher for persons with a psychiatric history.

No randomized controlled treatment trials for any of the postpartum mood conditions are available. Logic and clinical experience suggest that prophylactic lithium be given as soon as possible after delivery to prevent a postpartum precipitation in patients with a history of bipolar disorder. Likewise, given the high likelihood of recurrence, other previously effective psychotropic medications should be considered in those with a history of psychotic postpartum mood episodes immediately after giving birth.

Dysthymic Disorder

Clinical Features and Course

Guideline: The essential feature of dysthymic disorder is a chronic mood disturbance (sadness in adults; sadness and, possibly, irritability in children and adolescents) present most of the time for at least 2 consecutive years (1 year for children and adolescents). **(Strength of Evidence = A.)**

Patients with dysthymic disorder exhibit at least two of the associated symptoms noted in Table 4. The associated features of dysthymic disorder are similar to those of major depressive disorder, except that, by definition, delusions or hallucinations are absent. Dysthymic disorder usually begins in childhood or adolescence without a clear onset and with a chronic course.

Differentiation between dysthymic disorder and major depressive disorder can be difficult. Their symptoms are similar, differing only in duration and severity. Individuals who initially present with dysthymic disorder frequently go on to develop concurrent major depressive disorder. Some develop hypomanic episodes, a situation requiring a revised diagnosis of either bipolar disorder not otherwise specified or bipolar II disorder. If the onset of an apparent dysthymic disorder directly follows a major depressive episode, the correct diagnosis is major depressive disorder in partial remission. By definition, dysthymic disorder cannot follow an episode of major depressive disorder unless the major depressive episode has been in full remission for at least 6 months before the onset of the dysthymic condition. When a major depressive episode immediately follows a preexisting dysthymic disorder that has been present for at least 2 years, the diagnosis is concurrent major depressive disorder and dysthymic disorder.

Dysthymic disorders may be primary (i.e., unrelated to other preexisting disorders), or they may accompany coexisting nonmood psychiatric disorders or other nonpsychiatric medical conditions. In the latter case, they are called secondary dysthymic disorders. The presence of dysthymic disorder with no prior episodes of major depressive disorder should cue the practitioner to search for other nonmood psychiatric disorders, such as substance or alcohol abuse. The reanalysis of the ECA Study data showed that, in patients with dysthymic disorder (with and without major depressive disorder) who were reexamined 1 year later, 7 to 26 percent still had dysthymic disorder, 4 to 10 percent had major depressive disorder, 5 to 20 percent had both, 11 to 23 percent had DNOS, and 41 to 52 percent were well (Johnson and Weissman, unpublished manuscript).

Epidemiology

ECA Study data indicate a lifetime rate for dysthymic disorder (with and without major depressive disorder) of 4.1 percent for women and 2.2 percent for men. Women aged 25 to 64 had rates of almost 6 percent. Men 65 and over had the lowest rate (1.0 percent). The 1-month prevalence for dysthymic disorder without major depressive disorder was 0.8 percent. The 1-month prevalence for dysthymic disorder with major depressive disorder was 1.3 percent. ECA Study data indicate that 15 percent of those with dysthymic disorder also have a concurrent nonmood psychiatric disorder, usually alcohol or drug abuse. In adults, dysthymic disorder is more common in women than in men. In children, dysthymic disorder, like major depressive disorder, is equally frequent in both sexes. Dysthymic disorder is more common among first-degree biologic relatives of persons with major depressive disorder or with bipolar I and II disorders than among the general population. The point prevalence of dysthymic disorder in primary care outpatients is 2.1 to 3.7 percent.

Costs of Untreated Dysthymic Disorder

The functional and financial costs of untreated dysthymic disorder are substantial. In the ECA Study, 29 percent of general medical patients with dysthymic disorder had some chronic restriction of their activity (Wells, Golding, and Burnam, 1988b). Similarly, 27 percent of patients with dysthymic disorder in that community survey showed decreased activities in the previous week. Sixteen percent reported bed days within the previous 2 weeks, compared to only 5 percent of the general population. Furthermore, 39 percent of those with dysthymic

disorder said that they had poor or fair health, compared to 19 percent of the general population. Patients with dysthymic disorder reported an average of 3 disability days per 90-day interval, compared to 2 days for the general population.

Depression Not Otherwise Specified

Clinical Features and Course

Guideline: Depression not otherwise specified identifies mood conditions with depressive symptoms that do not meet either severity or duration criteria for dysthymic, major depressive, or bipolar disorders. It is a heterogeneous category. **(Strength of Evidence = B.)**

Examples of DNOS include minor depression (Merikangas, Ernst, Maier, et al., in press), recurrent brief depressive disorder (Merikangas, Hoyer, and Angst, in press), and mixed anxiety/depression (Zinbarg, Barlow, Liebowitz, et al., in press). Whether these three groupings are true disorders is under investigation. Currently, they are not formally recognized diagnoses. They are described here because less than major forms of depression are common in primary care settings. The treatment implications of these groupings are unclear.

Minor depressive disorder is symptomatically similar to major depressive disorder, but with fewer symptoms and less disability; symptoms come and go, but are present for at least 2 weeks at a time. Minor depressive disorder does not have the chronic/pervasive, multiyear pattern of dysthymic disorder.

Recurrent brief depressive disorder features brief (3 to 7 days) episodes that return 6 to 10 times per year and meet the symptomatic threshold and clinical features of a major depressive episode, but not the 2-week duration criterion (Angst, Merikangas, Scheidegger, et al., 1990). It occurs somewhat more often in women than in men, and the age of onset is late adolescence to the mid-20s. The likelihood of a positive history in first-degree relatives of patients with recurrent brief depressive disorder is 12 to 20 percent for major depressive disorder and 1 to 3 percent for bipolar disorder.

Studies (Zinbarg, Barlow, Liebowitz, et al., in press) have begun to suggest the existence of a disorder involving symptoms of both anxiety and depression that was particularly prevalent among primary care patients, but they did not use DSM nomenclature. Barrett, Barrett, Oxman, et al. (1988) found that 4.1 percent of a sample of 1,055 primary care patients had mixed anxiety/depression, defined as concurrent anxious and depressive symptoms, neither of which was of sufficient frequency or duration to meet criteria for a formal anxiety or mood disorder.

Epidemiology

An analysis of the ECA Study data showed that 11.0 percent of subjects met the criteria for DNOS. The point prevalence of DNOS in primary care outpatients is 8.4 to 9.7 percent (see Depression Guideline Panel, forthcoming).

A reanalysis of the ECA Study 1-year followup data on subjects who had a mood disturbance and two associated symptoms of major depression (an attempt to operationalize DNOS) was commissioned by the panel. The data indicated that for those with DNOS interviewed at 1-year followup, 38 percent were not ill, 52 percent still had DNOS, 3 percent had developed dysthymic disorder, and 9 percent had developed major depressive disorder (Johnson and Weissman, unpublished manuscript). For some patients, substantial morbidity is thus associated with DNOS over 1 year.

Fifty percent of patients with DNOS in the ECA sample had one or more of the following co-morbid nonmood psychiatric conditions: alcohol or substance abuse/dependence, panic disorder, obsessive-compulsive disorder, or somatization disorder. Phobic and generalized anxiety disorders were not included. The point prevalence for the 167 subjects with co-morbid DNOS was 40 percent for alcohol dependence, 15 percent for drug dependence, 37 percent for panic or obsessive-compulsive disorder, and 1 percent for somatization disorder.

Costs of Untreated DNOS

Preliminary evidence indicates that DNOS significantly affects patients' functioning, health, and disability. Patients with DNOS have decreased physical, social, and role functioning (Wells, Stewart, Hays, et al., 1989) and increased disability days. Their current health has been found to be worse than that of those with no chronic condition or those with only chronic medical conditions. Patients with DNOS reported 4 to 6 disability days per 90-day period, compared to the community population rate of 2 days per 90-day period (Broadhead, Blazer, George, et al., 1990).

Bipolar Disorders

Clinical Features and Course

Guideline: Bipolar disorders classically feature episodes of major depression interspersed with episodes of mania and/or hypomania. **(Strength of Evidence = A.)**

The major depressive episodes of bipolar disorder meet the criteria outlined in Table 1. Manic episodes are distinct periods of persistently elevated, abnormally expansive, or irritable mood associated with at least three of the symptoms noted in Table 5. About 3 percent of all bipolar disorder patients experience only manic episodes (so-called unipolar mania).

Delusions or hallucinations are sometimes present in manic episodes. Their content is usually consistent with the predominant mood (mood-congruent). For example, a patient may hear "God's voice" explaining that the patient has a special mission or special powers. Delusions may be based on the idea that the person is being persecuted because of some special relationship or attribute. Less commonly, hallucinations or delusions have no apparent content relationship to the expansive/irritable mood (mood-incongruent). Disorders with mood-incongruent psychotic features in the manic episode appear to have a poorer prognosis.

Although they are similar to manic episodes, hypomanic episodes are milder. They are usually brief periods (4 days to several weeks) in which patients are often mildly dysfunctional. Sometimes, they actually feel very well and are creative, but others see them as different from their normal selves. By definition, psychotic symptoms are never present in hypomanic episodes. Patients often do not recall hypomanic periods as times of illness, though others recognize the disturbance. Persons with bipolar I disorder may have hypomanic episodes as well as manic episodes.

In the course of classic bipolar disorder (so-called bipolar I disorder) manic, depressive, and/or mixed manic episodes may occur. (Mixed manic episodes refer to the simultaneous presence of both depressive and manic symptoms in the same episode within the same 24- to 48-hour period.) In bipolar I disorder, manic and depressive episodes are equally frequent. Mixed manic episodes occur in one-third of patients with bipolar I disorder, but these episodes represent only 6 percent of all episodes.

The mean age at onset of bipolar disorder is in the early 20s, and the decade for highest risk of onset is 20 to 29 years of age. The sexes do not differ in age at onset. Men are more likely to have initial manic episodes, while women are more likely to experience initial depressive episodes.

The mean duration of untreated manic episodes is 6 months; the mean duration of untreated major depressive episodes is approximately 8 to 10 months. The depressive episodes immediately precede and/or follow manic episodes in more than half of cases. The total number of episodes of illness experienced by a patient with bipolar disorder during a lifetime is variable. On the average, the episode risk is 0.3 to 0.4 episodes each year.

The time between episodes decreases with subsequent episodes. For individuals, the temporal pattern of episodes tends to repeat itself. Therefore, the future course of illness is best predicted by the individual's prior course. There is usually a full recovery between episodes, although roughly 25 percent have less than full recovery.

The morbidity and mortality associated with bipolar I disorder are high. Suicides, "accidental deaths," and intercurrent illnesses contribute to an excessive mortality rate. Ten to 15 percent of untreated patients commit suicide, which is 15 to 20 times the suicide rate in the general population (1 percent over a lifetime of 70 years). Women with bipolar disorder are much more likely than are men to attempt suicide; men are more likely to complete suicide. A large study found that prior to the availability of effective treatment, 23 percent of 4,341 patients with a manic episode admitted between 1912 and 1932 died in the hospital, 60 percent from "exhaustion" (Derby, 1933).

Patients with bipolar disorder experience considerable impairment in social and occupational functioning. While manic, they often need to be protected from the consequences of their poor judgment and overactivity, which often results in involuntary hospitalization. Over time, even with periods of remission, the chronicity and unpredictability of the disorder lead to secondary problems, such as joblessness, legal difficulties, divorce, and death by suicide, as well as medical morbidity.

Epidemiology

Bipolar I disorder affects men and women equally. It has a lifetime prevalence of 0.4 to 1.2 percent. The 1-month prevalence for bipolar disorder is 0.1 to 0.6 percent. Bipolar I disorder occurs at much higher rates in first-degree biologic relatives of persons with bipolar I disorder than in the general population. First-degree relatives of those with bipolar I disorder have a 12 percent chance of having the same disorder over their lifetimes. Another 12 percent have recurrent major depressive disorder, and roughly an additional 12 percent have dysthymic or other mood disorders (Goodwin and Jamison, 1990; Rush, Cain, Raese, et al., 1991).

Subtypes of Bipolar Disorder

Guideline: Psychoactive substances, such as cocaine and amphetamines; head trauma; certain neurologic diseases; endocrinopathies; and some other disorders can produce secondary manic and hypomanic episodes similar to those seen in primary bipolar disorder. In addition, in some patients with a family history of bipolar disorder, antidepressant medications can precipitate a manic or hypomanic episode. **(Strength of Evidence = A.)**

Case reports suggest that secondary bipolar disorders may be more effectively treated with anticonvulsants than with lithium. (For a review, see Goodwin and Jamison, 1990.)

A seasonal pattern has been found in a subset of patients who have bipolar II disorder (and in some, but fewer, cases of bipolar I disorder). The requisite feature is the occurrence of major depressive episodes in a seasonal pattern (typically, fall onset, spring offset). Perhaps 10 percent of patients with bipolar II disorder experience such seasonal episodes. It is unclear whether lithium is differentially effective in these patients and, indeed, whether the disorder becomes nonseasonal over time.

Some patients with bipolar I or II disorder exhibit a "rapid cycling" pattern, experiencing four or more mood episodes each year. Mood episodes include manic (or mixed manic-depressive), hypomanic, and major depressive episodes. The mood episodes may follow one another with or without intervening asymptomatic periods. According to nearly all studies, from 80 to 90 percent of those with a rapid cycling pattern are women.

Bipolar disorder begins with a rapid cycling pattern in some patients, while rapid cycling develops during the course of the illness for others. Rapid cycling may occur spontaneously or, in some cases, may be caused or maintained by tricyclic and possibly other antidepressant medications. Concurrent thyroid axis disease may also cause rapid cycling.

For those with a rapid cycling pattern, the prognosis is poorer than is that for others with bipolar disorder, as is the response to lithium. Treatment with high-dose thyroid hormone may be effective, even if there is no thyroid disease (three studies). Carbamazepine or other anticonvulsants may be particularly effective for both acute and prophylactic treatment of bipolar disorders with a rapid cycling pattern, according to at least four studies. (For a review of these studies, see Bauer and Whybrow, in press.)

Under DSM-III-R, bipolar disorder not otherwise specified is a residual category for disorders with manic or hypomanic features that do not meet the criteria for bipolar I disorder. This category presently includes what some investigators have called bipolar II disorder. Bipolar II disorder usually consists of multiple episodes of major depression interspersed with episodes of hypomania. If a manic episode develops, the diagnosis is changed to bipolar I disorder.

Bipolar II disorder has an earlier age of onset than does major depressive disorder and displays a relatively stable lifetime course, although 5 to 17 percent of bipolar II patients develop mania and convert their diagnoses to bipolar I disorder over 5 to 40 years. Compared with patients with major depressive disorder, those with bipolar II disorder have more frequent episodes, increased frequency of suicide attempts, greater propensity to commit suicide following hospital discharge, and higher familial incidence of suicide.

In addition to bipolar II disorder, the category of bipolar disorder not otherwise specified includes various bipolar conditions that are insufficiently clear-cut in their clinical presentation to be definitively considered either bipolar I or bipolar II disorders. Examples include single or recurrent hypomanic episodes without interepisode subsyndromal depressive symptoms (which, if continuous, would be diagnosed as cyclothymic disorder) and without major depressive episodes (which, if present, would lead to a bipolar II diagnosis). As a category, bipolar disorder not otherwise specified has not been subjected to randomized controlled treatment trials.

Cyclothymic Disorder

Guideline: Cyclothymic disorder features numerous, alternating hypomanic and mild depressive periods, lasting days to weeks and nearly continuous. There are few truly symptom-free periods. The symptoms fluctuate, but never reach the severity/duration criteria of major depressive or manic episodes. The course is chronic, often lasting years. **(Strength of Evidence = A.)**

A variety of clinical, family history, biologic, and treatment response characteristics suggest that this "subsyndromal" condition falls within the domain of mood disorders. A subgroup of those with symptoms of cyclothymic disorder do not have a significant family history of mood disorder or do not respond to lithium. However, various personality traits, temperaments, and disorders are associated with cyclothymic disorder. Socially problematic behaviors, such as marital discord, promiscuity, poor work performance, and substance abuse, are recognized as psychosocial complications of such subsyndromal mood disorders.

Accurate clinical assessment of these patients is difficult, especially when they manifest mood instability among their symptoms. For example, patients with borderline personality disorder frequently manifest a variety of mood symptoms, making it difficult to distinguish their illness from a mood disorder. On the other hand, many patients with borderline personality disorder may have unrecognized, and hence untreated, mood disorders. Given the likely clinical heterogeneity of cyclothymic disorder and its similarities to selected personality disorders, the clinician should carefully and comprehensively evaluate the conditions of patients with subtle, often more chronic, mood symptoms.

The onset of cyclothymic disorder is generally before age 30. During a 1- to 2-year followup of patients with cyclothymic disorder, 6 percent were reclassified as having bipolar I and 30 percent as having bipolar II disorder (Akiskal, Khani, and Scott-Strauss, 1979). However, this followup period is likely to be too short to assess the ultimate outcome of cyclothymic disorder. On the other hand, these findings indicate that a significant number of patients with cyclothymic disorder do go on to develop a formal bipolar condition.

The lifetime prevalence of cyclothymic disorder is 0.4 to 1.0 percent (Weissman and Myers, 1978). Cyclothymic disorder was diagnosed in 3 to 10 percent of a mental health clinic population (Akiskal, Khani, and Scott-Strauss, 1979).

Mood Disorders in Special Age Populations

Guideline: The clinical features of major depressive episodes are more similar than different in children, adolescents, adults, and geriatric patients; in men and women; and in all ethnic groups. **(Strength of Evidence = A.)**

Children and Adolescents

For children, it is important to differentiate between behavioral problems in those who are primarily depressed and depression in those who have a primary behavioral disorder. In the former, behavioral problems are less severe and follow the onset of depression. In the latter, the behavioral problems are more severe and chronic, and they precede the onset of depression.

In prepubertal children, boys and girls seem equally affected with major depressive disorder. After puberty, girls are two to three times more likely to be affected than are boys. The prevalence of clinical depression is reported to be 0.8 percent in preschool children, 2.0 percent in school-aged prepubertal children, and 4.5 percent in adolescents. In clinical samples, the prevalence of depression in children and adolescents is estimated to be 58 percent in educational clinics, 28 percent in outpatient psychiatric clinics, and 40 to 60 percent in psychiatric hospitals, compared to 7 percent in hospitalized pediatric patients (Weller and Weller, 1990). The offspring of one or more parents with a history of major depression are at markedly higher risk for major depression, including prepubertal onset illness (Weissman, Gershon, Kidd, et al., 1984).

The course of major depressive disorder in prepubertal children and adolescents has not yet been fully studied. On the other hand, one study found that up to 30 percent of adolescents hospitalized with severe major depressive disorder may go on to develop bipolar disorder over 3 to 8 years (Strober and Carlson, 1982). Early onset of major depression (first episode prior to age 20) is associated with a greater likelihood of a more recurrent pattern in adulthood (Giles, Jarrett, Biggs, et al., 1989; Grof, Angst, and Haines, 1974). To date, evidence suggests a problematic course for at least some patients with onset of major depressive disorder prior to age 20 particularly those with a positive family history.

Geriatric Patients

Depression in the elderly is a significant matter for primary care practitioners because of its prevalence and the complexity of the differential diagnosis. The clinical presentation of depression in the elderly is similar to that in other adults. However, it can be difficult to distinguish depression from dementia in those over age 65, as some symptoms of depression (e.g., disorientation, memory loss, and distractibility) may suggest dementia. Coexisting major depressive disorder and dementia are more common than is pseudodementia, and they tend to occur early in the course of Alzheimer's disease. The most representative prevalence estimate for elderly hospitalized patients with major depressive disorder is 6.0 to 11.5 percent.

The course of major depressive disorder or DNOS in the elderly is poorly studied. It is known from studies of adults that the co-occurrence of medical disorders is a poor prognostic factor in the longer term course of illness. The practitioner must consider the confounding problems created by co-morbid medical conditions in older patients with mood symptoms, as well as the concurrent use of selected prescription medications and occult alcohol or substance abuse (Table 6).

3. Guideline: Depression Co-Occurring with Other Psychiatric Conditions

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Guideline: Patients with depressive symptoms or in a major depressive episode may also be suffering from another nonmood psychiatric disorder. Treating one of the two disorders often clarifies the diagnostic picture. If the nonmood disorder is causing the mood symptoms, the nonmood disorder should usually be treated first. When formal major depressive syndrome is associated with another psychiatric condition, the decision of which to treat first rests on the nature of the nonmood disorder:

- If the nonmood disorder is an eating or obsessive-compulsive disorder (OCD), that is usually the initial treatment target. **(Strength of Evidence = A.)**
- If the nonmood disorder is generalized anxiety or personality disorder, the major depressive disorder is the first treatment target, because patients with either of these two nonmood conditions are not typically excluded from randomized controlled treatment trials of major depressive disorder. **(Strength of Evidence = B.)**
- If the associated nonmood condition is panic disorder, the practitioner must decide which is primary by considering the patient's personal or family history, as well as by gauging which of the two conditions is causing the greater impairment. **(Strength of Evidence = B.)**

Figure 4 provides an algorithm for deciding when to treat depression in the presence of a concurrent nonmood psychiatric condition.

Alcohol/Drug Abuse or Dependency

Guideline: Alcoholism and major depressive disorder are distinct clinical entities. They are not different expressions of the same underlying condition. While alcoholism is rarely a consequence of depression, many alcoholics do develop depressive symptoms or the full syndrome of major depression. **(Strength of Evidence = B.)**

The following conclusions are tentatively applicable to primary care settings since no data were found on depression in alcoholic patients seen in primary care settings or in alcoholics self-referred to self-help groups such as Alcoholics Anonymous. Most studies are of patients seen in psychiatric settings, who may be more likely to have other psychiatric problems in addition to alcoholism. Furthermore, the diagnostic criteria for alcoholism have become more inclusive over the last 15 years.

Nine studies have examined the extent to which patients with primary depression develop alcoholism (Deykin, Levy, and Wells, 1987; Hasin, Grant, and Endicott, 1988; Lewis, Helzer, Cloninger, et al., 1982; Powell, Read, Penick, et al., 1987; Robins, Gentry, Munoz, et al., 1977; Schuckit, 1983, 1985; Winokur, Reich, Rimmer, et al., 1970; Woodruff, Guze, Clayton, et al., 1973). Most revealed that alcoholism is rarely a consequence of depression; it occurs in less than 5 percent of patients. Overall, the prevalence of alcoholism in patients with primary depression is probably no higher than in the general population.

On the other hand, most studies have found that alcoholics do become depressed over time. Of the 24 studies reviewed, most found that between 10 and 30 percent of patients with alcoholism also suffered from depression at the time of evaluation (see Petty, 1992, and Depression Guideline Panel, forthcoming).

The ECA Study found the prevalence of alcoholism to be approximately 5 percent (Helzer and Pryzbeck, 1988). This study also found the odds ratio for the coexistence of depression and alcoholism to be 1.7. That is, persons in the community who met the diagnostic criteria for alcoholism were nearly twice as likely as those without alcoholism to meet the criteria for major depressive disorder.

Based on the ECA data reanalysis commissioned by the panel, 10 percent of those with major depressive disorder and a concurrent psychiatric condition (n = 31) had alcohol abuse as the second condition. For those with dysthymic disorder complicated by another psychiatric condition (n = 46), 30 percent abused alcohol. For those with DNOS and another psychiatric condition (n = 167), 67 percent abused alcohol. Thus, practitioners should always inquire about co-morbid alcohol and drug abuse or withdrawal in those with mood syndromes and symptoms.

The idea that depressed patients self-medicate with alcohol and, therefore, become alcoholic seems untrue for men, but may be true for some women. The few studies (Depression Guideline Panel, forthcoming) that focused specifically on women suggest that women alcoholics (perhaps as many as one in four) may be more likely to have had a preexisting mood disorder. They may also be more likely to develop depression as a consequence of prolonged heavy drinking, perhaps twice as often as their male alcoholic counterparts. Women reared by alcoholic fathers appear to be at greater risk for depression (Goodwin, Schulsinger, Knopf, et al., 1977).

Although family studies have provided strong evidence that alcoholism and major depressive disorder are independently transmitted, a family history of depression and alcoholism may be associated with a poorer prognosis for the alcoholism. However, there is no evidence for familial aggregation between alcoholism and depression. Adoption studies confirm the independent transmission of depression and alcoholism. Goodwin and colleagues (Goodwin, Schulsinger, Hermansen, et al., 1973; Goodwin, Schulsinger, Knopf, et al., 1977) found an increased incidence of alcoholism in both the adopted sons and daughters of alcohol abusers, but no increase in the incidence of depression. They also found that daughters of alcoholics reared by their biologic parents were more likely to experience depression as adults. This suggests that the environment can contribute to the development of depression, particularly in women. Two studies suggest an important additive interaction between alcoholism and depression (von Knorring, Bohman, von Knorring, et al., 1985; Zisook and Schuckit, 1987). It may be that the familial contribution of mood disorder to alcoholism indicates a poorer prognosis for the alcoholism.

The clinical course of depression with alcoholism has not been extensively studied. Available data from four studies suggest that most patients admitted to alcoholism treatment programs who also have clinical depression experience spontaneous remission of their depressive symptoms during the first 2 to 4 weeks of sobriety (Brown and Schuckit, 1988; Dorus, Kennedy, Gibbons, et al., 1987; Schuckit, 1983, in press; Willenbring, 1986). Depressive symptoms and syndromes seen in very recently detoxified alcoholics likely reflect the toxic effects of alcohol consumption.

The longer term course of illness for depression with alcoholism is more difficult to assess. Two studies that followed patients for more than a year determined that the existence of depression and alcoholism at initial assessment predicted a poorer outcome for the alcoholism, at least in men, 1 year later (Loosen, Dew, and Prange, 1990; Rounsaville, Dolinsky, Babor, et al., 1987). One 2-year followup study found no difference in alcoholic symptoms in patients with major depressive disorder plus alcoholism versus those with alcoholism alone at initial assessment (O'Sullivan, Rynne, Miller, et al., 1988). No lengthier followup studies are available.

For logistical reasons, the panel did not formally review the area of depression with drug abuse or dependency. However, depressive symptoms or major depressive episodes can occur concurrently with drug abuse. Intoxication with brain depressants is known to cause dysphoric mood and even suicidal ideation. Withdrawal from stimulants, such as cocaine or amphetamines, produces sadness, insomnia, apathy, and other depressive symptoms. The course and response to treatment of depressive disorders in patients who abuse drugs may differ from those of depressive disorders in patients who do not have substance dependency. In the ECA data reanalysis, drug abuse was the second condition in 19 percent of the 31 individuals with major depressive disorder and another psychiatric condition, in 30 percent of the 46 with dysthymic disorder and another condition, and in 26 percent of the 167 with DNOS and another psychiatric condition. Substance abuse is common in those with depressive syndromes and symptoms.

Guideline: It is recommended that depressed patients with concurrent substance abuse discontinue the abused substance and their condition be reevaluated 4 to 8 weeks later when they are in a drug-free state. If major

depressive disorder is still present, it is treated as a primary mood disorder. In certain clinical situations, however, earlier treatment of the depression may be needed. **(Strength of Evidence = B.)**

Anxiety Disorders

Guideline: Depressive symptoms or syndromes often accompany anxiety, panic, or phobic disorders. Furthermore, anxiety symptoms are frequent in major depressive episodes. The depression may precede the panic or anxiety disorder, or the anxiety disorder may be the forerunner of and part of the longitudinal course of a mood disorder. The presence of both anxiety/panic and a major depressive disorder results in a more severe disorder with greater impairment than does either disorder alone. When the patient complains of anxiety symptoms, major depressive symptoms should be elicited. **(Strength of Evidence = A.)**

Concurrent panic disorder is present in 10 to 20 percent of patients with major depressive disorder seen in ambulatory treatment settings. In possibly half of these, the panic disorder preceded the major depressive disorder. About 30 percent of outpatients with major depressive disorder may also have met the criteria for generalized anxiety disorder sometime during the course of their illness. In about half of these, the generalized anxiety disorder preceded the major depressive disorder.

Four community studies (Angst and Dobler-Mikola, 1985; Boyd, Burke, Gruenberg, et al., 1984; Hecht, von Zerssen, and Wittchen, 1990; Vollrath, Koch, and Angst, 1990) and one conducted in a primary care setting (Katon, Vitaliano, Russo, et al., 1986) have reported current co-morbidity of anxiety and mood disorders using DSM-III or DSM-III-R. In the ECA data reanalysis (Johnson and Weissman, unpublished manuscript), panic disorder was found in 19 percent of the 31 people with major depressive disorder and another psychiatric condition, in 7 percent of the 46 people with dysthymic disorder and another condition, and in 21 percent of the 167 people with DNOS and another psychiatric condition.

Most longitudinal studies of patients with anxiety disorders have found an increased incidence of depressive disorders over time. In one study, 91 percent of patients with agoraphobia developed a mood disorder over the 3-year followup (Munjack and Moss, 1981). Eighty-four percent of these patients had a family history of probable mood disorder. One study found that two-thirds of a group with agoraphobia or panic disorder developed major depressive disorder, 85 percent of which was of the melancholic type (Breier, Charney, and Heninger, 1985). Approximately half of those who developed major depressive disorder had experienced at least one prior major depressive episode that was separate from the onset of panic attacks. In a comparative family study of individuals with panic disorder with agoraphobia, limited phobic avoidance, or social phobia, a significantly higher percentage of agoraphobic patients had family histories of mood disorders compared to those with limited and social phobias (Munjack and Moss, 1981).

Available data are consistent with the idea that many persons with concurrent major depressive disorder and panic, social phobic, or generalized anxiety disorders may actually have only a single disorder that presents with both anxiety and depressive symptoms. The decision about which disorder to treat may in some cases be determined by one of the following:

- The patient's family history.
- The symptom complex that began first in this episode of illness.
- The symptom complex that is currently most incapacitating.

Given that followup studies of those with panic or other anxiety disorders reveal that many will subsequently develop major depressive disorder and that they often have had a prior major depressive disorder or have a family history of major depressive disorder, the depression is the appropriate main target of treatment in many cases. Sometimes, however, only a treatment trial and observation will answer this complex diagnostic question.

Whichever disorder is primary, the data are clear that the combination of panic and major depressive disorders results in a more severe disorder with greater impairment than does either disorder alone. For example, depressed

patients with associated panic attacks have a more severe depressive illness and are less likely to recover during a 2-year followup than are those without panic attacks (Coryell, Endicott, Andreasen, et al., 1988). The lifetime suicide attempt rate for persons with both panic and major depressive disorders is more than twice that of those with panic disorder, but without major depressive disorder (19.5 versus 7.0 per 100) (Johnson, Weissman, and Klerman, 1990). In two separate studies, panic disorder and primary major depressive disorder were each associated with high suicide rates (Coryell, Noyes, and Clancy, 1982, 1983). These data strongly suggest the importance of inquiring about, and even expecting to find, a concurrent mood disorder (especially major depressive disorder) in patients with anxiety complaints. If an individual presents with both conditions and if they are equally impairing, the practitioner should consider treatment with medications for which efficacy has been demonstrated for both conditions. These include MAOIs, SSRIs, TCAs, or in selected cases alprazolam.

Eating Disorders

Guideline: The practitioner is advised to ask about anorexia nervosa and bulimia nervosa in young women who present with any mood disorder, especially those with amenorrhea. If present, the eating disorder is the principal target of treatment. **(Strength of Evidence = B.)**

The eating disorders include anorexia nervosa and bulimia nervosa (American Psychiatric Association, 1987). Anorexia is a refusal to maintain body weight over a minimal normal weight, accompanied by intense fear of becoming fat, disturbance in body image, and amenorrhea. Anorexia occurs in 0.2 to 0.8 percent of adolescent girls in school cohort studies and in 0.05 to 0.1 percent of adults in community samples (Robins, Helzer, Weissman, et al., 1984).

Bulimia is characterized by recurrent episodes of rapid consumption of large amounts of food, accompanied by a feeling of loss of control; regular use of vomiting, laxatives, or other means to attempt to control weight; and overconcern with body shape and weight. The prevalence of bulimia is approximately 1 percent among adolescent and young adult women. Prevalence rates of 1.8 to 1.9 percent have been found in populations at family planning clinics, and rates ranging from 1 to 22 percent have been found in primary care settings.

No large studies of the prevalence of eating disorders among patients with major depressive disorder have been conducted. On the other hand, it is well established that one-third to one-half of patients with eating disorders (either anorexia or bulimia) suffer concurrently from a major depressive syndrome. Approximately 50 to 75 percent of eating disorder patients have a lifetime history of major depressive disorder. Dysthymic disorder and DNOS occur less frequently among patients with eating disorders by most reports.

Assuming a 1 percent prevalence of eating disorders and an 8 percent prevalence of major depressive disorder, and assuming that one-half of eating disorder patients also suffer from concurrent major depressive disorder, the likelihood of an eating disorder may be as high as 1/16 (6 percent) in women between the ages of 15 and 35 who suffer from a major depressive disorder.

Patients with undernutrition from various etiologies often exhibit depressive symptoms, including depressed mood, irritability, poor concentration, indecisiveness, loss of sexual interest, and sleep disturbance, all of which usually improve with weight gain. Thus, when significant depressive symptoms are found with anorexia nervosa, treatment is first aimed at the eating disorder. If mood symptoms persist after the malnourished state has been reversed, treatment is as for a primary mood disorder. A number of studies indicate that some antidepressant medications (e.g., imipramine, desipramine, fluoxetine, MAOIs) and formal cognitive behavioral psychotherapies may help treat the bulimia with or without associated depressive symptoms. (For examples, see Hughes, Wells, Cunningham, et al., 1986; Mitchell and Groat, 1984; Pope, Hudson, Jonas, et al., 1983; Walsh, Stewart, Wright, et al., 1982.) Such treatments, if successful, usually result in remission of the depressive symptoms.

Obsessive-Compulsive Disorders

Guideline: For those depressed patients whose disorder has some obsessive features, the mood disorder is the initial focus of treatment. If full-blown OCD is present with depressive symptoms or manic-depressive disorder, the OCD is usually the initial objective of treatment. Evidence from OCD medication treatment trials suggests that, if the OCD is treated successfully, the depressive symptoms usually abate. **(Strength of Evidence = A.)**

The ECA survey revealed some overlap between OCD, major depressive disorder, and schizophrenic disorder. Most studies agree that the lifetime occurrence of depressive symptoms is high (80 to 100 percent) among OCD patients, even though only about 10 to 30 percent of them meet the criteria for major depressive disorder at the time of admission to study. The major depressive disorder usually follows the onset of OCD, while schizophreniform symptoms are equally likely to precede or to follow OCD onset. A review of 13 followup studies found that OCD patients were at increased risk for major depressive disorder, but not for schizophrenia (Goodwin and Jamison, 1990). Whether currently or ever depressed, OCD patients are likely to have a family history of depression.

The ECA data reanalysis showed that OCD is relatively common among those with a mood disorder complicated by the presence of another psychiatric condition (Johnson and Weissman, unpublished manuscript). Specifically, OCD was found in 35 percent of the 31 subjects with major depressive disorder, in 15 percent of the 46 with dysthymic disorder, and in 40 percent of the 167 with DNOS, when the mood disorder was associated with another psychiatric condition.

The practitioner must differentiate severe depression, which may present with obsessive features, from true OCD. Severely depressed patients have recurrent ruminations, but rarely have compulsions. The content of their ruminations is usually consistent with a negative sad mood (e.g., guilty preoccupations). These patients often do not meet the formal criteria for OCD and often have had prior episodes of severe depression. The onset of these obsessive symptoms in the severely depressed occurs at the same time as the onset of the major depressive episode.

Somatization Disorder

Guideline: Somatization is defined as the presentation of somatic symptoms by patients with underlying psychiatric illness or psychosocial distress. These somatic symptoms have no, or insufficient, underlying organic cause. While most depressed patients have medically unexplained somatic complaints, they are rarely of sufficient intensity or frequency to meet the threshold for somatization disorder. **(Strength of Evidence = A.)**

Somatization may well be the main reason for the misdiagnosis of mental illness by primary care physicians (Bridges and Goldberg, 1985). In primary care settings, many depressed and nondepressed patients present with medically unexplained symptoms. Most patients with such complaints do not meet the formal criteria for somatization disorder, which in DSM-III-R require the presence of 13 or more medically unexplained symptoms. Most patients with diffuse unexplained somatic symptoms in primary care and community samples either have a treatable psychiatric illness (e.g., anxiety or depressive disorders) or are responding to stressful life events. Accurate differential diagnosis and treatment of the acute psychiatric illness often decrease the tendency toward somatization.

Twelve studies of a total of 976 primary care and medical specialty (e.g., gynecology) patients with clinically significant depressive symptoms revealed that 30 to 87 percent also had clinically significant pain complaints (Fishbain, Goldberg, Meagher, et al., 1986; Haley, Turner, and Romano, 1985; Katon, 1988; Katon, Ries, and Kleinman, 1984; Kramlinger, Swanson, and Maruta, 1983; Large, 1986; Lindsay and Wyckoff, 1981; Maruta, Vatterott, and McHardy, 1989; Schaffer, Donlon, and Bittle, 1980; Turner and Romano, 1984; Walker and Greene, 1989; Walker, Katon, Harrop-Griffiths, et al., 1988). A highly significant 30 to 50 percent met the formal

criteria for major depressive disorder. Two additional studies found that 50 to 70 percent of primary care patients with psychiatric illness (mainly mood disorders) presented with somatic complaints (Katon, 1987; Katon, Kleinman, and Rosen, 1982).

Conversely, pain symptoms occurred in approximately 60 percent of patients with major depressive disorder in three studies with 403 primary care and medical specialty patients, in which pain was documented by self-report (Lindsay and Wyckoff, 1981; Magni, Schifano, and de Leo, 1985; von Knorring, Perris, Eisemann, et al., 1983). Major depressive disorder patients had significantly more symptoms on a medical review of symptoms, even when the investigators controlled for chronic medical illness. In a study using a 1,000-patient sample from a health maintenance organization, patients with one pain complaint were no more depressed than were controls (Dworkin, von Korff, and LeResche, 1990). However, patients with two pain complaints were six times more likely, and patients with three pain complaints were eight times more likely, to have a clinical depression. The Medical Outcomes Study also showed that patients with major depressive disorder perceived their general health as poorer; had more limitations in physical, social, and vocational functioning; and had more pain complaints than did persons with chronic medical illnesses (Wells, Stewart, Hays, et al., 1989).

Guideline: The practitioner is advised to have a high index of suspicion for major depressive or other mood disorders if patients present with two or more unexplained pain complaints. A formal diagnostic evaluation for mood disorders is recommended. **(Strength of Evidence = B.)**

The majority of patients with major depressive disorder, DNOS, or dysthymic disorder have some pain symptoms. The most common complaints in such patients are joint pain, headaches, backaches, and abdominal pain. Treatment of major depressive disorder with somatic complaints usually results in complete relief of the pain complaints.

Personality Disorders

Guideline: Personality disorders are not uncommon among mood-disordered patients. The presence of a personality disorder does not exclude diagnosis of a mood disorder, if present. When both a major depressive and a personality disorder are present, more frequent and longer major depressive episodes, as well as poorer interepisode recovery (if untreated), may be anticipated. For some with major depression, symptoms that initially appear to be maladaptive personality traits remit once the depressive disorder improves. **(Strength of Evidence = B.)**

Studies of depressed patients using structured interviews indicate prevalences of personality disorders ranging from 35 percent in psychiatric outpatients to 72 percent in psychiatric inpatients. Most studies report rates of 45 to 65 percent. However, most of these studies were conducted in specialized research centers, which may attract a greater proportion of mood-disordered patients who also have personality disorders.

The DSM-III-R personality disorders are grouped into three clusters:

- Cluster A (odd/eccentric) paranoid, schizoid, and schizotypal disorders.
- Cluster B (dramatic/emotional/erratic) antisocial, borderline, histrionic, and narcissistic disorders.
- Cluster C (anxious/fearful) avoidant, dependent, obsessive-compulsive, and passive-aggressive disorders.

The presence of these personality disorders may negatively affect the natural course and treatment response of mood disorders. Five studies have examined patients with concurrent major depressive disorder and a personality disorder (Black, Bell, Hulbert, et al., 1988; Charney, Nelson, and Quinlan, 1981; Ionescu and Popescu, 1989; Pfohl, Stangl, and Zimmerman, 1984; Shea, Glass, Pilkonis, et al., 1987). Those with personality diagnoses had an earlier age of onset for their first depressive episode, more severe depressive symptoms, more frequent episodes, longer depressive episodes, poorer short-term recovery with both antidepressant medications and psychotherapy, and more residual symptomatology at later followup. A concurrent personality disorder diagnosis is associated with a more complicated, disturbed social history, especially in patients with Cluster A or B

personality disorders. When depression is complicated by personality disorder, most studies find increased rates of suicide attempts and self-harm.

The generally negative effect of personality disorders on the outcome of depression seems largely accounted for by Cluster B, or borderline personality disorder specifically. Depressed patients with co-morbid borderline personality disorder had poorer social outcomes and higher levels of residual symptomatology at both 4- and 7-year followups (Pope, Jonas, Hudson, et al., 1983). Borderline personality disorder seems highly prevalent among depressed psychiatric patients; a sample drawn from a general psychiatric population yielded an estimate of 6 percent. The estimated community prevalence of borderline personality disorder is 0.2 percent (Weissman and Myers, 1980). One study of people who were not psychiatric patients found a 1.6 percent prevalence of borderline personality disorder, but this population included a large sample of first-degree relatives of psychiatric inpatients (Zimmerman and Coryell, 1989). There are insufficient studies of the incidence of personality disorders in primary care settings to make prevalence estimates.

Grief and Adjustment Reactions

Guideline: DSM-III-R indicates that, if depressive symptoms begin within 2 to 3 weeks of a loved one's death, the diagnosis is uncomplicated bereavement, which is not viewed as a disorder but as a normal, relatively benign state that resolves spontaneously without treatment. While uncomplicated bereavement and major depressive episodes share many symptoms, active suicidal thoughts, psychotic symptoms, and profound guilt are rare in bereavement. However, if a major depressive episode is still present 2 months following the loss, the episode is likely to be prolonged and associated with substantial morbidity. Clinically, the diagnosis of major depressive disorder may be made during the period of "grief" in those who meet the criteria for a major depressive episode 2 months following the loss. **(Strength of Evidence = A.)**

Grief reactions are equally common in women and men. Over the course of the first year of bereavement, Clayton (1974) found that 35 percent of 109 widows and widowers met the criteria for a major depressive episode at 1 month, 25 percent at 7 months, 17 percent at 13 months, and 46 percent were depressed some time during the first year following the loss of a spouse.

Zisook and Shuchter (1991) studied 350 widows and widowers 2 and 13 months after their spouses' deaths. Twenty-four percent met the DSM-III-R criteria for a major depressive episode at 2 months. Since the deaths had occurred only recently, the condition of these subjects was diagnosed as uncomplicated bereavement rather than major depressive disorder. Those meeting the criteria for major depressive disorder early in the period of grief were more likely to have personal or family histories of major depressive episodes (not in response to the death of a loved one), current treatment with antidepressant medications, suicidal ideation, poor health, and poor current job satisfaction. Most important, they were likely to be in a major depressive episode 1 year following the loss. Given the anticipated prolonged suffering and disability, it is logical to consider treating these patients for the major depressive disorder, though randomized controlled trials of any treatment are lacking in this population.

A distinct, but poorly studied, segment of primary care patients present serious mood symptoms thought to require clinical management, though they do not fulfill the criteria for major depressive or dysthymic disorders. DSM-III-R classifies such "subthreshold" pathology as either DNOS or an adjustment disorder with depressed mood. Little is known of the presenting symptoms, clinical course, or outcome of an adjustment disorder with depressed mood. However, the clinical utility of the diagnosis is that it allows practitioners to identify mildly distressed patients, some of whom may need followup to determine whether the symptoms remit or whether they evolve into a formal mood syndrome. If such patients develop a major depressive or dysthymic disorder, treatment should be as for the primary mood disorder. There are no randomized controlled trials of treatment for adjustment disorder with depressed mood, but it is logical to consider treatment with psychotherapy or medication for those with substantial pain, suffering, incapacity, or chronicity.

4. Guideline: Depression Co-Occurring with Other General Medical Disorders

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Guideline: Many general medical conditions are risk factors for major depression. Major depressive disorder, when present, should be viewed as an independent condition and specifically treated. Treatment may include (a) optimizing the treatment of the general medical disorder and/or (b) providing specific treatment for the depression. **(Strength of Evidence = A.)**

Clinically significant depressive symptoms are detectable in approximately 12 to 36 percent of patients with another nonpsychiatric, general medical condition. Rates in patients with specific medical disorders may be even higher. These figures far exceed the approximate 4 percent prevalence of diagnosable depression in large community samples. On the other hand, most patients with a general medical condition do not have a mood disorder. Therefore, the mood disorder, when present, should be viewed as an independent condition (perhaps precipitated by the biologic or psychological vulnerability of the individual) that should be specifically treated.

Since every co-occurrence of major depression and every general medical disorder cannot be covered in this guideline, the panel has chosen several specific examples to outline a general approach to the diagnosis of depression in patients with other medical disorders and to illustrate the primary treatment principles. Somatic symptoms are part of the syndrome of major depression, according to DSM-III-R. Many other medical disorders also cause some criterion symptoms of depression, such as weight loss, sleep disturbances, and low energy. These disorders include endocrinopathies, such as diabetes; pituitary, adrenal, or thyroid disorders; certain malignancies; some infections; some neurologic disorders; collagen disorders; cardiovascular disease; and vitamin/mineral deficiency and/or excess states. The clinician can substitute cognitive and emotional symptoms, such as fearful or depressed appearance, social withdrawal or decreased talkativeness, brooding, self-pity, or pessimism and unreactive mood for the standard DSM-III-R somatic symptoms when there is concern that the suspected concurrent medical disorder may be causing the criterion somatic symptoms of depression (Endicott, 1984; Kathol, Mutgi, Williams, et al., 1990).

Once the syndrome of depression has been identified in patients with a general medical illness, the differential causes of depressive symptomatology must be reviewed to make sure the appropriate treatment is administered. The risk factors associated with primary mood disorders should be reviewed to determine whether the patient's condition fits a typical picture of primary mood disorder or whether alternative causes can explain the depressive syndrome or symptoms.

When depression and another medical condition occur together, there are several logically plausible explanations:

- The general medical disorder biologically causes depression; for example, hypothyroidism may cause depressive symptoms.
- The general medical disorder triggers the onset of the depression in those who are genetically vulnerable to depressive disorders; for example, Cushing's disease may precipitate a major depressive episode.
- The general medical disorder psychologically causes the depression; for example, a patient with cancer may become clinically depressed as a psychological reaction to the prognosis, pain, and incapacity.
- The general medical disorder and the mood disorder are not causally related.

It is important for the practitioner to differentiate among these options for patients with depressive and other psychiatric or medical conditions. In the first two instances, treatment aims first at the general medical disorder. If the depression persists, it is treated once the general medical disorder is stabilized. In the third case, the general medical disorder is treated while counseling, education, support, and medication are used to treat the depression. In the last instance, specific treatment is initiated for both disorders(Figure 5; see also Figure 2) While one uncontrolled study (Hall, Gardner, Stickney, et al., 1980) suggests that depressive symptoms resolve with treatment of the general medical illness alone in more than 60 percent of patients with depression associated with treatable general medical disorders, the prognosis for such patients remains ill-defined.

Once it has been established that the depressive symptoms are due to a primary mood disorder, treatment is aimed at the mood disorder. If, on the other hand, the depression is caused by the general medical condition, several additional steps are necessary. First, treatment of the general medical illness should be optimized. Thereafter, sufficient time should be allowed for this treatment to alter the course of the mood symptoms. If the patient's mood disorder or symptoms do not respond to treatment for the general medical illness, or if the patient has an illness, such as cancer or diabetes, that is under optimal control but is not curable, the depression should be treated as a primary mood disorder.

Stroke

Guideline: Depression following stroke is not fully explained as a psychological response to the associated impairment. There appear to be subgroups of depressed post-stroke patients whose depression is causally related to the injury, possibly including its strategic location in the brain (left dorsal lateral frontal cortex or left basal ganglia);a family history of depression; premorbid subcortical atrophy; and premorbid or ongoing social factors. When a patient with a recent stroke meets the criteria for a major depressive episode, organic (secondary) mood disorder is diagnosed. **(Strength of Evidence = B.)**

The association between cerebral infarction and depression has long been recognized. However, systematic studies (Depression Guideline Panel, forthcoming) have found only a weak relationship between depression severity and physical/cognitive impairment following stroke. Case reports (Ross and Rush, 1981) indicate that post-stroke patients who are also depressed, especially those with major depressive disorder, are less compliant with treatment, are more irritable and demanding, and have an apparent personality change.

Six prospective evaluations of depressive symptoms/syndromes using various criteria revealed the prevalence of major depressive disorder to be between 10 and 27 percent in post-stroke patients, with an additional 15 to 40 percent showing less severe forms of illness within 2 months of the stroke (Eastwood, Rifat, Nobbs, et al., 1989; Ebrahim, Barer, and Nouri, 1987; House, Dennis, Magridge, et al., 1991; Morris, Robinson, and Raphael, 1990; Robinson, Starr, Kubos, et al., 1983; Wade, Leigh-Smith, and Heuer, 1987). In the four studies using DSM-III criteria (total n = 378), the same approximate prevalence rates for major depressive disorder and DNOS were found as in those studies not using such criteria (Eastwood, Rifat, Nobbs, et al., 1989; House, Dennis, Magridge, et al., 1991; Morris, Robinson, and Raphael, 1990; Robinson, Starr, Kubos, et al., 1983).

Two studies have prospectively examined the longitudinal course of depression following stroke (Morris, Robinson, and Raphael, 1990; Robinson, Bolduc, and Price, 1987). Both found the mean duration of major depressive disorder to be just under 1 year. The course of DNOS is more variable and may be either short (2 to 3 months) or prolonged (more than 2 years).

Dementia

Guideline: In patients presenting with signs of both depression and dementia, if symptoms suggestive of dementia are significantly more prominent than depressive symptoms, the diagnosis is dementia with depressive symptoms. If symptoms suggesting a major depressive episode are at least as prominent as those consistent with dementia, the diagnosis is major depressive disorder. In selecting treatment, it is prudent to assume that symptoms suggesting dementia may be manifestations of the depressive disorder until proven otherwise. When the depressive episode ends, so should the symptoms suggestive of dementia. If they do not, the diagnosis of early dementia should be entertained. **(Strength of Evidence = B.)**

Distinguishing depressive disorders from early dementing disorders (from known or unknown causes) is a complex clinical problem. Apathy, impaired concentration, or memory loss may occur in primary major depressive episodes in the elderly, as well as early in the course of dementing disorders with or without depression. The term pseudodementia refers to the clinical presentation of cognitive impairment due to

depression in the elderly. The co-occurrence of depression and dementia is by far the more frequent clinical problem. In some patients with symptoms of both depression and dementia, a personal or family history of depression suggests a depressive condition as the primary diagnosis.

If treatment for the depression succeeds and is associated with disappearance of the "dementing" symptoms, the appropriate diagnosis is major depressive disorder without dementia. If the symptoms of dementia persist, the appropriate diagnosis is dementia and major depressive disorder.

Guideline: Depressive symptoms are associated with both cortical and subcortical dementing disorders. **(Strength of Evidence = A.)**

Parkinson's disease is associated with mild dementia in approximately 38 percent of patients, while 46 percent suffer severe dementia in the end stages of the disease. Approximately 50 percent of Parkinson's patients with dementing symptoms have major depressive disorder sometime during the course of the illness. Unlike primary degenerative dementia, Parkinson's dementia is considered a subcortical dementia; it is associated with physiologic changes in the subcortical regions (substantia nigra and globus pallidus). In those with subcortical dementia (e.g., patients with Parkinson's or Huntington's disease), cognitive symptoms appear to improve with improvement of mood, so assessment for and treatment of the depression may be particularly helpful to these patients (Blazer, 1993).

Guideline: Depression is often seen in patients with and/or antecedent to primary dementia. **(Strength of Evidence = A.)**

Approximately 30 to 40 percent of Alzheimer's disease patients demonstrate formal depressive mood syndromes and/or psychotic symptoms sometime during their illness. The exact relationship between the two disorders is not clear. The earlier or concurrent presence of depression does not alter either the progression of dementia per se or its neuropsychological features. Some suggest that depression may occur during the early stages of dementia and that treatment of the depression may reduce some of the cognitive difficulties. However, long-term followup shows that many older patients presenting with both depression and cognitive difficulties go on to develop primary degenerative dementia without depressive features (Blazer, 1993).

Diabetes

Guideline: The symptomatic expression of depression in patients with diabetes is analogous to that in patients without diabetes. Given the impact of depression on the management of diabetes and the fact that most diabetic patients do not develop major depression, the practitioner is advised to screen, assess fully, and treat major depression when present in these patients. **(Strength of Evidence = A.)**

A variety of metabolic and endocrinologic diseases (e.g., vitamin B12 deficiency; thyroid, parathyroid, and renal diseases) are associated with depressive symptoms/syndromes. The following discussion of diabetes illustrates one such condition.

Numerous recent studies that have estimated the prevalence of depression in treated samples of diabetic adults suggest that major depressive syndrome is approximately three times more common in patients with diabetes than in the general population (Biglan, Toobert, Farmer, et al., unpublished manuscript; Fris and Nanjundappa, 1986; Geringer, Perlmuter, Stern, et al., 1986; Lustman, Griffith, Clouse, et al., 1986; Montague, Eaton, Larson, et al., 1990; Popkin, Callies, Lentz, et al., 1988; Robinson, Fuller, and Edmeades, 1988; Slawson, Flynn, and Kollar, 1963; Wing, Marcus, Blair, et al., 1990). The prevalence of major depression in patients with insulin-dependent diabetes mellitus (IDDM) is similar to that in patients with non-insulin-dependent diabetes mellitus (NIDDM).

General population surveys (i.e., nontreated samples) indicate that the prevalence of depression is elevated in persons with diabetes, compared to those without a chronic medical condition. The sex-and age-adjusted prevalence of lifetime depression was significantly higher in patients with diabetes than in patients without a

chronic illness (14.4 and 6.9 percent, respectively) (Wells, Golding, and Burnam, 1989). The excess prevalence of depression in diabetics suggests either an etiologic relationship or a higher detection rate secondary to increased contact with the health care system in patients with co-morbid diabetes and depression. The mean age of onset of depression was 22.1 years in patients with IDDM and 28.6 years in patients with NIDDM. In patients with NIDDM, the onset of depression occurred significantly earlier than did the onset of diabetes (Lustman, Griffith, and Clouse, 1988). A family history of depression was also significantly more common in diabetic patients with depression (35 percent) than in those without depression (3 percent). Depression in association with diabetes is a female-preponderant illness, as it is in general.

Depressions are recognized and treated in fewer than one-third of diabetic patients. Diabetes per se is not associated with sufficient depressive symptoms to impair clinical recognition of depression in diabetes. The symptom of weight loss in diabetes is not specific to depression and should not be used to diagnose the presence of depression in diabetic patients.

Only one systematic followup study of depressed diabetic patients is available (Lustman, Griffith, and Clouse, 1988). Eighteen (64 percent) patients had been depressed within the previous 12 months, and 12 met the criteria for a current major depressive episode at the time of reevaluation. By contrast, only 10 percent of a comparison group of diabetic patients without a mood disorder at index evaluation had developed depression by the time of followup. This significant difference suggests that the risk of developing depression is restricted to a predisposed group and is less related to diabetes per se. These modest data suggest that the natural course of major depression in diabetes is chronic and severe, perhaps even more so than in those with major depressive disorder without other general medical illnesses. No randomized controlled studies of the efficacy of pharmacotherapy and/or psychotherapy have been performed in depressed diabetic patients.

Depression in diabetes is associated with poor glucose regulation, probably because of poor adherence. Since poor glucose regulation is associated with increased complications, attention to treatment of depressive symptoms is particularly relevant in management of patients with diabetes. Even without empirical studies, logic argues for treating the major depression in diabetics as a primary mood disorder, once the diabetes is optimally controlled by routine means.

Coronary Artery Disease

Guideline: The relationship between depression and increased morbidity and mortality is well documented in both post-myocardial infarction patients and in coronary artery disease patients without myocardial infarction. Given the higher morbidity and the fact that most of these patients do not develop a major depression, the practitioner is advised to screen, assess fully, and treat major depression when present in these patient groups. **(Strength of Evidence = A.)**

The prevalence of various forms of depression in patients who have had a myocardial infarction is estimated at 40 to 65 percent. High prevalence rates have also been found in patients undergoing coronary artery or heart transplant surgery. The prevalence of minor and major depressive disorders combined has been reported to be as high as 40 percent in patients who have coronary heart disease and 45 percent in those who recently experienced a myocardial infarction (Schleifer, Macari-Hinson, Coyle, et al., 1989). The point prevalence of major depressive disorder is 18 to 25 percent for those with a recent myocardial infarction and 18 to 20 percent in those without a history of myocardial infarction, but with angiographically proven coronary artery disease. Most studies have found that depression in these patients is seldom diagnosed or treated.

The ECA survey ascertained that, over 15 months, patients aged 55 and older with mood disorders had a mortality rate four times higher than expected, and that 63 percent of these deaths were from coronary heart disease or stroke. Other studies have also shown higher myocardial infarction rates in depressed patients. Unfortunately, risk factors for coronary artery disease, such as smoking, were not controlled in these studies.

Carney, Rich, Freedland, and colleagues (1988) found that major depressive disorder leads to equal and additive disability in patients with coronary artery disease, perhaps resulting from the effects of depression on

amplification of symptoms. Several studies have also linked depression with poor adherence to cardiac treatment regimens (Blumenthal, Williams, Wallace, et al., 1982; Guiry, Conroy, Hickey, et al., 1987). Kellet (1990) speculated that depression may be responsible for the poor compliance and, consequently, for the worse outcomes among noncompliant patients.

Some evidence indicates that major depressive disorder generally runs a chronic course during the first 12 months after an acute infarction. Patients who have never experienced a psychiatric disorder before their myocardial infarction have a shorter duration of symptoms. Major, but not minor, depressions follow a chronic course, suggesting that "minor" forms of depression (officially DNOS) may be better understood as transitory adjustment reactions to the medical illness (Schleifer, Macari-Hinson, Coyle, et al., 1989).

Patients with moderate to severe depression during the weeks following the myocardial infarction are more likely than are nondepressed controls to experience social problems over the first year of recovery. They are also slower to return to work and report more stress than do their nondepressed counterparts. Whether their ultimate life expectancy is shorter is not yet clear.

Cancer

Guideline: It is essential to separate the symptoms of cancer or its treatment from those of a depressive disorder. A history and clinical interview are needed for a definitive diagnosis. The symptoms of persistent dysphoria, feelings of helplessness and worthlessness, loss of self-esteem, and wishes to die are the most reliable indicators of clinical depression in patients with cancer. Since major depression occurs in approximately 25 percent of patients with cancer, it should be independently diagnosed and treated. **(Strength of Evidence = B.)**

The diagnosis of cancer can be a catastrophic event to which many individuals initially react with shock and denial. This early reaction is often followed by emotional turmoil accompanied by anxiety, depressed mood, poor concentration, and cessation of daily activities. This response is normal. Dysphoria and sadness are parts of this normal reaction. These symptoms usually abate within a week or two with support from caregivers, family, and friends (Massie and Holland, 1990). Patients return to normal adaptation over the ensuing weeks to months.

Physicians must be able to differentiate between this normal reaction and a psychiatric disorder. Considerable evidence indicates that, for patients with cancer, a depressive disorder leads to greater distress; decreased physical, social, and occupational functioning; and decreased ability to adhere to medical recommendations. Therefore, diagnosis and effective management of the depressive disorder in patients with cancer are potentially very important.

Several risk factors predispose cancer patients to develop depressive disorders:

- Social isolation.
- Recent losses.
- A tendency to pessimism.
- Socioeconomic pressures.
- A history of mood disorder.
- Alcohol or substance abuse.
- Previous suicide attempt(s).
- Poorly controlled pain.

The depressed patient with cancer must be assessed for suicidal risk. Suicidal risk factors include:

- A prior psychiatric diagnosis (especially depression).
- Increasing age.
- Family history of suicide.
- Poor social support.

- Delirium.
- Advanced disease.
- Disfiguring disease or surgery.
- Substance abuse.
- Poorly controlled pain.

Many drugs used to treat cancer are associated with depressed mood as a side effect (Lesko, Massie, and Holland, 1987). The practitioner is also advised to consider other concurrent medical conditions, medications, and uncontrolled pain, all of which can contribute to depressed mood, especially in the elderly.

The prevalence of clinical depression in cancer patients ranges from 5 to 50 percent. The most systematic study of psychiatric disorders in ambulatory patients with cancer (200 patients) found that 53 percent were coping well and did not have a formal DSM-III diagnosis (American Psychiatric Association, 1980). Of the remaining 47 percent, 68 percent had an adjustment disorder; 13 percent had major depressive, dysthymic, or bipolar disorder; and 19 percent had organic mental, personality, or anxiety disorders. Adjustment disorders with depressed mood and major mood disorders were the most common psychiatric disorders identified in cancer patients.

The highest rates of clinical depression are in those with advanced cancer and with a greater level of disability and discomfort. One study found that 77 percent of bedridden patients met criteria for major depressive syndrome, compared to only 23 percent of functionally independent patients (Bukberg, Penman, and Holland, 1984).

Most studies suggest that 20 to 25 percent of cancer patients suffer major depression at some point during their illness. These percentages are remarkably similar to the rates of depression associated with other medical illnesses and a similar level of physical functioning. The finding that patients with cancer do not evidence a greater rate of major depression than do those with other medical disorders invalidates the common, but incorrect, assumption that persons with cancer should be depressed an assumption that contributes to underdiagnosis and undertreatment of these depressions.

Chronic Fatigue Syndrome

Guideline: Nearly all depressed patients complain of fatigue and low energy. This symptom is associated with a 46 to 75 percent lifetime rate of major depressive disorder. Complaints of chronic fatigue must be differentiated from the formal chronic fatigue syndrome. **(Strength of Evidence = B.)**

Only a small minority of patients with complaints of chronic fatigue meet the Centers for Disease Control (CDC) criteria for chronic fatigue syndrome. When the patient meets criteria for major depression, dysthymia, or other formal mood syndromes, the mood syndrome is diagnosed. The complaint of chronic fatigue per se is insufficient for the diagnosis of chronic fatigue syndrome. The symptom of chronic fatigue (not the syndrome) is the seventh most common complaint among adult patients in primary care settings and may be a significant problem in as many as 20 to 25 percent of these patients. Studies of patients with chronic fatigue symptoms reveal lifetime rates of psychiatric disorders in the 50 to 77 percent range, based on structured psychiatric interviews. In all studies, major depressive disorder was the most commonly reported illness (lifetime rates ranging from 46 to 75 percent). These studies also found that various anxiety disorders and somatization disorder occurred in 15 to 40 percent of patients with chronic fatigue symptoms (Hickie, Lloyd, Wakefield, et al., 1990; Kroenke, Wood, Mangelsdorff, et al., 1988; Kruesi, Dale, and Straus, 1989; Manu, Lane, and Matthews, 1988; Manu, Matthews, and Lane, 1988).

Most studies that examined the temporal sequence of chronic fatigue symptoms found a 50 to 90 percent onset rate of psychiatric illness (most commonly, major depressive disorder) prior to the onset of chronic fatigue symptoms (Kruesi, Dale, and Straus, 1989; Manu, Matthews, and Lane, 1988).

While the central feature of chronic fatigue syndrome is persistent, excessive fatiguability, it must be

accompanied by various other somatic and psychological symptoms, including aching muscles and joints, headache, sore throat, painful lymph nodes, muscle weakness, sleep disturbance, mental fatigue, difficulty in concentrating, emotional lability, and sadness. In chronic fatigue syndrome, the somatic and fatigue complaints are out of proportion to physical and laboratory findings. According to the CDC criteria, the presence of a diagnosable formal psychiatric disorder, such as major depressive or dysthymic disorder, excludes the diagnosis of chronic fatigue syndrome. That is, patients who present with the formal symptomatic CDC criteria for chronic fatigue syndrome and who also meet the criteria for a formal mood disorder are treated for the mood disorder. Whether this mood disorder is etiologically connected to the chronic fatigue syndrome or whether it is an independent illness is unclear.

Fibromyalgia

Guideline: As with other medical conditions, patients with fibromyalgia may or may not have clinical depression. If present, it should be diagnosed and treated as a separate entity. **(Strength of Evidence = B.)**

Fibromyalgia (fibrositis) is a syndrome of diffuse, aching, musculoskeletal pain associated with chronic insomnia, daytime tiredness, morning stiffness, dysesthesia in the hands, and symptoms of irritable bowel type. The American College of Rheumatology has published the currently accepted criteria for the diagnosis of fibromyalgia (Wolfe, Smythe, Yunus, et al., 1990).

Two studies have compared fibromyalgia and rheumatoid arthritis patients in structured psychiatric interviews. In one, patients with fibromyalgia had significantly higher rates of lifetime major depressive disorder than did rheumatoid arthritis patients (71 versus 14 percent), and they had significantly more first-degree relatives with mood and anxiety disorders (Hudson, Hudson, Pliner, et al., 1985). The second study also found higher rates of mood disorders in patients with fibromyalgia than in those with rheumatoid arthritis (20 versus 8.7 percent). Statistical significance was not attained, probably because of the small sample size (Alfici, Sigal, and Landau, 1989).

5. Guideline: Depression Associated with Medications

Various medications have long been reported to cause or to be associated with mood symptoms or formal disorders as side effects. The development of depression in some patients taking reserpine formed one of the bases for the biologic theories of depression. Most of the evidence rests on case reports of medications "causing" mood symptoms. Table 7 lists those agents reported to have been associated with depression in some patients.

It is essential to recognize that idiosyncratic reactions to medications do occur. Even without data to suggest a causal relationship between a drug and mood symptoms, good clinical judgment dictates that it should be stopped or changed if a patient develops depression after beginning use. However, such an event does not suggest that the particular medication should not be used in other patients who appropriately require it, but may have either a depression or a propensity for depression. That is, the reaction should be regarded as truly idiosyncratic and should not form the basis for a general conclusion about the medication in all patients.

Antihypertensives

Various blood pressure medications have been linked to depressive symptomatology, although much of the evidence for the association has been weak or equivocal.

Goodwin and Bunney (1971) found a 5 to 20 percent risk of depression in patients treated with reserpine. Depression was related to the dosage; more severe depressions were reported in patients receiving more than 0.5

mg per day. A history of depression was associated with a higher incidence of depressive symptoms and a higher incidence of severe depression. These data suggest that, if reserpine is used, the dosage should not exceed 0.5 mg per day, and the drug should be avoided in patients with a history of mood disorders.

Beta-adrenergic blocking agents have been associated with depressive symptomatology, with lethargy being the main symptom reported. In one study, depression was found to be no greater, and perhaps less, in the beta-blocker group than in controls (Bartels, Glasser, Wang, et al., 1988). Another study evaluated various beta-blockers at varying dosages (Carney, Rich, teVelde, et al., 1987). The treated group experienced a 21 percent incidence of depression, but the control group of hypertensive patients on other medications had a 33 percent incidence of depression. Bant (1978) compared hypertensive patients on various medications and a control group of medically ill (nonhypertensive) patients. He found a "high" prevalence of depression in both groups, but no preponderance in the hypertensive patients. Hypertensive patients with a personal or family history of psychiatric illness had a higher level of depression. The Veterans Administration Cooperative Study used patient symptom questionnaires and reported only a 1 percent incidence of depression with propranolol, which is consistent with that found in the general population (VA Cooperative Study Group on Hypertensive Agents, 1982). On the other hand, patients with a personal or family history of depression may be prone to develop depression when treated with propranolol. Data are not available to recommend avoiding propranolol in such patients, but the clinician should be alert to the possibility of depressive reactions in patients beginning this treatment. There is no clear-cut contraindication for its use in any particular patient group.

Studies reviewed fail to show a causal relationship between alpha-methyldopa given in typical dosages and depression. While alpha-methyldopa can be used in patients with a history of depression, they appear to be at greater risk for depression while they are taking it.

A review of 44 studies evaluating the use of clonidine for hypertension found a 1.5 percent incidence of depression (Paykel, Fleminger, and Watson, 1982). This finding indicates that clonidine is rarely associated with depression.

The psychiatric side effects of calcium-channel blockers have been reported to include depression. While most of the data are from case reports, some comprehensive, double-blind, crossover studies have evaluated the potential use of verapamil in the treatment of bipolar disorder. Since there are no controlled reports of depressive disorders associated with calcium-channel blockers, they can be used in depressed patients. At present, there is no evidence that angiotensin I converting enzyme (ACE) inhibitors are associated with depression.

Hormones

Glucocorticoids are well known to cause depression or psychosis. Lewis and Smith (1983) found that 5 percent of steroid-treated patients experienced severe psychiatric reactions (mostly mood disorders), which usually occurred early in the course. Risk factors were female gender, a diagnosis of systemic lupus erythematosus, and high doses of prednisone.

The practitioner is advised to monitor patients on steroids carefully for development of mood syndromes (both manic and depressive types). If they occur, treatment with steroid taper and use of neuroleptics or ECT is indicated. Tricyclic antidepressants may be less useful and may be ineffective or actually aggravate symptoms (Hall, Popkin, and Kirkpatrick, 1978). In patients for whom steroids are medically necessary, lithium prophylaxis can be tried (Falk, Mahnke, and Poskanzer, 1979).

Anabolic steroids used for athletic enhancement deserve comment. Pope and Katz (1988) found that 22 percent of young bodybuilders who returned their questionnaires suffered from a full mood syndrome, 12 percent had psychotic symptoms, and 12 percent suffered depression when cycled off the drug. The greatest use of these drugs seems to be among young men and women focused on enhancing their physiques. Practitioners should be aware of these drugs and ask about them in all who present with a mood syndrome.

Case reports of depression associated with the use of oral contraceptives are available, but many of the better documented studies found little relationship. Slap (1981) found that 9 of 12 studies reported some depressive

symptoms in 15 to 56 percent of oral contraceptive users. However, many of these studies were not well controlled or did not use standard criteria to define depression. One study found a 6.6 percent incidence of depression in those who used oral contraceptives versus a 2 percent incidence in those who had never used them (Herzberg and Coppen, 1970); a 10 percent incidence rate was found in a followup study (Herzberg, Johnson, and Brown, 1970). These agents are not contraindicated in depressed or formerly depressed patients; however, careful observation is recommended when initiating treatment.

Histamine-2 Receptor Blockers

Multiple case reports have linked histamine-2 receptor blockers (cimetidine and ranitidine) to depressive, manic, and psychotic behaviors. When closely evaluated, however, these cases occur in patients who are otherwise severely ill with multiple system failure or renal or hepatic insufficiency. The panel recommends individualized dosage reduction if the drug is to be used in patients known to have renal or hepatic impairment.

Anticonvulsants

Numerous investigators have evaluated the depressant effects of phenobarbital and carbamazepine. Many, however, do not define depression in standard ways. "Depression" is usually attributed to the generalized psychomotor slowing and sedation noted in association with these drugs. In a carefully documented study of patients on phenobarbital and carbamazepine using depression criteria, 40 percent of 64 patients on anticonvulsant drugs had clinical major depression (34 percent with a family history of mood disorder) (Robertson, Trimble, and Townsend, 1987). Patients on phenobarbital were more depressed than those on carbamazepine. There are no comparative controlled studies.

The panel suggests close monitoring of all patients on phenobarbital for signs of depression, especially those with a known personal or family history of depression. No current data suggest that drug levels predict the risk of depression in these patients, and carbamazepine has actually been an effective prophylactic agent for both depressive and manic episodes in bipolar disorder (Ballenger and Post, 1980).

Levodopa

Another therapeutic agent long associated with mood symptoms is levodopa (L-dopa). Most of the studies reviewed did not use currently accepted criteria for diagnosis of depression and employed variable assessment scales.

In an evaluation of 33 Parkinson's disease patients on various forms of therapy (anticholinergics, amantadine, L-dopa, and L-dopa plus carbidopa), 22 were depressed (12 had a history of mood disorders) and 11 had no mood symptoms (none had a history) (Mindham, Marsden, and Parkes, 1976). There was no general relationship between L-dopa dosage and psychiatric disturbance, though those on L-dopa may have had increased mood symptoms. Given the frequency of depression in untreated Parkinson's disease, the effects of these medications remain unclear. However, there is no clear evidence that L-dopa increases the incidence of depression in these patients when there is no history of depression.

Antibiotics

Mood disorders associated with antibiotics have largely been noted in case reports, without controlled studies. Dapsone has been reported to cause depression and anger. In these cases, symptoms have resolved within days of discontinuing the drug, and the symptoms have recurred on rechallenge. Isoniazid is reported to be related to psychotic syndromes and delirium. Amphotericin B shows a dose-related delirium and electroencephalograph changes when injected intrathecally. By and large, antibiotic use should be based on medical indications rather than on concern about mood disorders.

Antiarrhythmics

Digoxin has been studied only with regard to its toxicity and the related delirium. There are no reports of mood disorders per se related to digoxin. Procainamide has been linked in several case reports to mania.

6. Guideline: Detection of Depression

Clinical Clues

Major depressive disorder is common in primary care outpatients (4 to 8 percent), and nonmajor forms are even more common (6 to 14 percent). Both recognition and diagnosis of depression rest on an awareness of risk factors for depression, as well as elicitation of the key signs, symptoms, and history of illness. The primary risk factors for depression are:

- Prior episodes of depression.
- Family history of depressive disorder.
- Prior suicide attempts.
- Female gender.
- Age of onset under 40.
- Postpartum period.
- Medical co-morbidity.
- Lack of social support.
- Stressful life events.
- Current alcohol or substance abuse.

A variety of clinical clues may further alert the practitioner to the likelihood of a mood disorder.

Guideline: A history of major depressive episodes increases risk for subsequent major depressive episodes. **(Strength of Evidence = A.)**

One major depressive episode is associated with a 50 percent chance of a subsequent episode; two episodes, with a 70 percent chance of a subsequent episode; and three or more episodes, with a 90 percent chance of recurrent depression over a lifetime (NIMH Consensus Development Conference, 1985).

Guideline: A history of mood disorders in first-degree relatives increases the probability of a patient's developing a mood disorder. **(Strength of Evidence = A.)**

First-degree relatives of bipolar disorder patients are at substantially higher risk for developing either a recurrent major depressive disorder (roughly 12 percent) or bipolar disorder (roughly 12 percent). Strong scientific evidence points to a genetic vulnerability to bipolar disorder. For those with more recurrent forms of major depressive disorder, genetic factors also appear to play a significant role. For those with less recurrent forms of major depressive disorder, the role of genetic factors is unclear. It is known, however, that patients who develop major depressive disorder before age 20 have a greater familial morbidity for depression (Goodwin and Jamison, 1990).

Guideline: A history of suicide attempts should trigger the practitioner to inquire specifically about depressive symptoms. **(Strength of Evidence = A.)**

Suicide attempts are frequently associated with mood disorders. In addition, a history of suicidal ideation and/or attempts increases the patient's risk for subsequent suicidal ideation/attempts. Additional risk factors for suicide

include:

- Hopelessness.
- Physical illnesses.
- Family history of substance abuse.
- Caucasian race.
- Depression.
- Substance abuse.
- Male gender.
- Advanced age.
- Presence of psychotic symptoms.
- Living alone.

The signs and symptoms of depression can be sought by direct interview, which may be supplemented with self-report ratings and/or by a history obtained from the patient's spouse or a friend. Depressive disorder is diagnosed on the basis of positive evidence -- not by exclusion. For example, patients with or without other general medical conditions either do or do not have a depressive syndrome. Depression should not be explained away or discounted as a commonplace "reaction" to the concurrent general medical condition. Similarly, life events, including losses of important people or key roles, usually precede the onset of major depressive episodes. Thus, the presence of selected untoward life events should not be used to explain away the major mood episode.

Guideline: The clinical interview is the most effective method for detecting depression. The interview elicits the nine criterion symptoms of major depressive disorder and the longitudinal course of illness. Similarly, interviewing for symptoms and course of illness is essential to identifying bipolar, dysthymic, and other mood disorders. Specific questions regarding the criterion symptoms are asked. Since either a depressed, blue, or sad mood or a loss of interest or pleasure is required, these symptoms are elicited first. The clinician who suspects or diagnoses a depressive disorder is advised to perform and record the results of a mental status examination, which includes whether the patient has suicidal ideation/intention; is oriented, alert, cooperative, and communicative; exhibits a normal level of motor activity; and is psychotic. **(Strength of Evidence = A.)**

Some patients may initially deny the depressed mood, but may identify the somatic symptoms (sleep, appetite, and weight changes). Upon further discussion, the interviewer should return to the issues of mood and interest. Patients may initially complain about sleep, appetite, energy, concentration, and sex drive changes or about chronic or intermittent pain or anxiety. The clinician should be alert to considering the diagnosis of depressive illness in these patients.

If symptoms of depression are present, it is important to determine their time course. How long has the patient been in an episode of major depressive disorder? Were there prior episodes? What degree of interepisode recovery has occurred? How severe are the current symptoms? The more severe forms of depression, characterized by marked suicidal thinking, multiple neurovegetative symptoms, and markedly impaired functioning, argue strongly for the use of medication. A chronic or multiepisode history argues for more prolonged treatment. Symptom severity should be gauged by either clinical interview or rating scales, since severity plays a role in treatment planning (Depression Guideline Panel, forthcoming).

When there is historical, symptomatic, or physiologic evidence to suggest an underlying general medical disorder as the cause of the depression, physical examination and laboratory tests to detect the specific disorder(s) should be used as appropriate in the differential diagnosis. The presence of another medical condition does not exclude the depressive syndrome. In fact, it increases the probability that a depressive syndrome may be present. The depression is either present or absent, based on the patient's signs/symptoms. If the patient has a depression, the first steps in its treatment differ according to whether another general medical condition is present and thought to be causal, whether alcohol or substance abuse is present, and whether another nonmood psychiatric disorder is present and causal.

Screening Instruments

Patient Self-Report Questionnaires

Easily administered self-report questionnaires can be used as a low-cost, but valuable, case-finding tool to help clinicians better detect currently depressed patients. Numerous scales are available for assessment of depression (Beckham and Leber, 1985; Marsella, Hirschfeld, and Katz, 1987). It is not uncommon for primary care practitioners to have patients complete self-report depression rating scales in the waiting room to elicit these symptoms. These self-reports are not diagnostic, but they are very sensitive to depressive symptoms.

These self-report scales are also useful in detecting milder mood conditions. The four used most commonly in ambulatory medical care settings are the General Health Questionnaire (GHQ), which has one subscale for depression; the Center for Epidemiological Studies -- Depression Scale (CES-D); the Beck Depression Inventory (BDI); and the Zung Self-Rating Depression Scale (ZSRDS) (Coulehan, Schulberg, and Block, 1989). Patient responses to these instruments cannot be used directly to formulate a diagnosis of depression; however, a high score on one of these instruments warrants a clinical interview based on DSM-III-R criteria. Some of these limitations have been addressed by newly developed measures--the Inventory to Diagnose Depression (Zimmerman, Coryell, Stangl, et al., 1987) or the Inventory for Depressive Symptoms- Self-Report (Rush, Giles, Schlesser, et al., 1986). Although initial results are promising, these instruments have not yet been applied extensively in primary care settings.

All four self-report measures commonly used in primary care settings (GHQ, CES-D, BDI, and ZSRDS) help to identify potentially depressed patients with varying degrees of power exceeding chance. All have positive predictive values between two and four times the 6 to 8 percent base rate of major depression. They identify many patients who ultimately prove not to have a mood disorder. In essence, there are few false-negative results, but many (25 to 40 percent) false-positive results.

Fifteen studies have rigorously evaluated the predictive value of self-report questionnaires for depression in primary care populations by using the diagnosis from a structured psychiatric assessment as the "gold standard" against which the self-report formulation is compared (Coulchan, Schulberg, and Block, 1989). This body of research leads to the following recommendations for case finding with self-report measures:

- Since the positive predictive value of self-report questionnaires relates to the prevalence of the disorder in the clinical population, depression scales are most appropriately and efficiently administered to those at higher risk for this disorder. This group includes patients with disabling chronic diseases; unexplained or ill-defined symptoms; sleep complaints; history of prior psychiatric illness; headaches, abdominal pain, or other pain complaints; or either a sad mood or reduced interest or pleasure.
- Cutoff thresholds for each questionnaire must be established at levels specific to primary care populations. Since positive predictive value is linked to the disorder's prevalence, the threshold most appropriate to particular medical patient groups differs from that to be used with psychiatric or community cohorts. Several investigators have recommended that significantly higher cutoff scores be used with self-report instruments in medical practices to reduce the proportion of false-positives produced by cutoff scores established in community studies (Schulberg, Saul, McClelland, et al., 1985; Turner and Romano, 1984). If the practitioner is already highly attuned to and inquires regularly about depressive symptoms, the self-reports may add little to his or her practice.
- Since these questionnaires identify patients as "depressed" when they have only some symptoms, but not the disorder, the practitioner should not rely exclusively on them to make a diagnosis of depressive disorder.

Clinician-Completed Rating Scales

Several available rating scales are to be completed by the clinician: the Hamilton Rating Scale for Depression (HRS-D) (Hamilton, 1968), the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the Inventory for Depressive Symptomatology -- Clinician Rated (IDS-C) (Rush, Giles, Schlesser,

et al., 1986), the Bech-Rafaelsen Depression Scale (BRDS) (Bech, Kastrup, and Rafaelsen, 1986), and depression items of selected structured interviews such as the Present State Examination (PSE) (Wing, Birley, Cooper, et al., 1967) and the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978). These may be more sensitive to improvement in the course of treatment and may have slightly greater specificity than do self-reports in detecting depression.

A systematic approach to the identification of depressive disorders can be derived from the information obtained on these questionnaires and scales:

1. Self-report questionnaires can be used to identify those unlikely to have major depressive disorder. No further questioning or evaluation need be performed with these patients.

   The condition of those who have significant depressive symptoms based on a self-report should be further evaluated by clinical interview to determine whether the symptoms are of sufficient intensity, number, and duration to meet the criteria for major depressive disorder (or another mood disorder) according to DSM-III-R.

   Some patients who meet the criteria for major depressive disorder, but have a very mild condition (not chronic, psychotic, significantly disabling, or suicidal), may either begin treatment or wait for a reevaluation of their condition in 1 to 2 weeks before starting specific treatment, since some 15 to 25 percent (or higher) of these patients respond to supportive care from the practitioner. Should the patient respond fully to supportive care, the practitioner is advised to see the patient again, as some patients' symptoms return.

   Those whose major depressive symptomatology is persistent, disabling, or moderate to severe should be treated. Those with moderate to severe symptoms, in a prolonged depressive episode, or with recurrent episodes with poor interepisode recovery are less likely to respond to clinical management and reassurance alone, and treatment should not be delayed.

Differential Diagnosis of Depression

Differential diagnosis of depressive disorders rests largely on clinical phenomenological grounds. The practitioner is advised to proceed according to the following steps:

1. Conduct a clinical interview to assess the patient for the nine specific signs/symptoms of major depressive disorder according to DSM-III-R. This step is essential, since the evidence for the efficacy of various treatments for major depressive disorder is very strong, but is relatively unstudied for nonmajor forms of depression or for dysthymic disorder without a history of major depressive disorder.

   Interview the patient to investigate the possibility of concurrent substance or alcohol abuse and current use of medications that may cause depressive symptomatology (see Figure 2)

   Conduct a medical review of systems to detect the existence of medical disorders that may biologically cause or be commonly associated with depressive symptoms.

   Interview the patient further to detect the presence of another concurrent nonmood psychiatric condition that may be associated with and be responsible for the depressive symptoms.

   Exclude alternative causes (1 through 4, above) for depressive symptoms or syndromes to diagnose a primary mood disorder.

This process is summarized in Table 8.

Laboratory Tests

Guideline: The descriptive diagnosis of depression is based entirely on the patient's signs, symptoms, and personal history. Therefore, the practitioner should spend substantial time carefully interviewing the patient and, where appropriate, other informants (i.e., close relatives or friends) before embarking on extensive biologic, neuropsychological, or psychological testing. The main principle is to conduct only a limited number of basic

laboratory tests to detect potential general medical causes for the depression unless specific risk factors, specific positive symptoms on the medical review of systems, unusual symptom profiles, or an atypical course of illness is present, in which case selected additional tests are called for to answer specific diagnostic questions. **(Strength of Evidence = B.)**

There are two kinds of laboratory tests: (1) those that screen for underlying medical causes for the depression and (2) those that identify biologic abnormalities characteristic of depression.

At the point at which a differential diagnosis is framed, with specific alternative conditions being relatively likely based on history, physical examination, or other risk factors, the primary care provider may use selected tests to determine whether these associated conditions are indeed present. In addition, various laboratory tests, such as the thyrotropin-releasing hormone stimulation test, the dexamethasone suppression test, and the sleep electroencephalogram, identify biologic abnormalities characteristic of the depressed state (see Rush, Cain, Raese, et al., 1991; Goodwin and Jamison, 1990 for reviews). These tests are not recommended for routine use in primary care outpatients. They lack sufficient specificity and sensitivity to be useful as screening tools.

The general principle of laboratory testing is that the likelihood of the disorder for which the test is being conducted should be relatively high in the patient being tested because virtually all tests have certain false-positive as well as false-negative rates. If the false-positive rate of the test is 5 percent and the incidence of the condition in the population is 1 percent, 5 of 100 patients will test positive when only 1 in 100 really has the condition. The clinician should have a rational basis, independent of the laboratory test per se, for selecting and conducting the test. For example, if a depressed patient shows significant symptoms suggesting a dementing process or a clinical history suggestive of higher cortical impairment, further neuropsychological or neurologic laboratory tests, such as the electroencephalogram or magnetic resonance imaging, may be useful either to establish or exclude the diagnosis, or to identify the causes of the dementia. If, on the other hand, the patient simply complains of concentration problems that are not out of the ordinary for a person with a typical major depressive disorder, the use of such tests is both inappropriate and likely in at least some patients to lead to false-positive findings, thereby requiring additional testing, unnecessary specialized consultation, delay in appropriate treatment, and unnecessary worry to patients and family members.

Large epidemiologic studies in the general population suggest that previously unrecognized laboratory abnormalities occur in between 0.8 and 4.0 percent of the population (Korvin, Pearce, and Stanley, 1975). A significant portion of these abnormalities, however, either are predictable based on clinical assessment (Dolan and Mushlin, 1985) or represent false-positive test findings for the reasons cited previously. Those populations at highest clinical risk for meaningful abnormalities on these screening laboratory examinations include those who cannot care for themselves entirely, those who currently abuse alcohol or other substances, and those who merit a more thorough evaluation because of age or clinical circumstances (Ferguson and Dudleston, 1986; Koran, Sox, Marton, et al., 1989; Roca, Breakey, and Fischer, 1987; Sox, Koran, Sox, et al., 1989).

These general population findings are supported by three studies in which a psychiatric population was prospectively investigated for identification of previously unrecognized illness (Ferguson and Dudleston, 1986; Kolman, 1985; Willett and King, 1977). The principal findings in these studies, which involved more than 1,300 adult psychiatric inpatients, suggest an abnormality rate of 6 to 17 percent in this psychiatric population. Most of these abnormal findings, however, were predictable based on history and physical examination or were false-positives. A side finding was that many test results were never reviewed by the ordering physician.

Laboratory tests should be tailored to the population served and should be specifically based on patient findings. Reliance on laboratory tests in general evaluation of the condition of depressed patients should be greater if:

- The medical review of systems reveals signs or symptoms that are rarely encountered in depression.
- The patient is older.
- The depressive episode first occurs after the age of 40 to 45.
- The depression does not respond fully to routine treatment.

The issue of thyroid disease and depression is a case in point. Studies using thyroid function tests to screen nearly

15,000 general medical patients for either hyper- or hypothyroidism indicate that such a procedure is not cost-effective in identifying patients with the disorder (0.3 percent detection of hyperthyroidism [women/men = 10/1]; 0.5 percent detection of hypothyroidism [women/men = 2/1]).

At least two studies indicate that using fatigue and depression as prescreening symptoms does little to improve the likelihood of identifying hyper- or hypothyroidism with thyroid function tests as a general screen. The first study included 250 patients and found no increase in the identification rate of patients with hyper- or hypothyroidism when mental disorders or tiredness were present compared with the general population (Eden, Sundbeck, Lindstedt, et al., 1988). The second study suggested that, while the likelihood of identifying true cases of disease on laboratory testing improved when the symptoms of hyper- or hypothyroidism were elicited in advance, depression and fatigue were not among the most highly discriminant symptoms (Drake, Miller, and Evans, 1982).

These studies suggest that the optimal means to screen for thyroid disorders are through history and physical examination. The one exception is in the identification of hypothyroidism in women over the age of 50, in whom the identification rate is 10.3 percent in previously unidentified cases (Eden, Sundbeck, Lindstedt, et al., 1988; Hodkinson and Denham, 1977; Taylor, Tomson, and Caird, 1974). Thus, for women over 50 with depressive symptoms, thyroid function tests have a key role in detecting thyroid disease. The prevalence of this illness in women over age 50 is the same in women with major depressive disorder. The same cannot be said of older men, who are far less likely to suffer thyroid disease as a group than are older women.

When symptoms of thyroid disease are present, case finding with thyroid function tests increases to 12 percent for hyperthyroidism (Nuutila, Irjala, Viikari, et al., 1988) and to 3 to 4 percent for hypothyroidism (Goldstein and Mushlin, 1987; Nuutila, Irjala, Viikari, et al., 1988). As the symptoms of thyroid disease increase in number, case finding with such laboratory testing increases (more than five symptoms, 50 percent identification rate) (Drake, Miller, and Evans, 1982). Although fatigue is seen as a symptom of thyroid disease, in isolation it does not increase case finding with laboratory tests over that obtained in the general population (Sugarman and Berg, 1984).

When a treatment trial is conducted, the patient's symptomatic response should be monitored. If the patient does not respond fully, then the diagnostic workup (history, medical review of systems, and physical examination) should be repeated. At that juncture, a differential diagnostic picture may appear that was not obvious at initial evaluation. Appropriate laboratory testing for the differential diagnostic questions raised at the reassessment should then be undertaken.

As noted earlier, some laboratory tests that may be relatively specific to depressive conditions are now under clinical investigation. These include selected sleep electroencephalogram features and failure to suppress cortisol following a dexamethasone challenge, among others (Rush, Cain, Raese, et al., 1991). While many severely depressed patients, especially those with psychotic or melancholic symptoms, display abnormalities on these tests, the tests are not indicated as routine screens for depression because they lack specificity and have lower sensitivity in the less severely ill. However, they can play a role in selected differential diagnostic situations (for example, using the dexamethasone suppression test to differentiate psychotic depression from schizophrenia or using the sleep electroencephalogram to differentiate sleep/wake disorders such as sleep apnea from depression), which are typically managed by specialists rather than primary care providers.

Psychological Tests

Most psychological tests are standardized in the general population (Dobson, 1985). In general, recommendations for the use of psychological and neuropsychological tests in screening for depressive disorders are similar to those for laboratory tests. They are not recommended for routine use in screening for depression. However, in selected cases, psychological and neuropsychological tests may be very useful in differential diagnosis of depression. Neuropsychological tests, such as the modified Halstead-Reitan battery, should be considered when it is necessary to distinguish dementia from depression. Depressed patients have been found to show significantly different test profiles on the Minnesota Multiphasic Personality Inventory (MMPI), the Symptom Checklist 90,

and the Millon Clinical Multiaxial Inventory than do nondepressed patients with psychiatric diagnoses (Weitzler, Strauman, and Dubro, 1989). While these psychological tests predicted depression at a rate surpassing chance, such instruments were not substitutes for a thorough clinical evaluation. In other words, these tests may confirm, but they do not independently render, the diagnosis.

Perhaps the most commonly faced differential diagnosis in primary care practice is that between depressive and anxiety disorders. Dobson (1985) determined that the self-report symptom ratings for these two disorders have poor divergent (discriminative) validity, which is not surprising, since many depressed patients also have anxiety symptoms or suffer from concurrent, co-morbid anxiety disorders.

With regard to distinguishing subtypes of depression, the MMPI and Rorschach are of limited value in differentiating major depressive from bipolar disorder and melancholic from nonmelancholic major depressive disorder. In one study, patients with major depressive disorder showed elevated scores on most MMPI scales, compared to those with bipolar disorder, depressed phase (Donnelly, Murphy, and Goodwin, 1976), although subsequent studies failed to replicate this finding (Lumry, 1978; Silver, Isaacs, and Mansky, 1981). Another study found Rorschach responses to be of no value in distinguishing melancholic from nonmelancholic depressions (Carney, Roth, and Garside, 1965).

It is not appropriate to use psychological tests, including the MMPI, as the sole means to determine whether a patient with a concurrent symptomatic nonpsychiatric medical illness "really" has a depression, because symptoms from the medical illness itself affect test results. To illustrate, medical patients typically have a depressive/hypochondriacal pattern on the MMPI, because the MMPI somatic symptoms that emanate from the nonpsychiatric medical illness contribute to the depressive/ hypochondriacal symptom scales.

In summary, the available empirical data do not support the routine use of self-report or projective instruments to differentiate depression from anxiety disorders. These tests can distinguish depressive from other nonanxious psychiatric conditions, and they can enhance a careful clinical formulation rendered by a clinician well trained in the diagnosis of depressive disorders. Where the differential diagnosis is in doubt, psychological tests may help to tip the balance in favor of one or the other condition. Like laboratory tests, however, psychological tests should not be used for routine screening purposes or administered for all differential diagnostic situations.

Ongoing Clinical Reassessment

Guideline: A critical element in the differential diagnosis of depressive disorders is ongoing clinical reassessment. **(Strength of Evidence = B.)**

Most patients with major depressive disorder respond partially to medication within 2 to 3 weeks, and full symptom remission is typically seen in 6 to 8 weeks. Most patients receiving time-limited psychotherapy respond partially by 5 to 6 weeks and fully by 10 to 12 weeks. Patients who fail to show this pattern can be detected through careful interviewing or by clinical or self-report rating scales. In these patients, a reevaluation is indicated. The clinical reevaluations may include repeating a thorough general medical and psychiatric history, physical examination, and a more thorough medical laboratory evaluation. For patients on selected medications, blood level measurements may help gauge whether the serum level of antidepressant is in the therapeutic range.

A significant subset of patients with major depression also exhibit maladaptive personality traits or disorders. When the underlying mood disorder is successfully treated, the expression of these maladaptive traits may partially or completely resolve (Joffe and Regan, 1988; Thompson, Gallagher, and Czirr, 1988). However, studies suggest that patients with such preexisting personality disorders are less likely to exhibit a full therapeutic response in affective symptoms to either medication or time-limited psychotherapy, or they may take longer to respond fully. In those who respond only partially to treatment and in whom personality disorders are suspected, psychological testing may be useful to determine the presence of personality disorders. If present, the case for combined treatment with medication and psychotherapy may be stronger.

These are general principles whose application to individuals requires judgment, logic, and flexibility. First, it is necessary to define a response, which is usually thought to be at least a 50 percent improvement in baseline

(pretreatment) symptom severity or a global judgment that the patient is at least much improved. A remission is defined as either the presence of few or no symptoms or a global patient report of marked improvement. In some cases, other ongoing problems, such as chronic severe life stresses, may slow the response or impair the likelihood of attaining a fully asymptomatic state in 10 to 12 weeks. In such patients, longer observation periods may be needed while treatment continues.

Finally, improvement in some symptoms (e.g., insomnia) may not be the best way to judge overall treatment effectiveness. For example, the side effects of medication (e.g., sedation) or psychotherapy (e.g., improved sense of hope or optimism) may result in abatement of selected symptoms while failing to remove all symptoms of the depressive disorder.

The timing and type of reassessment, and the interpretation of the results of this reassessment are important. Based on panel consensus and an awareness that most psychopharmacology studies have used assessments conducted every 1 to 2 weeks to evaluate response in efficacy trials, it is recommended that medication treatment visits or telephone contacts initially be weekly to ensure adherence, adjust dosage, and detect and manage side effects. After 3 to 4 weeks, visits may be less frequent for most patients. The degree of response/remission can be assessed at each visit, as well as any evidence of side effects. Whether the clinical interview is supplemented with a symptom-rating scale or not, the practitioner should inventory all of the criterion symptoms of depression included in the patient's initial complaint. For those with personality disorders or severe ongoing life stresses, as long as the patient is showing some significant improvement over baseline, the treatment need not be changed for 8 to 10 weeks. For others, an earlier judgment can be made to change the treatment if no meaningful response is found (or to change earlier, if adverse side effects are encountered).

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Acronyms

AHCPR
: Agency for Health Care Policy and Research

BDI
: Beck Depression Inventory

BRDS
: Bech-Rafaelsen Depression Scale

CDC
: Centers for Disease Control

CES-D
: Center for Epidemiological Studies--Depression Scale

DIS
: Diagnostic Interview Schedule

DNOS
: Depression not otherwise specified

DSM-III-R
: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised

ECA
: Epidemiologic Catchment Area

ECT
: Electroconvulsive therapy

GHQ
: General Health Questionnaire

HRS-D
: Hamilton Rating Scale for Depression

ICD-9
: International Classification of Diseases, Ninth Edition

IDDM
: Insulin-dependent diabetes mellitus

IDS-C
: Inventory for Depression Symptomatology--Clinician Rated

MADRS
: Montgomery-Asberg Depression Rating Scale

MAOI
: Monoamine oxidase inhibitor

MMPI
: Minnesota Multiphasic Personality Inventory

NIDDM
: Non-insulin-dependent diabetes mellitus

NIMH
: National Institute of Mental Health

OCD

Obsessive-compulsive disorder

PSE

Present State Examination

RDC

Research Diagnostic Criteria

SADS

Schedule for Affective Disorders and Schizophrenia

SADS-L

Schedule for Affective Disorders and Schizophrenia--Lifetime Version

SCL

Symptom Checklist

SSRI

Selective serotonin reuptake inhibitor

TCA

Tricyclic antidepressant

WHO

World Health Organization

ZSRDS

Zung Self-Rating Depression Scale

Glossary

Acute Treatment.

Formally defined procedures used to reduce and remove the signs and symptoms of depression and to restore psychosocial function.

Adequate Treatment

Analysis. Analysis of data in terms of the relationship between the number of patients who received a predetermined minimum amount of treatment and the number who responded.

Agoraphobia.

A disorder characterized by a fear of open, public places or of situations where crowds are found.

Anhedonia.

An absence of or the inability to experience a sense of pleasure from any activity.

Behavioral Therapy.

A form of psychotherapy that focuses on modifying observable problematic behaviors by systematic manipulation of the environment.

Bipolar Disorder.

A major mood disorder characterized by episodes of major depression and mania or hypomania, formerly called manic-depressive psychosis, circular type. The diagnosis of bipolar I disorder requires one or more episodes of mania. The diagnosis of bipolar II disorder requires one or more episodes of hypomania and is excluded by the history or presence of a manic episode. Current episode may be manic, depressed, hypomanic, or mixed manic type.

Clinical Management.

Education of and discussion with patients and, when appropriate, their families about the nature of depression, its course, and the relative costs and benefits of treatment options. It also includes assessment and management of the patient while in treatment, along with resolution of obstacles to treatment

adherence, monitoring and management of treatment side effects, and assessment of outcome.

Cognitive Therapy.

A treatment method that focuses on revising a person's maladaptive processes of thinking, perceptions, attitudes and beliefs. Cognitive therapy has been developed for different specific disorders, including depression.

Completer Analysis.

Analysis of data in terms of the relationship between the number of patients whose condition improved and the number who completed the treatment protocol.

Continuation Treatment.

Treatment designed to prevent the return of the most recent mood episode.

Cyclothymic Disorder.

A mood disorder of at least 2 years' duration characterized by numerous periods of mild depressive symptoms not sufficient in duration or severity to meet criteria for major depressive episodes interspersed with periods of hypomania. Some view this condition as a mild variant of bipolar disorder.

Dementia.

A group of mental disorders involving a general loss of intellectual abilities, including memory, judgment, and abstract thinking. There may be associated poor impulse control and/or personality change. Dementias may be progressive, reversible, or static and have a variety of causes.

Dysthymia.

A mood disorder characterized by depressed mood and loss of interest or pleasure in customary activities, with some additional signs and symptoms of depression, that is present most of the time for at least 2 years. Many patients with dysthymia go on to develop major depressive episodes.

Electroconvulsive Therapy.

A treatment method usually reserved for very severe or psychotic depressions or manic states that often are not responsive to medication treatment. A low-voltage alternating current is sent to the brain to induce a convulsion or seizure, which accounts for the therapeutic effect.

Hypomania.

An episode of illness that resembles mania, but is less intense and less disabling. The state is characterized by a euphoric mood, unrealistic optimism, increased speech and activity, and a decreased need for sleep. For some, there is increased creativity, while others evidence poor judgment and impaired function.

Intent-to-Treat Analysis.

Analysis of data in terms of the relationship between the number of patients randomized to treatment and the number whose condition improved.

Interpersonal Psychotherapy.

A time-limited psychotherapeutic approach that aims at clarification and resolution of one or more of the following interpersonal difficulties: role disputes, social isolation, prolonged grief reaction, or role transition. The patient and therapist define the nature of the difficulty and work to its resolution.

Maintenance Treatment.

Treatment designed to prevent a new mood episode (e.g., depression, mania, hypomania).

Major Depressive Disorder.

A major mood disorder characterized by one (single) or more (recurrent) episodes of major depression, with or without full recovery between episodes.

Mania.

An episode of illness usually seen in the course of bipolar I disorder and characterized by hyperexcitability, euphoria, and hyperactivity. Rapid thinking and speaking, agitation, a decreased need for sleep, and a marked increase in energy are nearly always present. During manic episodes, some patients also experience hallucinations or delusions. Manic episodes can also be caused by selected general medical

disorders.

Melancholic Features.

Symptoms usually found in severe major depressive episodes, including marked loss of pleasure, psychomotor retardation or agitation, weight loss, and insomnia.

Mood Disorders.

A grouping of psychiatric conditions that have as a central feature a disturbance in mood (usually profound sadness or apathy, euphoria, or irritability). These disorders may be episodic or chronic.

Obsessive-Compulsive Disorder.

A condition that is characterized by the presence of obsessions and/or compulsions. Obsessions are recurrent, intrusive thoughts usually irrational worries that often necessitate behaviors to prevent untoward consequences (e.g., fears of contamination from dirt requiring the individual to wear gloves at all times). Compulsions are recurrent behaviors beyond the normal range that the individual feels compelled to undertake, usually to preserve personal safety, to avoid embarrassment, or to perform adequately (e.g., checking multiple times to see that the gas is turned off before leaving home). The disorder affects 1 to 2 percent of the population.

Open Trial.

A trial of a treatment in which both patient and practitioner are aware of the treatment being used.

Panic Disorder.

An anxiety disorder characterized by discrete intense periods of fear and associated symptoms. Panic disorder may be accompanied by agoraphobia.

Remission.

A return to the asymptomatic state, usually accompanied by a return to the usual level of psychosocial functioning.

Somatization Disorder.

A disorder characterized by multiple, often long-standing somatic complaints of bodily dysfunction (e.g., pain complaints, gastrointestinal disturbances). The disorder usually begins before the age of 30 and has a chronic, albeit fluctuating, course.

Supportive Therapy.

Psychotherapy that focuses on the management and resolution of current difficulties and life decisions using the patient's strengths and available resources.

Symptom Breakthrough.

The return of symptoms in the course of either continuation or maintenance phase treatment.

Vegetative Symptoms.

A group of symptoms that refer to sleep, appetite, and/or weight regulation.

Contributors

These guidelines could not have been developed without the expertise and assistance of many types of contributors who, together, made the effort feasible. All of those listed here willingly assisted in the intense effort required to develop guidelines on an issue as complex as the appropriate treatment of major depressive disorder. The resulting document reflects the many important interactions that occurred during the guideline development process.

Depression Guideline Panel Members: Biosketches

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Betty Jo Hay Distinguished Chair in Mental Health Professor and Vice Chairman for Research,

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Dr. Rush received his BA from Princeton University and his MD from the College of Physicians and Surgeons of Columbia University.

He is currently the Director of the Mental Health Clinical Research Center, an NIMH-funded center studying the biology, psychology, pharmacology, and psychotherapy of mood disorders. Dr. Rush has published extensively on both the psychology and biology of depression. He has received several NIMH grants to study depression and has helped develop and study the efficacy of cognitive therapy in treatment of depressed outpatients. His research has sought to identify biologic and psychological predictors of specific treatment responses, as well as relapse and recurrence. He serves as the Chair of the DSM-IV Work Group on Mood Disorders for the American Psychiatric Association.

Dr. Rush is a Fellow of the American College of Psychiatry, the American Psychiatric Association, and the American College of Neuropsychopharmacology. He is Past President of the Society for Psychotherapy Research.

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Dr. Golden received his AB from Brown University (1975) and his MD from Baylor College of Medicine (1978). He completed his internal medicine residency and chief residency at Rush-Presbyterian St. Luke's Medical Center in Chicago (1983). Dr. Golden is Director of the Quality Assurance Research and Education Center, Director of the Division of General Internal Medicine, and Associate Professor of Medicine at the University of Arkansas for Medical Sciences. He is currently Chairman of the Quality Assurance Committee of University Hospital. He has had several funded projects in quality assurance and has expertise in perioperative care and medical informatics. He has authored more than 40 journal articles and book chapters on perioperative care, medical education, and quality improvement.

Dr. Golden is a trustee of the American Society of Internal Medicine and a member of the board of directors of the American Medical Review Research Center. He serves on the American Medical Association Council on Medical Education and has recently been appointed to the Liaison Committee on Medical Education. He is a member of many internal medicine societies and has served numerous roles in educational activities and policy-making matters for these organizations.

Gladys Walton Hall, PhD, MSW

Associate Professor, School of Social Work

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Dr. Hall received her BS from Morgan State University (1966), MSW from the University of Connecticut (1971), and PhD from the University of Maryland (1982). She recently completed a post-doctoral fellowship at the National Institute of Mental Health (1990).

Dr. Hall teaches clinical social work methods courses and is a licensed clinical social worker with experience in the private and public sectors. Her private practice is in a comprehensive medical setting and includes the treatment of depressed women. She has authored several publications in the area of depression (childhood depression) and served on various professional boards, both national and local (including the D.C. Mental Health Association). Her research focus is on the psychosocial factors related to the co-morbidity of depression and conduct disorder among children.

Col. Moses Herrera, MD

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Dr. Herrera is a Fellow of the American Academy of Family Practice. He has many years of experience in the practice of family medicine, including obstetrics, geriatrics, pediatrics, and adolescent medicine, as well as in short-term psychotherapy and in the diagnosis and treatment of depression. He has served on the Mental Health Committee of the American Academy of Family Practice. With his experience, Dr. Herrera can speak with particular regard to the utility of guidelines as they may be applied to family practice in military medicine.

Artie Houston

Consumer Representative

Fort Worth, Texas

Mrs. Houston represents patients (consumers). She has lived successfully with manic-depressive illness, which was diagnosed in 1968. She played a prominent role in the establishment of the National Depressive and Manic-Depressive Association (NDMDA) and served as its executive vice president and president in 1988-89. Mrs. Houston founded the first NDMDA chapter in Tarrant County, Texas, and served as its president for 2 years. She has a background in business and public relations. She served for 15 years as the business director of a large blood center in Fort Worth, Texas. Mrs. Houston has an extensive history of volunteer work in the areas of depression, manic-depressive illness, and hemophilia.

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Dr. Kathol received his BA from the University of Kansas (1970) and his MD from the University of Kansas School of Medicine (1974). He completed his residency in internal medicine at the University of Iowa (1978) and his residency in psychiatry at the University of Iowa (1980). He completed a 1-year fellowship in endocrinology at the University of Otago in Wellington, New Zealand (1981).

Dr. Kathol is the director of the combined Internal Medicine/Psychiatry Unit and the General Hospital Psychiatry Services at the University of Iowa Hospitals and Clinics. He currently teaches both psychiatrists and internists about the diagnosis and treatment of medical and psychiatric disorders in patients with complex and combined medical/psychiatric difficulties. He has received NIMH and private foundation grants for clinical research on depressive disorders in the medically ill, on endocrine changes in patients with primary depression, and on pharmacokinetic drug interactions. His research has contributed to the understanding of depression in the medically ill, as well as the potential relationship of hypothalamic-pituitary-adrenal axis dysfunction in patients with primary affective disorder.

Dr. Kathol has lectured widely, is on the editorial board of several journals, holds membership on the boards of national organizations, and is published widely in the area of psychiatric pathology as seen in medically ill patients. He is board-certified in both internal medicine and psychiatry, and is a Fellow of the American College of Physicians, the American Psychiatric Association, and the American Academy of Psychosomatic Medicine. He is the current president of the Academy of Clinical Psychiatry and is a founding officer of the Association of Medicine and Psychiatry.

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Dr. Katon received his BA from the University of Vermont (1971) and his MD from the University of Oregon

(1976). He completed his residency in psychiatry at the University of Washington (1979).

Dr. Katon is Chief of the Division of Consultation-Liaison at the University of Washington and head of the Psychiatry Liaison Service to Family Medicine at University and Providence Medical Centers. Dr. Katon received the American Academy of Family Practice Award for Excellence in Teaching. He has taught medical students, psychiatric residents, and family medicine practitioners in the area of psychiatric disorders in family practice and primary care. He has received independent NIMH funding for the study of depression and chronic tinnitus, a randomized trial of psychiatric consultation for patients who are high medical service utilizers, and a randomized trial of psychiatric consultation in treatment of major depression in primary care.

Dr. Katon has published widely in the area of psychopathology (depression, panic disorders, and somatization) in the primary care setting. He has authored more than 100 journal articles and chapters and a book commissioned by NIMH entitled Panic Disorder in the Medical Setting. His research has sought to identify the psychological and social factors associated with medically unexplained somatic symptoms (chest pain, back pain, irritable bowel syndrome, tinnitus, pelvic pain, and dizziness). He is a recognized national and international authority on psychiatric disorders in family practice and general internal medicine.

Catherine L. Matchett, MD

Matchett Medical Center, President

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Dr. Matchett is a Fellow of the American Academy of Family Practice in private practice, who serves approximately 3,500 families in the North Texas area. She completed a rotating internship and 2 years in a psychiatry residency, passing the written boards in psychiatry before completing a amily practice residency.

Dr. Matchett is Vice President of the Dallas Chapter of the American Academy of Family Practice. She has a strong interest in preventive medicine and patient education. She has developed and lectured on the utilization of patient education materials and educational methods to facilitate detection and recognition of a wide variety of common health problems, including several disorders that are commonly missed or misdiagnosed by primary care physicians, including depression, anxiety disorders, premenstrual syndrome, and headache disorders. These materials are used to engage patient participation in the process of identification and translation of symptoms into a proper diagnosis so that recognized treatment strategies may be employed. There is an assumption that patient compliance with treatment increases when the patient is educated and actively involved in the treatment process.

Frederick Petty, PhD, MD

Associate Professor, Department of Psychiatry

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Dr. Petty received his PhD from the Georgia Institute of Technology (1971) and his MD from the University of Tennessee (1976). He completed his residency in psychiatry at the University of Iowa (1980).

Dr. Petty is the recipient of a Research Career Development Award from the Department of Veterans Affairs. He was the Director of the Consultation/Liaison Service at both the Iowa City and Dallas Department of Veterans Affairs Medical Centers. He conducts both basic and clinical research on the biology of stress and depression, as well as on biologic markers for alcoholism. Dr. Petty has received independent, peer-reviewed funding to conduct his research from the Veterans Administration Merit Review Board, NIMH, and NIAAA. He has lectured widely to family practice and general internal medicine physicians regarding the differential diagnosis and management of mood disorders. Dr. Petty is Director of the Depression Clinic at the Department of Veterans Affairs Medical Center in Dallas.

Herbert C. Schulberg, PhD

Professor of Psychiatry, Psychology and Medicine

University of Pittsburgh School of Medicine

Pittsburgh, Pennsylvania

Dr. Schulberg received his BA from Yeshiva College (1955), his PhD from Columbia University, and his MS Hygiene from the Harvard School of Public Health (1963). He completed 2 years of pre-doctoral internships in clinical psychology at several Veterans Administration facilities.

Dr. Schulberg is Director of the Primary Care Consultation Program at the Western Psychiatric Institute and Clinic. He is a Fellow of the American Psychological Association, and was previously president of the American College of Mental Health Administration and a Visiting Scientist at the NIMH. He has published more than 125 peer-reviewed articles, chapters, and books that focus on the delivery and evaluation of psychiatric services, as well as the recognition, differential diagnosis, and treatment of depression and other psychiatric disorders in the primary care setting. Dr. Schulberg is a recognized national authority in this area. He has received several NIMH grants that support his research efforts. Presently, Dr. Schulberg is directing an NIMH-funded 4-year study of the clinical efficacy and cost efficiency of various treatments for major depression in primary care practice.

G. Richard Smith, Jr., MD

Professor and Director

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Dr. Smith received his MD from the University of Arkansas (1977), where he completed his residency in psychiatry. He was a Fellow in Psychiatry and Medicine at the University of Rochester (1980-81). He has served as residency director in the Department of Psychiatry at the University of Arkansas. He has published in the areas of alexithymia, somatization disorder, consultation-liaison, and immunology. He has received NIMH and Robert Wood Johnson Foundation research support for studies of somatization disorder and psychosocial disabilities associated with myocardial infarction. He has been developing disease-specific outcome modules for psychiatric conditions.

Dr. Smith currently serves as Chair of the NIMH Initial Review Group on Mental Health Services Research. He is Director of the Centers for Mental Healthcare Research, which include the NIMH Center for Rural Mental Healthcare Research and the Veterans Affairs Field Program for Mental Health.

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Associate Professor and Chief, Division of Psychiatric Nursing

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Dr. Stuart received her MS in psychiatric nursing from the University of Maryland (1973) and her PhD in behavioral sciences from Johns Hopkins University (1985). She is a certified specialist in adult psychiatric and mental health nursing from the American Nurses Association and maintains a private practice of psychotherapy.

Dr. Stuart's clinical and research interests involve the study of depression, anxiety disorders, and mental health care delivery systems. As Chief of the Division of Psychiatric Nursing, in the Department of Psychiatry, Dr. Stuart is responsible for overseeing the clinical inpatient units at the Institute of Psychiatry. She is also the coordinator of the graduate program in psychiatric nursing at the Medical University of South Carolina in Charleston.

Dr. Stuart has received multiple honors and awards for her work from a large number of organizations and is a Fellow of the American Academy of Nursing. She serves on the NIMH Task Force on Psychiatric Nursing and the NIMH Research Resource Panel for the Severely Mentally Ill, among other national appointments. Dr. Stuart has been the principal investigator or coinvestigator on several independent research grants, including studies of the pharmacotherapy and childhood environments of patients with panic disorder, bulimia, and depression. She has written several nationally recognized textbooks on psychiatric nursing and has a substantial list of

peer-reviewed journal publications in both the areas of psychiatric disorders and the role of nursing in health care delivery.

Reviewing Consultants for Diagnosis Issues [1]

The Psychobiology of Fibromyalgia (Fibrositis) Syndrome

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Screening Laboratory Evaluation in Psychiatric Patients: A Critical Review

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Screening Ambulatory Depressives for Causative Medical Illnesses: The Example of Thyroid Functioning

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Chronic Fatigue Syndrome

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Depression vs. Dementia

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Depression Rating Scales

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Treatment of Depression in Patients with Co-morbid Eating Disorders

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Completed Suicide: A Review

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Critical Review of Data Supporting Affective Disorder Caused by Nonpsychotropic Medication

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Depression in Adults with Diabetes

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Depression in the Cancer Patient

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The Depressed Alcoholic: Clinical Features and Medical Management

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The Detection of Personality Variables Relevant to the Treatment of Depression in Primary Care: A Review of the Literature

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Treatment of Depressive Disorders Following Stroke

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Epidemiology of Depression in Primary Care

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Self-Report and Projective Measures in the Detection, Differential Diagnosis, and Management of Depressive Disorders in Outpatient Primary Care Settings

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The Epidemiology and Treatment of Coexisting Depression, Somatoform Disorders, Somatization, and Pain

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Depressive Syndromes and Their Treatment in Children and Adolescents

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[Attachments - incorporated in text in printed version]

Tables

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/gain.
4. Insomnia/hypersomnia.
5. Psychomotor agitation/retardation.
6. Fatigue (loss of energy).
7. Feelings of worthlessness (guilt).
8. Impaired concentration (indecisiveness).
9. Recurrent thoughts of death or suicide.

Source: American Psychiatric Association, 1987.

Table 2. Prevalence of major depressive and other mood disorders in primary care settings

Study	Number of Subjects	Interview	Major Depression	Other Mood Disorders
Barrett, Barrett, Oxman, et al., 1988	1,055 screened with SCL depression subscale; 260 interviewed	SADS-RDC	2.2% (6.4% masked major depression)	3.6% episodic minor depression; 2.1% chronic depression
Blacker and Clare, 1988	2,308 screened with GHQ; 1,019 interviewed	SADS & PSE RDC	4.8%	5.0% intermittent depression; 3.4% minor depression
Burnam, Wells, Rogers, et al., 1989	RAND Medical Outcome Study; Los Angeles, Chicago	DIS & DSM-III	4.1-5.4%	Not reported
Coulehan, Schulberg, Block, et al., 1990	University general internal medicine clinic; 618 patients	DIS & DSM-III	6.6%	Not reported

Hoeper, Nycz, Cleary, et al., 1979	1,072 screened with GHQ; 247 completed SADS-L	SADS-L & RDC	5.6%	5.0% intermittent depression; 3.4% minor depression
Hoppe, Leon, and Realini, 1989	Family health center, San Antonio; 165 patients	DIS & DSM-III	F = 9.8% MDD or dysthymia; M = 11.1% MDD or dysthymia	Not reported separately
Kessler, Cleary, and Burke, 1985	ECA users of health care	DIS & DSM-III	F = 6.9-9.3% M = 3.3-6.5%	Not reported
Ormel, Van Den Brink, Koeter, et al., 1990	2,237 screened with GHQ	PSE & PSE-10 Bedford College Criteria	5.6%	4.7% borderline depression (similar to minor depression)
Schulberg, Saul, McClelland, et al., 1985	1,554 screened with CES-D; 294 completed DIS	DIS & DSM-III	6.2%	3.0% dysthymic and adjustment disorder
von Korff, Shapiro, Burke, et al., 1987	1,242 screened with GHQ; 730 patients interviewed	DIS & DSM-III	5%	3.7% dysthymic disorder
Zich, Attkisson, and Greenfield, 1990	University general internal medicine: 65 patients	DIS & DSM-III	7.7%	Not reported

Note: SCL = Symptom Checklist. SADS-RDC = Schedule for Affective Disorders and Schizophrenia Research Diagnostic Criteria. GHQ = General Health Questionnaire. PSE = Present State Examination. DIS = Diagnostic Interview Schedule. SADS-L = Schedule for Affective Disorders and SchizophreniaQLifetime Version. MDD = major depressive disorder. ECA = Epidemiologic Catchment Area. CES-D = Center for Epidemiological Studies Depression Scale.

Table 3. Major depressive disorder subgroups

Subgroup	Essential Features	Diagnostic Implications	Treatment Implications	Prognostic Implications
Psychotic	Hallucinations, Delusions	More likely to become bipolar than nonpsychotic types. May be misdiagnosed as schizophrenia.	Antidepressant medication plus a neuroleptic is more effective than are antidepressants alone. ECT is very effective.	Usually a recurrent illness. Subsequent episodes are usually psychotic. Psychotic subtypes run in families. Mood-incongruent features have a poorer prognosis.
Melancholic	Anhedonia, Unreactive mood, Severe vegetative symptoms	May be misdiagnosed as dementia. More likely in older patients.	Antidepressant medication is essential. ECT is 90% effective.	If recurrent consider maintenance medication.

Atypical	Reactive mood Overeating/weight gain, Oversleeping, Rejection sensitivity, Heavy limb sensation, Fewer episodes	Common in younger patients. May be misdiagnosed as personality disorder.	TCAs may be less effective. MAOIs are preferred. SSRIs preferred.	Unclear.
Seasonal	Onset, fall Offset, spring Recurrent	More frequent in non-equatorial latitudes. Pattern occurs in major depressive and bipolar disorders.	Medications have ? efficacy. Psychotherapy has ? efficacy. Phototherapy is an option.	Recurs.
Postpartum psychosis/ depression	Acute onset (<30 days) in postpartum period. Severe, labile mood symptoms. 1/1,000 is psychotic form.	Often heralds a bipolar disorder.	Hospitalize. Treat medically.	50% chance of recurring in next postpartum period.

Note: ECT = electroconvulsive therapy. TCA = tricyclic antidepressant. MAOIs = monoamine oxidase inhibitors. SSRIs = selective serotonin reuptake inhibitors.

Table 4. DSM-III-R criteria for dysthymic disorder

- A. Depressed mood for most of the day, more days than not, for at least 2 years
- B. While depressed, presence of at least two of the following:
    1. Poor appetite/overeating.
    2. Insomnia/hypersomnia.
    3. Low energy/fatigue.
    4. Low self-esteem.
    5. Poor concentration or difficulty making decisions.
    6. Feelings of hopelessness.
- C. During a 2-year period of the disturbance, never without the symptoms in A and B for more than 2 months at a time.
- D. No evidence of a major depressive episode during the first 2 years.
- E. Never had a manic or hypomanic episode.
- F. Not superimposed on a chronic psychotic disorder, such as schizophrenia or delusional disorder.
- G. Cannot be established that an organic factor initiated and maintained the disturbance.

Source: American Psychiatric Association, 1987.

Table 5. DSM-III-R criteria for a manic episode

- A. A discrete period of abnormal, persistently elevated, expansive, or irritable mood.
- B. At least three of the following in the same period:
    1. Inflated self-esteem/grandiosity.
    2. Marked decrease in need for sleep.
    3. Much more talkative (pressured speech) than usual.
    4. Flight of ideas (rapidly racing thoughts).
    5. Marked distractibility.
    6. Increased goal-directed activity/psychomotor agitation.
    7. Excessive involvement in pleasurable activities without regard for negative consequences (e.g., unrestrained buying sprees, sexual indiscretions, foolish business ventures).
- Symptoms severe enough to impair function markedly or require hospitalization to prevent harm to self or others.
- Not caused by schizophrenia, schizoaffective disorder, or substance abuse.

Source: American Psychiatric Association, 1987.

Table 7. Medications reportedly associated with depression

Cardiovascular Drugs	Hormones	Psychotropics
Alpha-methyldopa (+/-) Reserpine (++) Propranolol (+/-) Guanethidine Clonidine Thiazide diuretics Digitalis	Oral contraceptives (+/-) ACTH (corticotropin) and glucocorticoids (++) Anabolic steroids (+)	Benzodiazepines Neuroleptics
Anticancer Agents	**Anti-Inflammatory/Anti-Infective Agents**	**Others**
Cycloserine Ethambutol Disulfiram Sulfonamides Baclofen Metoclopramide	Nonsteroidal anti-inflammatory agents Amphetamines (withdrawal) (++) L-dopa (+/-) Cimetidine Ranitidine	Cocaine (withdrawal) (++)

Note: These medications have been reported to induce depression in some cases. Not everyone receiving one of these will necessarily be depressed. The cause of depression in a depressed person receiving treatment is not necessarily the medication. This list indicates some medications that should be evaluated as possible causes of depression in particular patients. The degree of certainty of a causal relationship is shown in parentheses for selected drugs.
Source: Derived from Popkin MK. "Secondary" syndromes in DSM-IV: a review of the literature. In: Frances AJ, Widiger T, editors. DSM-IV sourcebook. Washington, DC: American Psychiatric Press; in press.

Table 8. Steps in detecting and treating depressive conditions

(1) Maintain high index of suspicion and evaluate risk factors.

(2) Detect depressive symptoms with clinical interview and/or self-report questionnaire.

(3) Define mood syndrome (clinical history, interview, report by spouse or significant other).

(4) Define potential known causes of mood syndrome (medical, medications, substance abuse, other causal nonmood psychiatric disorders).[1]

(5) Treat potential causes.

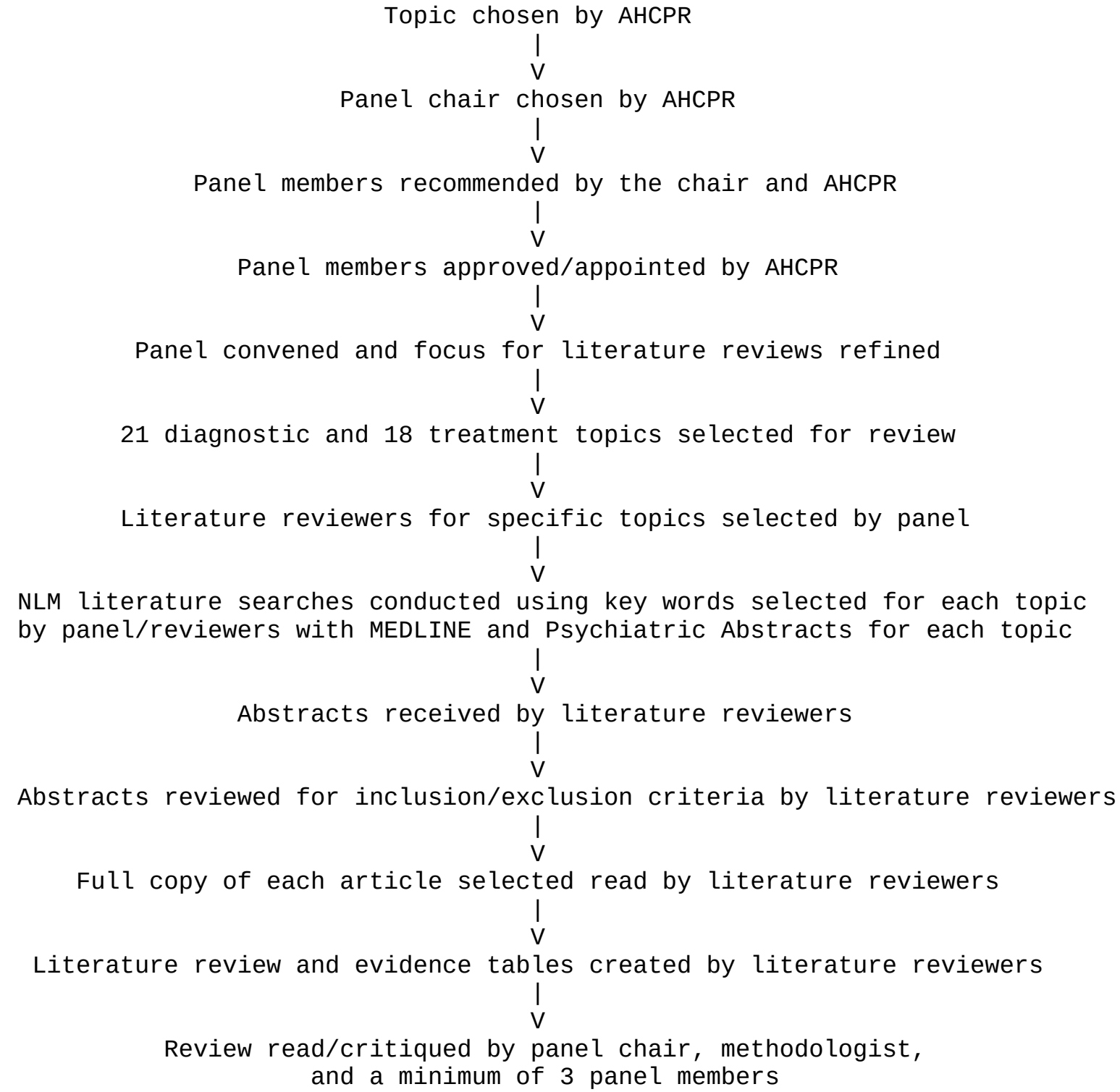
(6) Reevaluate for mood syndromes.

(7) If mood syndrome is still present, treat as primary mood disorder.

[1] In some cases, the mood syndrome itself and the underlying cause must each be specifically treated.

Figures

Figure 1. Guideline development process



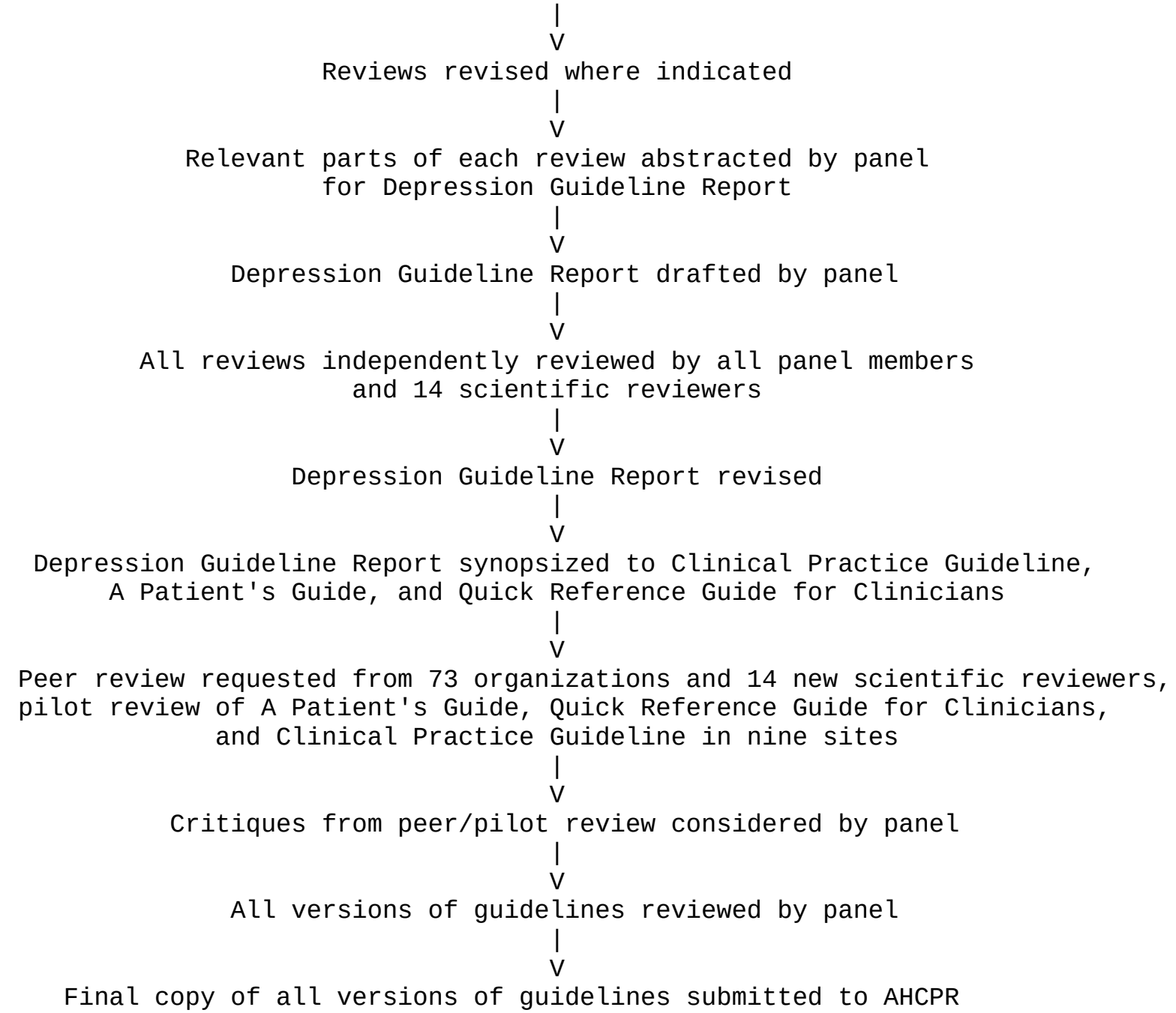


Figure 2. Conditions associated with mood symptoms or major depressive episodes

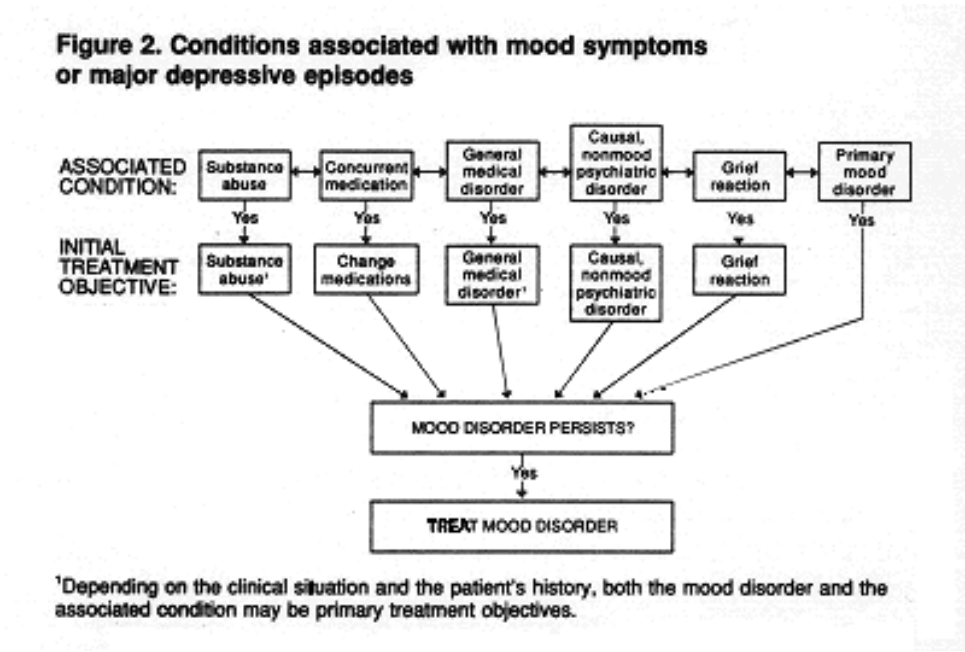


Figure 3. Differential diagnosis of primary mood disorders

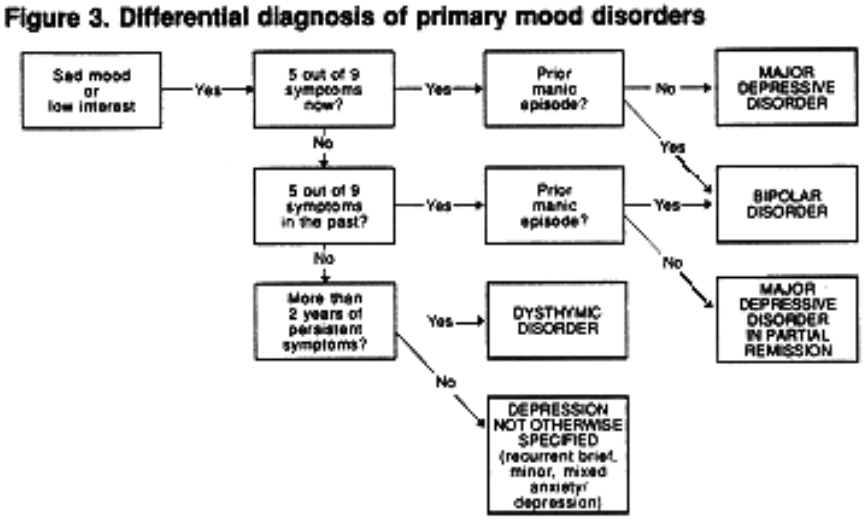


Figure 4. Relationship between major depressive and other current psychiatric disorders

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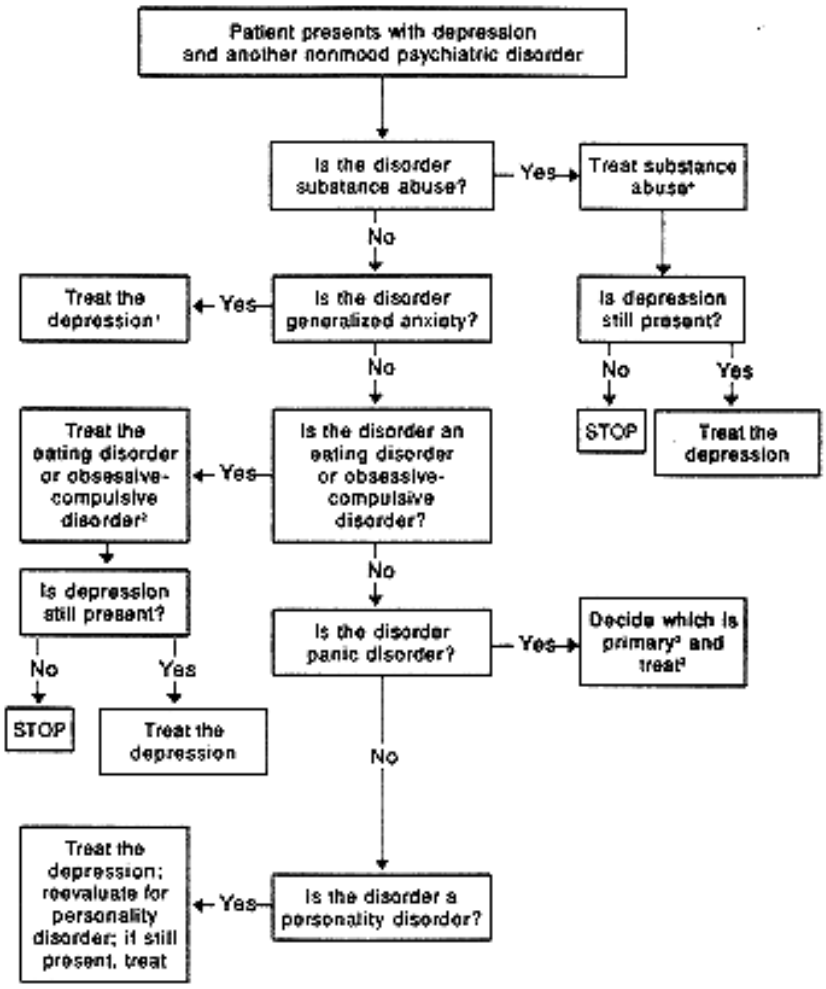

'When the depression is treated, the anxiety disorder should resolve as well.
²Choose medications known to be effective for both the depression and the other psychiatric disorder.
³Primary is the most severe, the longest standing by history, or the one that runs in the patient's family.
⁴In certain cases (based on history), both major depression and substance abuse may require simultaneous treatment.

Figure 5. Relationship between major depressive and other current general medical disorders

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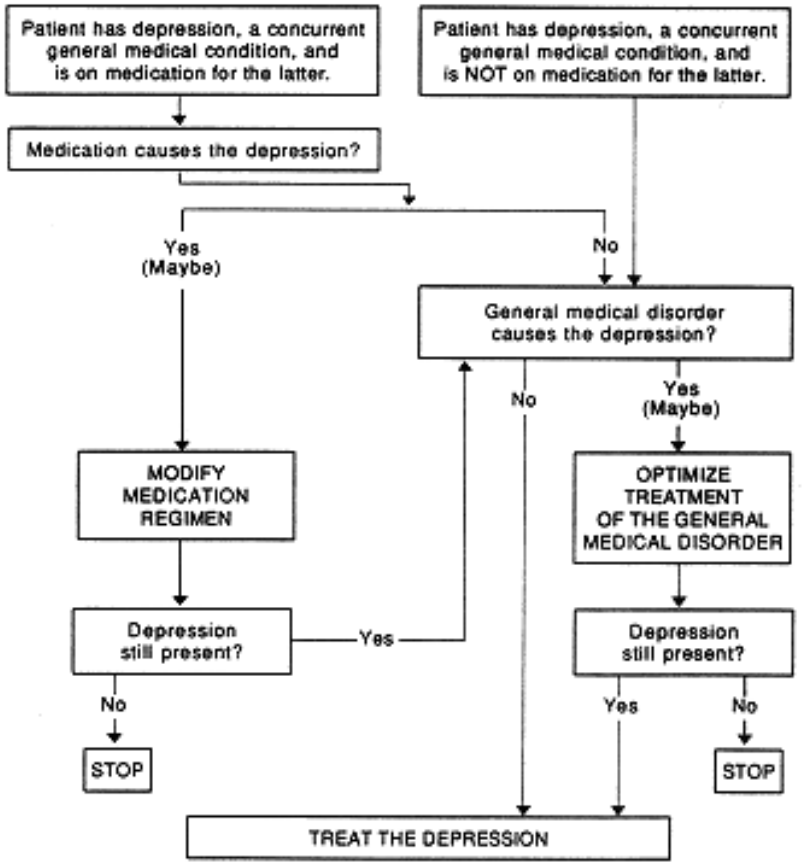

Note: In some clinical situations, treatment of the depression (e.g., if severe, incapacitating, or life-threatening) cannot be delayed until treatment for the general medical disorder has been optimized.

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