VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER** IN ADULTS

Veterans Health Administration
Department of Defense

Prepared by:

THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER**
Working Group

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INTRODUCTION

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Introduction

MDD is a serious public health problem in the Veteran Health Administration (VHA) health care systems, the Department of Defense (DoD), and in the nation at large; hence, timely diagnosis and effective treatment is an important responsibility of health care providers. Major depression and its milder variant, dysthymia, affects about 13 million (5 percent) Americans at any given time and one out of every twenty Americans over the course of their individual lives will develop depressive symptoms severe enough to merit the diagnosis of MDD (Blazer, 1994). The Global Burden of Disease Study has estimated that MDD is currently the fourth leading worldwide cause of disability adjusted life years (the sum of lost life due to mortality and years of life adjusted for the severity of disability) (Murray (a), 1997). Projections into the early part of the next century suggest that it will rise to become the second most important cause of disability adjusted life years, behind only ischemic heart disease (Murray (b), 1997). There is little room for doubt that MDD is a major cause of impaired productivity and organizational inefficiency within government, including the Department of Veterans Affairs (VA) as well as in those communities served by U.S. Army, Navy, and Air Force.

It is now well known that MDD is a critical health care priority. About ten to fifteen percent of all primary care patients have MDD, easily making it perhaps the most common disorder that primary care providers see in their practices (Simon, 1999). A recent survey of 2000 veterans seen in primary care clinics of the Department of Veterans Affairs (VA) in Boston revealed a 40 percent incidence of depression, post-traumatic stress disorder (PTSD), or an alcohol-related disorder (mostly in combination) in that population, a considerately higher rate than in non-VA primary care populations (Hankin, 1999). Indeed, over half of depression-related health care in the U.S. occurs in the offices of family practitioners, general internists, and other general medical providers, while only about a fifth of depression-related health care occurs in specialty mental health care settings (Regier, 1993; Regier, 1978). MDD sufferers often present to their doctors with vague physical symptoms rather than emotional complaints (somatic equivalents), so that MDD is often never even suspected (Docherty, 1997). Primary care physicians miss the diagnosis in over half of their patients suffering from MDD, and when they recognize it, the quality of depression care is often less than optimal (Coyne, 1995; Brody, 1995). MDD assumes particular importance among the working age population such as exists in the military, because it affects both young and old equally (and women, two times as often as men), in contrast to many other chronic diseases that differentially affect older Americans (Roberts, 1997).

The tragedy of how often MDD is missed or underdiagnosed in the primary care setting is that it is an imminently treatable disorder. Research now shows that a range of cost-effective treatments is feasible and efficacious in both the primary care and specialty mental health care settings (Davidson, 1999). Effective treatment can reduce and/or eliminate depression symptoms (Mulrow, 1998), improve health-related quality of life, (Heiligenstein, 1995), and, in some research, even improve occupational performance and productivity among those with MDD (Mintz, 1992). Other research has shown that guideline-driven improvements in the quality of depression care can result in improved symptoms and symptom-related quality of life for those affected (Katon, 1995).

Guideline Development Process

Version 1.0 of the Major Depressive Disorder Clinical Practice Guideline was released to the Department of Veterans Affairs in January, 1997. This initial guideline and algorithm was the product of fifteen months of consensus building among experts in the treatment of major depression and professionals from all aspects of the Veterans Health Administration care continuum: psychiatrists, psychologists, social workers, nurses, chaplains, administrators, primary care physicians, program specialists in geriatrics, external peer review physicians, and expert consultants in the field of guideline and algorithm development. The guideline and algorithm draw heavily from APA (American Psychiatric Association, 1993) and AHCPR (Depression Guideline Panel, 1993) practice guidelines for depression. Version 1.0 contained five modules focusing on primary care, outpatient mental health, psychiatric hospital care, co-morbid substance abuse, and co-morbid PTSD, respectively. Version 1.1 released on March 10, 1998, changed two sections of the Module A annotations: the section on brief screening for mood disorder and the section on pharmacological management. The new section on pharmacological management was taken directly from The Pharmacologic Management of Major Depression,

prepared by the Medical Advisory Panel (MAP) for the Pharmacy Benefits Management Strategic Health Group, August, 1997. Both versions have been widely disseminated throughout VHA and their adoption has been a national performance requirement in all 22 Veterans Integrated Service Networks (VISNs) for two years.

The importance of Army, Navy, and Air Force participation in the development of Version 2.0 of specific treatment guidelines for MDD should be obvious in view of the above facts. Both the VHA and DoD are proud to participate jointly in the development of these guidelines. The current MDD Clinical Practice Guidelines, redesigned for both VHA and DoD, represent hundreds of hours of diligent effort on the part of participants from the VHA, DoD, academia, and a team of private guideline facilitators. An experienced moderator who has developed clinical practice guidelines for nearly 20 years facilitated the multidisciplinary expert panel that included internists, family practitioners, psychiatrists, psychologists, psychiatric nurses social workers, and chaplains, from a wide-variety of specialty and primary care settings, diverse geographic regions, and both VHA and DoD health care systems, civilian practitioners, and policy-makers. The process is evidence-based whenever possible, and in the places where evidence is weak or nonexistence, the vast clinical experience within the room was used to guide the development of consensus recommendations.

The resulting MDD clinical practice guideline may be found herein. We are confident it represents a significant step forward for mental health care in VHA and DoD. However, it is only the first step in the mission to improve the care of those with depression. In the future, the challenge will be in:

- Guideline implementation
- Guideline promotion
- Development of teaching tools for graduate and continuing medical education
- Development of automation tools that include:
  - Provider specific report cards
  - Performance monitors that assist the practitioner/facility in outcome tracking based on guideline use.

Future iterations and performance measures will be needed to sustain state-of-the-art VHA and DoD care of beneficiaries afflicted with MDD.

The clinical practice guideline is presented in an algorithmic format. An algorithm is a set of rules for solving a problem in a finite number of steps. A clinical algorithm allows the practitioner to follow a linear approach to the recognition and treatment of MDD. Clinical practice, however, often requires a nonlinear approach. For example, MDD may be the initial presenting complaint, but a coexisting condition may require attention first.

A letter within the box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are noted in each box of the algorithm. These annotations include a reference, when required, and evidence grading for each of these recommendations, the strength of recommendation (SR) and the quality of evidence (QE) (U.S. PSTF, 1996). The reference list at the end of each module includes all the sources used directly or indirectly in the substantiation of this guideline.

Although several grading systems are available, the participants reviewed the articles for relevance and graded the evidence using the task force rating scheme published in *The Guide to Clinical Preventive Services, Second Edition,* (1996*).* Virginia: International Medical Publishing, Inc.

The rating scheme is as follows:

Strength of Recommendation (SR)

A	There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
B	There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination
C	There is insufficient evidence to recommend for or against the inclusion of the condition in a periodic health exam, but recommendations may be made on other grounds.
D	There is fair evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.
E	There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

Quality of Evidence (QE)

I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees**.**

The strength of recommendation (SR) uses evidence that supports (or does not support) the suggested intervention. The quality of the evidence (QE) is related to study design, such as large randomized control trials.

It should be noted that an exact correlation does not have to exist between the SR and the QE. There are times when the SR of "C" leads to and QE of "I" and visa versa. For many preventive services, there is insufficient evidence to determine whether or not routine intervention will improve clinical outcomes. Circumstances resulting in an SR of "C" recommendations include:

- Insufficient statistical power
- Unrepresentative populations
- Lack of clinically important endpoints
- Design flaws (The Guide to Clinical Preventive Services, 2nd Ed., 1996).

This Guideline integrates the recommendations developed by VHA's Medical Advisory Panel (MAP) to the Pharmacy Benefits Management Strategic Health Group examining the pharmacological management of persons with MDD.

Overview of the Major Depressive Disorder Guideline

Modules and Appendices

The Major Depressive Disorder guideline is organized into three modules with a linkage to the major depressive disorder algorithm providing an overview of the relationship between the modules:

Module A—MDD in the Primary Care Setting
Module B—MDD in the Outpatient Mental Health Specialty Setting
Module C—MDD in the Inpatient Setting.

Module A is designed for practitioners working in primary care clinics with connections to outpatient mental health specialty clinics (Module B) and inpatient mental health settings (Module C). In contrast to the previous MDD Guidelines, these modules are designed for patients already suspected of a diagnosis of depression at some level as a result of a specific screen or clinical judgement.

This guideline also contains multiple appendices that provide screening instruments and more detailed information about a condition or treatment option to inform the provider of the spectrum of treatment options and settings to accommodate the remote primary care provider through specialty advise and treatment options. These appendices are referred to as references from within each module. Such appendices include:

Appendix 1. Assessment Instruments
Appendix 2. Unstable and High Risk Conditions
Appendix 3. Suicidality
Appendix 4. Empirically Supported psychoTherapies (ESTs) of MDD
Appendix 5. Pharmacological Therapy of MDD
Appendix 6. Non-MDD Conditions Deserving Consultation
Appendix 7. Patient Education
Appendix 8. Electro-convulsive Therapy (ECT).

A comprehensive list of contact information about each of the participants is provided in the last section.

The guideline/algorithms are designed to be adapted to the individual facility's needs and resources. They will also be periodically updated or when relevant research results become available. The guideline should be used as an impetus for administrators at each of the federal agencies and care access sites to develop innovative plans to break down the barriers preventing primary care providers, subspecialists and allied health professionals from working together, and from preventing patients from having prompt access to preventive care. The ultimate goal is to improve local management of patients with major depressive disorder and thereby improve patient outcomes.

Literature Review

The majority of literature supporting the science for this guideline is referenced throughout the document and is based on selected review queries. Just recently the Evidence-Based Practice Center (EPC) in San Antonio, Texas, published a systematic review of the literature on Depression. This report proved to be timely since the VHA and DoD had just begun the revision process of the Major Depressive Disorder (MDD) guideline. In addition to the EPC report, the MDD working group leaders identified three questions dealing with diagnosis and treatment of depression in primary care using cognitive therapy. They include identifying:

1. Depression in primary care
2. Criteria for treating depression in primary care settings
3. Efficacies of psychosocial therapies in treating depression in primary care settings.

The search was limited to publication dates between 1997 and 1999 in the English language only since the previous version contained references and rating through 1998. The literature search was carried out using the National Library of Medicine's (NLM) MEDLINE database. To find candidate titles, the term Depressive Disorder was used as the first medical subject heading (MeSH). As a result the following entries were used to frame the query:

- Psychiatry and Psychology (MeSH Category)
  - Mental Disorders
  - Mood Disorders
  - Depressive Disorder
  - Depression.

In addition, the following Boolean expressions and terms were used concomitantly with the above approaches: cognitive therapy, criteria efficacy, primary care, protocols, psychosocial, screening instruments, therapy (all types), treatment.

Each search was conducted using the above parameters plus a qualifier dealing with specific types of publication such as clinical trial, meta-analysis, practice guideline and random control trial.

Each article was then categorized into a table from which supporting information could be determined to be relevant:

- Title
- Author(s)
- Author(s) affiliation
- Publication type
- Abstract
- Source
- Relevance.

Copies of these tables as well as the EPC report were made available for all MDD workshop participants. Copies of specific articles were provided on an as needed basis.

Other articles were selected for review and inclusion as possible evidence based upon a clinical review through Pub Med and Grateful Med, yielding many more articles that provided evidence to support or not support the efficacy of a given treatment or diagnostic or follow-up modality that related to specific aspects of the already defined questions. Where existing literature is ambiguous or conflicting, recommendations are based on Expert Panel opinion. In the guideline you will note that the evidence grading is not valid for the content of the whole article, but about a specific criterion being recommended. These criteria have been noted in the evidence section of the guideline so that the reader and user of the guideline can know the quality of the evidence or study represented and the strength of recommendation of the specific action being recommended.

Performance Measurement

The inability of consumers and health care purchasers to determine if medical care is appropriate and effective has given rise to the concept that the health care system should be held accountable for what is done and the outcomes achieved. This principle of accountability has resulted in the development of so-called "performance and outcome measures," administered through "report card" systems. Measures must be seen as fair and reasonable, and able to be achieved in various practice settings, and when carried out either by mental health experts and/or generalists.

Performance measures are indicators or tools to assess the level of care provided within systems of care to populations of patients with major depression. The measures are constructed to make the best use of the evidence available for assessing care or outcomes of care in systems where test reliability, patient characteristics, (co-morbidity), and compliance can not be easily determined and taken fully into consideration (e.g., the measures are not case-mix adjusted). This decision was made since the current state of the art does not allow full adjustment for factors outside the control of the health care system.

The VHA instituted performance measures for implementation of clinical practice guidelines, including MDD, Modules A (Initial Assessment and Treatment), and Module C (Inpatient Mental Health Specialty), in FY 1998. These measures included screening all patients for depression in general medicine, primary care, and women's clinics as well as obtaining a Global Assessment of Functioning (GAF) rating on all discharged patients diagnosed with MDD (APA, 1995). In FY 1999, these performance measures were expanded to include data collection on screening for alcohol use and post-traumatic stress disorder (PTSD) in the same clinics. Results for FY 1998 were an average of 44 percent nationally (ranging from 14 to 83 percent) for depression screening and an average of 97 percent (ranging from 56 to 100 percent) for GAF ratings.

With this version of the MDD Guideline, both VHA and DoD will be instituting similar performance measures developed by consensus after developing the guideline.

Disease Management

Disease state management can be defined as the continuous process of identifying and delivering, within selected patient populations, the most efficient combination of resources for the treatment of, or prevention of, disease. The rationale assumes that there are systematic ways health care delivery can be provided to a population that will be more efficient than the status quo. There is no intent to prevent practitioners from using their best judgement in the care of an individual patient. Rather, the intent is to establish verifiable treatment objectives for persons with MDD that will lead to early diagnosis and treatment resulting in remission and full functional ability. The enclosed clinical guideline should be viewed as the cornerstone for Major Depression as Disease State Management Program in the VHA and DoD.

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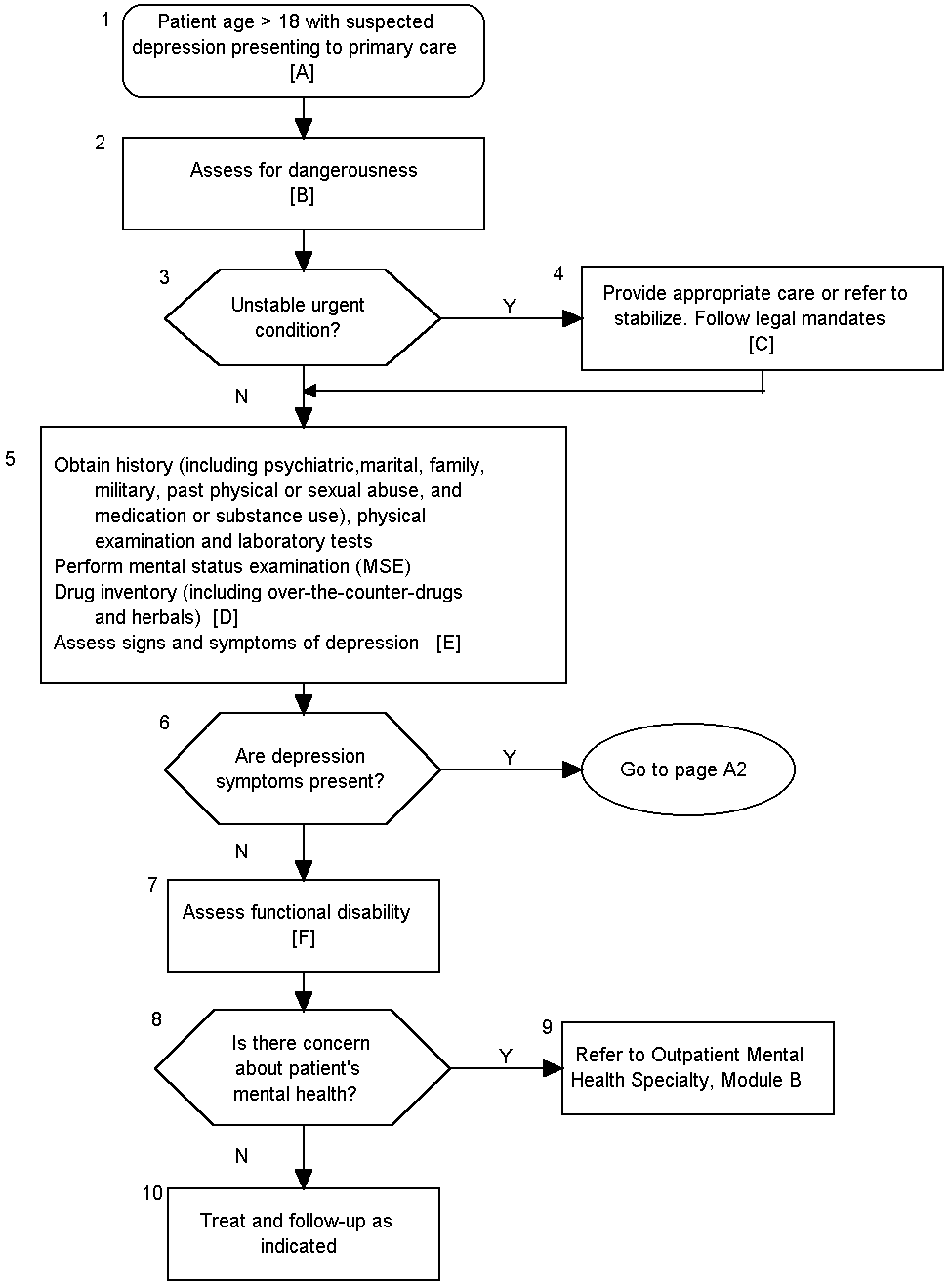
VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER** IN ADULTS IN THE PRIMARY CARE SETTING

ALGORITHMS AND ANNOTATIONS

Module A

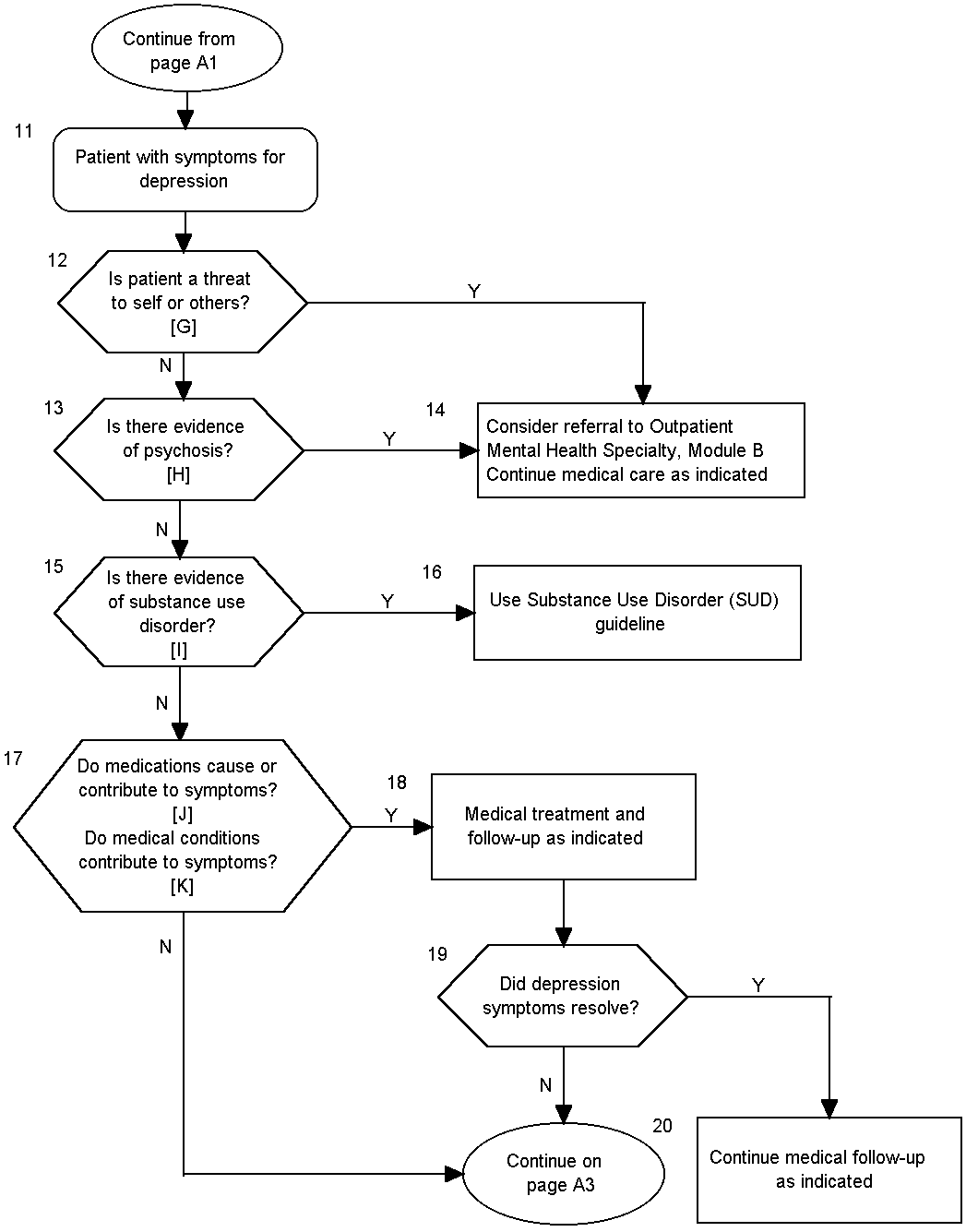
Management of Major Depressive Disorder in Adults in the Primary Care Setting Initial Assessment

A1



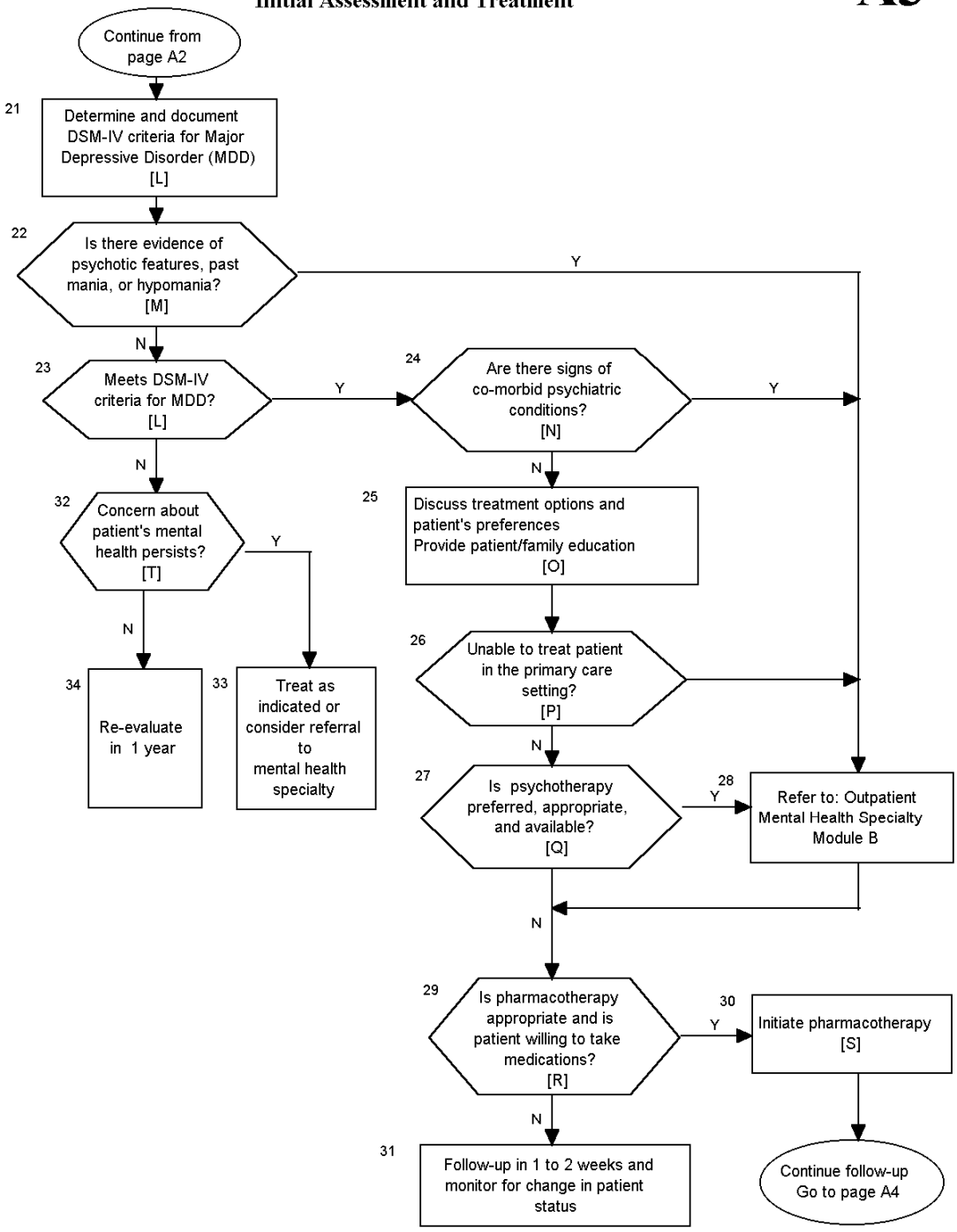
Management of Major Depressive Disorder in Adults in the Primary Care Setting
Establish Diagnosis

A2



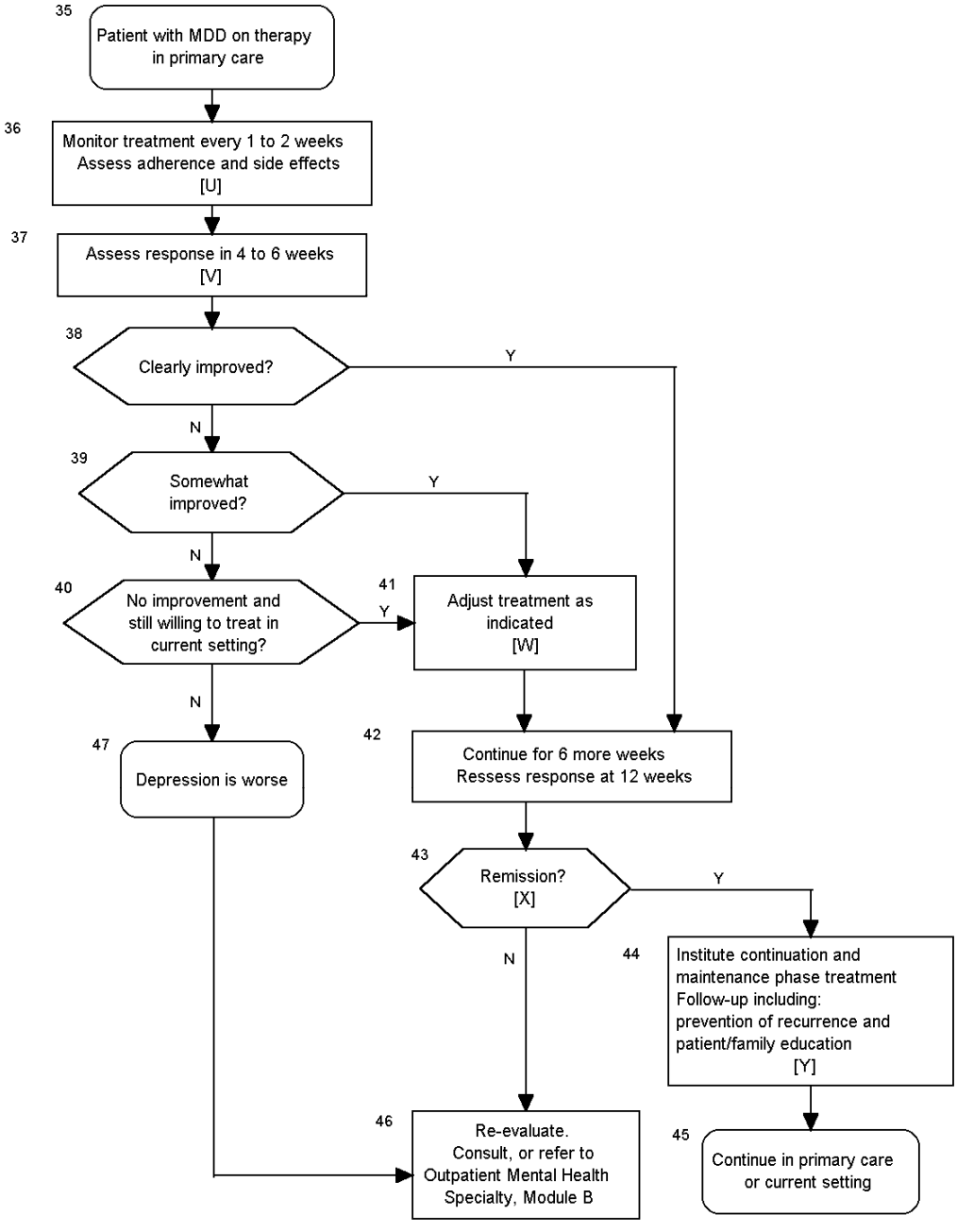
Management of Major Depressive Disorder in Adults in the Primary Care Setting
Initial Assessment and Treatment

A3



Management of Major Depressive Disorder in Adults in the Primary Care Setting
Follow-up Treatment

A4



Management of Major Depressive Disorder in Adults in the Primary Care Setting
Module A

A. Patient Age > 18 with Suspected Depression Presenting to Primary Care

DEFINITION

All patients > 18 who have a positive screen for depression.

DISCUSSION

Depression is known to be under-diagnosed in primary care settings. There is some controversy regarding the value of screening patients in primary care settings, (U.S. PSTF, 1996; Brody DS, et al., 1998; Perez-Stable EJ, et al., 1990). Since recent studies suggest screening is feasible in primary care, the working group decided screening should be recommended (Spitzer RL, et al., 1995; Whooley MA, et al., 1997).

In recognition of the evolving nature of the literature, other published validated scales can be used. Care should be taken to assure scale validation with similar patient populations as those seen in the VA and DoD settings. There are several available screening tools, each with its own strengths and problems. Appendix 1, Assessment Instruments, offers descriptions of a number of screening instruments that may also be used to quantify symptom severity and samples of these tools. Some of the validated screening tools available are listed:

- PRIME MD – Primary care Evaluations of Mental Disorders – depression questions
- CES-D – Center of Epidemiological Studies-Depression Scale
- Zung – Zung Depression Rating Scale
- Beck Depression Inventory – Click Here
- MOS – Medical Outcomes Study Depression Scale
- Ham-D - Hamilton Depression Scale.

In all settings, a validated screening tool should be filled out before the patient sees the primary care provider, and results of the screening should be made available to the provider. Each setting should determine which screener will be adopted, at what point in the check-in process the screener will be utilized, and who will administer the screener (e.g., clerk, nurse who takes vital signs).

B. Assess for Dangerousness

OBJECTIVE

To identify patients that are at high risk of harm to self or others and with any medical or psychiatric conditions requiring immediate attention.

ANNOTATION

Unstable conditions, whether physiological or psychiatric, represent situations that require immediate attention. They include the following:

1. Delirium – Delirium (also known as organic brain syndrome, organic psychosis, acute confusional state, acute brain syndrome and various other names) is a very common disorder of cognition and consciousness of abrupt onset that is commonly unrecognized. This is especially true in the elderly and chronically ill (Farrell KR, 1995).

2. Marked psychotic symptoms – "Psychosis," in and of itself, is not a disorder. Rather, it is a symptom which may present in a variety of conditions. Psychotic patients have an impaired sense of reality, which may manifest in several ways (hallucinations, delusions, mental confusion or disorganization).

3. Severe depressive symptoms/depression (e.g., catatonia, malnourishment, severe disability) – The clinical presentation of depressed patients is marked by considerable variation, not only in the expression of various neurovegetative symptoms themselves, but also in the magnitude of severity of these symptoms. While many mild to moderate illnesses may not necessarily present situations requiring immediate attention, the presence of severe depressive symptoms may represent an urgent condition, even in the absence of suicidal ideation.

4. Suicidality – Suicidal behavior is best assessed with the following criteria: current suicidal ideas or plans, presence of active mental illness (severe depression or psychosis), presence of substance use disorder, past history of suicidal acts, formulation of plan, availability of means for suicide (firearms, pills, etc.), disruption of important personal relationship, or failure at important personal endeavors (Simon RI, 1992). If some or all of these criteria are present, a referral or consultation with a mental health professional is indicated.

5. Potential for violence – Violence often emerges as a response to perceived threat or marked frustration resulting from the inability to meet goals by nonviolent means. The specific factors which contribute to violent behavior include psychiatric, medical, environmental and situational/social (Hastings EJ, 1997; Thienhaus OJ, 1998). Whatever the cause, the following situations may serve as warning signs of violence:

   - Ideas about or intent to harm others
   - History of violent behavior
   - Severe agitation or hostility
   - Active psychosis.

   Immediate attention and intervention may be required in order to stave off the potential for escalation of agitation or violent impulses.

6. Unstable urgent medical conditions – Any condition immediately threatening to life, limb, or eye sight or requiring emergency medical care. These may include acute myocardial infarction, respiratory failure, hypertensive crisis, diabetic ketoacidosis, crushing radiating chest pain, etc.

For more information on these conditions see Appendix 2, Unstable and High Risk Conditions and Appendix 3, Suicidality.

EVIDENCE

Specific factors that contribute to violent behavior include psychiatric, medical, environmental and situational/social. (Hastings EJ, 1997; Thienhaus OJ, 1998; U.S. PSTF, 1996) QE = II-1, SR = B

Insufficient evidence to support routine screening of depression, suicide risk, child abuse or domestic violence. (U.S. PSTF, 1996) QE = II-2, SR = B

Clinicians should maintain a high index of suspicion for depressive symptoms in persons at increased risk of depression, suicide risk, child abuse or domestic violence. (U.S. PSTF, 1996) QE = III, SR = B

C. Provide Appropriate Care or Refer to Stabilize and Follow Legal Mandates

OBJECTIVE

To assure appropriate care and protocols are followed during diagnosis and stabilization.

ANNOTATION

If a patient represents a risk to self or others, providers should follow local, state, and federal guidelines which should be already well established. For VA patients, these procedures should also reflect the opinion and guidance of the VHA District Council. For DoD patients, these procedures are directed by DoD Directive 6490.1, "Mental Health Evaluation of Members of the Armed Forces," DoD Instruction 6490.4, "Requirements for Mental Health Evaluations of Members of the Armed Forces," and related Service regulations/instructions. These regulations/instructions may require a number of notifications (e.g., commanders) which would not be made in a civilian practice. Primary care and administrative staff should be familiar with the applicable policies and procedures. Mental health staff should be prepared not only to manage patients who pose a risk, but should also be prepared to consult with primary care and other medical specialties concerning patients who may be encountered in their clinics. Patient care management plans must reflect the realities of local resources, staffing, and transportation.

If patients represent a risk to others, additional notifications may be required by state or federal laws and/or regulations. When making notifications, it is wise to consult a peer and/or medical law consultant on the legal and ethical requirements.

D. Obtain History (including Psychiatric, Marital, Family, Military, Past Physical or Sexual Abuse, and Medication or Substance Use), Physical Examination and Laboratory Tests. Perform Mental Status Examination (MSE), Drug Inventory (Including Over-the-Counter (OTC) Drugs and Herbals).

OBJECTIVE

To develop an appropriate clinical understanding of the patient that will inform subsequent provider decisions.

ANNOTATION

In primary care and long-term care settings, depression is often undiagnosed and untreated because patients with significant symptoms of depression rarely identify depression as a chief complaint (Heston LL, et al., 1992). Depression may be suspected based entirely on a history of the present illness that reveals recent depressive symptoms. In some cases, the patient may not relate current depressive symptoms, but a screening psychiatric history may reveal one or more past depressive episodes. In other cases, a history of the present illness and the past psychiatric history are unrevealing, but certain medical and psychosocial risk factors suggest that a high index of suspicion is appropriate. For example, multiple unexplained physical symptoms suggest a high likelihood of depression.

After determining that the patient is stable, the priorities are now:

1. Recognizing current signs and symptoms of depression
2. Obtaining a careful psychiatric history, looking for past depressive episodes
3. Remaining attentive to "red flags" suggesting that a higher than usual index of suspicion is necessary.

Obtain a psychiatric history – Key elements of the past history of depression include: prior antidepressant use, past hospitalization for depression or suicidality, and inability to function in usual life roles (Valenstein, 1997). Substance use and misuse can cause and/or exacerbate depression. Use of screening tools (such as the CAGE, AUDIT, MAST or DAST – see Substance Use Guideline, for substance use assessment tools) can improve detection of substance use disorders.

There is a high likelihood of depression among individuals with past or present physical or sexual abuse history or a history of substance use disorders. Primary care physicians should respectfully ask each patient direct and specific questions about physical or sexual abuse during the history.

"Red Flags" suggesting need for a higher than usual index of suspicion – Certain physiological and psychological conditions or life events may contribute to the development or exacerbation of depression symptoms. These may include, but are not limited to:

- Medically unexplained physical symptoms
- Chronic, debilitating medical condition
- Current substance abuse/use (Rost K, et al., 1993)
- Decrease in sensory, physical, or cognitive function
- Victim of current or past physical or sexual abuse or emotional neglect
- Family history of major depression
- Loss of significant relationship, primary support system, or economic status
- Neurological disorder (e.g., Multiple Sclerosis, Parkinson's disease, stroke) or history of closed head injury
- Protracted care-giving role for a family member with a chronic, disabling condition
- Spousal bereavement and widowhood
- Symptoms or signs of PTSD.

Physical Examination – A brief, screening physical examination may uncover endocrine, cardiac, cerebrovascular, or neurologic disease that may be exacerbating or causing depressive symptoms. Particularly in the elderly patient, a full Mental Status Examination (MSE) includes cognitive screening assessment that may consist of a standardized instrument such as the Folstein Mini-Mental State Examination (MMSE) (Crum RM, et al., 1993; Cummings JL, 1993; Folstein MF, et al., 1975) (See Psychoses Guideline). If screening is suggestive of cognitive impairment and the patient is not delirious, then a laboratory evaluation to assess for reversible causes of dementia is appropriate. The depression assessment should be continued (Forsell Y, et al., 1993). If delirium is present, consider it an emergency and stabilize the patient before proceeding, then return to the algorithm and continue with depressive assessment Box 4. Other MSE findings of importance in depression include slow speech, sighing, psychomotor retardation or agitation, downcast eyes, and little or no smiling.

Laboratory Evaluation – Use the history and physical examination findings to direct a conservative laboratory evaluation. There is no test for depression, so testing is directed toward detection of associated general medical conditions. Appropriate laboratory studies to rule out medical disorders that may cause symptoms of depression include complete blood count (CBC), chemistry profile, thyroid studies, and toxicology screen (Rosse, et al., 1995). For patients over the age of 40, an ECG may be useful.

Diagnostic imaging and neuropsychological or psychological testing is not a part of the standard laboratory evaluation for depression. Proceed with the algorithm while awaiting the completion of the laboratory evaluation.

EVIDENCE

Brief Screening may be useful in identifying depression. (Rost, et al., 1993; U.S. PSTF, 1996) QE = II-2, SR = B

E. Assess Signs and Symptoms of Depression

OBJECTIVE

To identify core signs and symptoms that may lead to a diagnosis of depression versus other conditions.

ANNOTATION

Core symptoms and signs of depression include:

1. Depressed mood
2. Loss of pleasure in normally pleasurable activities (anhedonia)
3. Feelings of guilt, hopelessness, and helplessness
4. Fatigue or energy loss
5. Poor concentration or memory problems
6. Persistent appetite changes and weight loss or gain
7. Psychomotor slowing or agitation
8. Morbid thinking to include suicidal ideation and behaviors (Burke WJ, et al., 1992; APA, 1994)
9. Significant altered sleep (too much or not enough) (DSM-IV).

F. Assess Functional Disability

OBJECTIVE

To ensure that patient has no other mental health concerns before discharge from the clinic.

ANNOTATION

Prior to concluding the interview and examination, the clinician should inquire about the patient's ability to carry out personal and daily activities not covered by either the chief complaint or the depression screening questions. This may be elicited in the following manner:

- "During the past few weeks, have any physical or emotional problems interfered with your typical daily activities?
- Has it been more difficult to do things on your own or with your (family, friends, neighbors, church, etc.)?"

If positive, areas for brief inquiry include: job, pleasurable hobbies, social activities, and important personal relationships. As well, the clinician should ask:

- "Are there any other problems that we have not discussed?"

If any patient responses are affirmative, the clinician should define any impediments to optimal daily functioning, recognizing that the patient may have already denied depression and substance abuse. One should be alert for alternative ways of expressing discouragement, distress, or demoralization, especially in those individuals who tend to avoid emotional words for describing themselves.

G. Is Patient a Threat to Self or Others?

OBJECTIVE

To identify patients who pose active risk for dangerousness and who should be assessed further in mental health.

ANNOTATION

Eliciting Suicidal Ideation or Intent – Direct and nonjudgemental questioning regarding suicidal ideation/intent is indicated in all cases where depression is suspected. A significant number of patients who contemplate suicide are seen by a physician in the month prior to their attempt. Direct assessment of suicidal ideation and intent does not increase the risk of suicide. Consider gathering collateral information from a third party, if possible.

One recommended line of questioning uses the following (modified from Hirschfeld RMA, et al., 1997):

- "Have you had thoughts about death or about killing yourself?"
- "Tell me about your hopes for the future?"
- "Do you have a plan for how you would kill yourself?"
- "Are there means available (e.g., pills, a gun and bullets, or poison)?"
- "Have you actually rehearsed or practiced how you would kill yourself?"
- "Do you tend to be impulsive?"
- "How strong is your intent to do this?"
- "Can you resist the impulse to do this?"
- "Have you heard voices telling you to hurt or kill yourself?"
- Ask about previous attempts, especially the degree of intent.
- Ask about suicide of family members or significant others.

Homicidal Ideation – Homicidal ideation and suicidal ideation may co-occur. Risk of violence towards others should be assessed by asking directly whether or not the patient has thoughts of harming anyone.

- Assess whether the patient has an active plan and method/means (i.e. weapons in the home).
- Assess whom the patient wishes to harm
- Assess whether the patient has ever lost control and acted violently
- Assess seriousness/severity of past violent behavior.

If some or all of these are present, a referral or consultation with a mental health professional is indicated. In the event of expressed dangerousness to self or others, steps must be taken to insure patient safety until further evaluation.

EVIDENCE

Suicide Risk Factors and related conditions:

Psychiatric illness. (U.S. PSTF, 1996). QE = I, SR = B

Serious medical illness. (U.S. PSTF, 1996) QE = I, SR = B

Persons with social adjustment problems. (U.S. PSTF, 1996) QE = I, SR = B

Living alone. (U.S. PSTF, 1996). QE = I, SR = B

Recent bereavement. (U.S. PSTF, 1996) QE = I, SR = B

Personal or family history of suicide attempt. (U.S. PSTF, 1996) QE = I, SR = B

Family history of completed suicide. (U.S. PSTF, 1996) QE = I, SR = B

Divorce or separation. (U.S. PSTF, 1996) QE = I, SR = B

Unemployment. (U.S. PSTF, 1996). QE = I, SR = B

Caucasian race, male gender. (U.S. PSTF, 1996) QE = I, SR = B

Advanced age. (U.S. PSTF, 1996). QE = I, SR = B

Family history of substance abuse. (U.S. PSTF, 1996) QE = I, SR = B

Substance abuse. (U.S. PSTF, 1996).QE = I, SR = B

H. Is There Evidence of Psychosis?

OBJECTIVE

To identify patients with acute or chronic psychosis who may require treatment in mental health.

ANNOTATION

Psychosis is defined as a mental state in which the patient is significantly out of touch with reality to the extent that it impairs functioning (Kaplan HI, et al., 1996 p. 539).

Patients with psychotic symptoms may present in an acutely agitated state with a fairly recent onset of disturbed and/or disturbing symptoms. Patients may also present with enduring, chronic symptoms which are long-standing and to which patients have made a reasonably comfortable adaptation. Examples of acute psychotic symptoms that are inappropriate to treat in a primary care setting include: (Kaplan HI, et al., 1996 pp. 539, 681)

- Serious delusions (e.g., fixed false beliefs)
- Visual or (typically) auditory hallucinations
- Incoherence
- Confusion
- Catatonic behavior (e.g., motoric immobility or excessive agitation
- Extreme negativism or mutism, peculiar voluntary movement
- Inappropriate affect of a bizarre or odd quality.

In particular, paranoid concerns that others wish to harm the patient and voices (especially command hallucinations) telling the patient to hurt him or herself or someone else, are indications for an immediate mental health consultation or referral. Patients who have longstanding psychotic illness and who are able to attend to present circumstances without responding to their psychosis may be evaluated and treated for a co-morbid depression in the primary care setting (Kaplan HI, et al., 1996 p. 1391).

It is important to bear in mind that psychotic symptoms may be the direct result of an underlying medical condition, toxic state, alcohol or substance use disorder, or may be associated with a mental health condition such as schizophrenia or affective illness (Kaplan HI, et al., 1996 p. 1391).

I. Is There Evidence of Substance Use Disorder?

OBJECTIVE

To identify patients who require evaluation and treatment according to the guideline for substance use disorder.

ANNOTATION

All patients should be asked about any current or recent use of nicotine, alcohol, or other psychoactive substances.

Screening can be based on:

1. Brief self-report screening instruments for alcohol problems (AUDIT, CAGE, PRIME-MD), nicotine, or other drug problems (DAST, Drug Abuse/Dependence Screening Tool) (Conners GJ, 1995; Schorling JB, et al., 1997; U.S. PSTF, 1996)
2. Reports from responsible others
3. Laboratory tests (e.g., blood or breath alcohol tests, breath carbon monoxide for smoking, urine toxicology elevated carbohydrate deficient transferrin, increased mean corpuscular volume (MCV) or gamma glutamic transferase (GGT) (Anton RF, et al.,1995).

Laboratory tests are not recommended for routine screening of asymptomatic persons. Patients who screen positive should receive a more thorough assessment for substance use disorder and the relationship of substance use to depression (U.S. PSTF: Guide to Clinical Preventive Services, 1996).

See the Substance Use Disorders Guideline for further diagnosis and treatment. The CAGE is a beneficial mnemonic consisting of questions about alcohol use (Buchsbaum DG, et al., 1991 p. 774-7). One or more positive responses to the following questions can be considered a positive result to the CAGE test: Scoring:

C Have you ever attempted to *cut* down on your drinking?

A Have you ever been *annoyed* by other people criticizing your drinking?

G Have you ever felt *guilty* about your drinking?

E Have you ever taken a morning *eye-opener?*

If the CAGE score is 2 or higher, further investigation of substance use is warranted. (Buchsbaum DG, et al., 1991).

EVIDENCE

Brief self-report screening instruments for alcohol problems may help identify drug problems. (APA, 1995, ASAM, 1996; U. S. PSTF, 1996) QE = II-3 SR = B

J. Do Medications Cause or Contribute to Symptoms?

OBJECTIVE

To identify patients who may be experiencing depressed symptoms as a side effect of medication.

ANNOTATION

Many prescription or over-the-counter (OTC) drugs contribute to depression. Although there is little published information on alternative medicines causing depression, consideration should also be given to herbal, nutritional, vitamins and body building supplements, particularly when consumed in large doses. Table 1. provides supportive evidence.

Table 1. Compounds That Commonly Cause Depression

Drug/Drug Class	QE	SR
ACE inhibitors	II-2	C
Amphetamine withdrawal	I	B
Anabolic Steroids	I	B

Drug/Drug Class	**QE =**	**SR =**
Antihyperlipidemics	II-2	C
Benzodiazepines	II-2	C
Cimetidine, Ranitidine	II-2	C
Clonidine	II-2	C
Cocaine withdrawal	I	C
Cycloserine	II-2	C
Digitalis	I	B
Glucocorticoids	I	B
Gonadotropin-releasing agonists	II-2	A
Interferons	II-2	C
Levodopa	II-2	C
Methyldopa	II-2	C
Metoclopramide	II-2	C
Oral contraceptives	II-2	C
Pimozide	II-2	A
Propanolol (Beta Blockers)	II-2	B
Reserpine	II-1	C
Topiramate	II-2	C
Verapamil (Calcium channel Blockers)	II-2	C

Table adapted from *Drug Safety* 1994;10(3):203-19 and modified using information from Bloch M, et al., 1997; Borras C, et al., 1999; Boumendil E, et al., 1995; Crawford P. 1998; Durelli L, et al., 1996; Ganzini L, et al., 1993; Hallas J, 1996; Metzger ED, et al., 1994; Patten SB, et al., 1993; Patten SB, et al., 1994; VA Medical Advisory Panel Guidelines. 1997; VA Medical Advisory Panel Guidelines. 1999; and Warnock JK, et al. 1998.

K. Do Medical Conditions Contribute to Symptoms?

OBJECTIVE

To identify patients who may be experiencing depressed symptoms as a result of an underlying medical condition.

ANNOTATION

Table 2 includes many of the pathobiologies associated with depression. Simultaneous treatment is often required for both the medical problem and psychiatric symptoms. Additionally, there is often a strong association between the level of disability from the medical condition and the depressive symptom requiring treatment.

A useful mnemonic for remembering these is $[TIC]^2p^2m^2d^3$. The mnemonic stands for:

- Trauma
- Tumor
- Infection - immune and autoimmune
- Cardiac/vascular
- Congenital/heriditary
- Physiologic - seizure
- Metabolic malignancy
- Degenerative
- Drug toxicity
- Demyelinating.

Patients with chronic pain may also have associated mood disturbance. This may be encountered among individuals suffering conditions such as Chronic Obstructive Pulmonary Disease (COPD), or Asthma, or more commonly, bone pain with cancer.

Table 2. Pathobiologies Related to Depression

Pathology	Disease
Cardio/vascular	Coronary artery disease Congestive heart failure Uncontrolled hypertension Anemia Stroke Vascular Dementias
Chronic Pain Syndrome	Fibromyalgia, Reflex sympathetic dystrophy, Low back pain (LBP), Chronic pelvic pain Bone or disease related pain
Degenerative	Presbyopia Presbycusis Alzheimer's disease Parkinson's disease Huntington's disease Other Neurodegenerative diseases
Immune	HIV (both primary and infection-related) Multiple Sclerosis Systemic Lupus Erythematosis (SLE) Sarcoidosis
Infection	Systemic Inflammatory Response Syndrome (SIRS) Meningitis
Metabolic/Endocrine Conditions (include renal and pulmonary)	Malnutrition, Vitamin deficiencies Hypo/Hyperthyroidism Addison's Disease Diabetes Mellitus Hepatic disease (cirrhosis) Electrolyte disturbances Acid-base disturbances Chronic Obstructive Pulmonary Disease (COPD) or Asthma Hypoxia
Neoplasm	Of any kind, especially pancreatic or central nervous system (CNS)

L. Determine and Document DSM-IV Criteria for MDD

OBJECTIVE

To identify patients with a major depressive disorder.

ANNOTATION

The essential feature of MDD is a clinical course characterized by one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes, or without being better accounted for by other

medical or mental disorders. At least five of the DSM IV symptoms have been present during the same 2-week period, nearly every day, and represent a change from previous functioning. At least one of the symptoms must be either (1) depressed mood or (2) loss of interest or pleasure. See Appendix 1, Assessment Instruments, for the formal criteria including four additional required symptoms for a diagnosis of major depressive episode (APA, 1994).

The criteria for a major depressive episode are set at a fairly high threshold. At least five symptoms must occur simultaneously, and the symptoms must be present for most of the day, nearly every day and for at least two weeks.

Symptoms can be indicated by either subjective account of the patient or the observation of others. Contacts with family members may help make an accurate diagnosis.

M. Is There Evidence of Psychotic Features, Past Mania or Hypomania?

OBJECTIVE

To differentiate unipolar from bipolar depression.

ANNOTATION

Some depressed patients manifest periods of mania. According to DSM-IV, a manic episode is a distinct period of persistently elevated, expansive, or irritable mood, lasting at least four days, that is clearly different from the usual nondepressed mood and is observable by others. During this period of abnormal mood at least three of the following symptoms are present to a significant degree and have persisted:

- Inflated self esteem or grandiosity
- Decreased need for sleep
- Pressure to keep talking
- Flight of ideas or subjective experience that thoughts are racing
- Distractibility
- Increase in goal-directed activity or psychomotor agitation
- Excessive involvement in pleasurable activities that have a high potential for painful consequences.

These symptoms are severe enough to cause marked impairment in social or occupational functioning or require hospitalization. Symptoms are not secondary to a substance use or general media condition. Hypomania is characterized by a manic episode without accompanying impairment or psychosis. A past history of mania or hypomania excludes a patient from a diagnosis of MDD. These patients may require referral to a mental health professional. These patients often need specialist's treatment and follow-up, since initiating or titrating routine antidepressant medication can precipitate a manic episode.

N. Are There Signs of Co-morbid Psychiatric Conditions?

OBJECTIVE

To determine whether other psychiatric conditions are present in addition to MDD that may complicate treatment.

ANNOTATION

Patients with evidence of psychiatric disorders in addition to MDD may require referral to a specialist. Evidence of co-morbid disorders that should prompt the primary care provider to consider referral include:

1. Extensive history of childhood abuse, unstable or broken relationships, or criminal behavior starting before or during adolescence suggestive of a personality disorder
2. Extreme weight loss suggestive of anorexia nervosa
3. A pattern of "binging" (rapid and excessive consumption of food) and/or "purging" (use of self-induced vomiting, laxatives, or diuretics) to control weight that may suggest bulimia nervosa
4. Frequent and disabling nightmares or flashbacks suggestive of post traumatic stress disorder
5. Other major mental disorders (e.g., schizophrenia or bipolar disorder) likely to significantly complicate the primary care management of depression symptoms.

Patients with medically unexplained physical symptoms suggestive of a somatoform disorder may sometimes require referral to a mental health specialist. However, patients with unexplained physical symptoms often resent psychiatric referral and fail to follow through. Primary care providers should initiate MDD treatment if possible by building a trusting relationship with the patient. The practitioner should carefully explain the reason for referral before and after it is recommended, and set a follow-up appointment after the referral. These measures will help to allay patient concerns that their physical symptoms are being addressed, yet they require more specialized attention to their state of well being and, therefore, are being referred for consultation.

O. Discuss Treatment Options and Patient's Preferences. Provide Patient/family Education

OBJECTIVE

To provide the patient and significant others an understanding of the available treatment options.

ANNOTATION

There are four broad treatment options for patients with MDD. These are:

1. Pharmacotherapy including other somatic therapies, including Electroconvulsive Therapy (ECT)
2. Empirically Supported psychoTherapies (EST)
3. Combined psychotherapy and pharmacotherapy
4. Clinical evaluation of one to three visits.

Patients should be educated about the potential consequences of untreated MDD, and encouraged to return.

DISCUSSION

A balanced presentation of the relative benefits and drawbacks of each approach should be provided, to help the patient and provider make a reasoned decision about which approach to select. Points to consider when presenting the options appear below and in Appendix 7, Patient Education.

Pharmacotherapy – There is a wide range of available antidepressant medications for patients to select from (see Appendix 5, Pharmacological Therapy of MDD). The specific medication choice is generally based on side effect profiles, safety in overdose, history of prior response, concomitant medical conditions, family history of response, and type of depression.

Benefits of pharmacotherapy include:

1. Potential of a more rapid initial treatment response
2. Patient's preference for medications over talk therapies.

Risks or drawbacks of pharmacotherapy include:

1. Need to take medications consistently and exactly as prescribed
2. Potential for medication side-effects or interactions with other medications or medical problems
3. Potential for need to take medication for an indefinite or extended period.

Psychotherapy – This is the use of one of the ESTs, offered in either one-on-one or group format. See Appendix 4, Empirically Supported psychoTherapy (EST), for a full list of the ESTs and supporting evidence. Generally these approaches aim to help depressed individuals thoughtfully examine their behavior, beliefs, emotions, stressors, and personal relationships in an effort to lead to lasting change in factors that may have contributed to the development of depression. For the purposes of this guideline, psychotherapy is NOT simply unstructured and brief support commonly offered in the context of a primary care office visit.

Benefits of psychotherapy include:

1. Effects may persist beyond the duration of treatment
2. The need to take antidepressant medications or experience medication side-effects may be reduced
3. An opportunity for the patient to make meaningful self-improvements or life changes.

Risks or drawbacks of psychotherapy include:

1. Patients need to come consistently for therapy appointments on a frequent basis for several months at a time
2. A therapist trained in an empirically supported psychotherapy may not be available in every care setting.

Clinical Evaluation – For patients that do not meet criteria for complexity, an extended (two to three visits) can often identify those patients whose depressive symptoms are transient. Some individuals will have spontaneous remission of symptoms, particularly when symptoms have bee precipitated by a life crisis. The main risk of extended clinical evaluation is that MDD may not respond and may worsen without active treatment.

EVIDENCE

Neither pharmacotherapy nor empirically supported psychotherapy have been shown to be consistently superior in the immediate or long term outcomes. (Rush & Hollon, 1991; Reynolds et al., 1999) QE=I, SR=A

Medication treatment may lead to faster response, whereas psychotherapy (particularly cognitive behavioral therapy) may reduce risk of relapse. (Fava, et al., 1994; Rush & Hollon, 1991) QE = I, SR = A

Combination of an empirically supported psychotherapy with medication has not been shown to produce consistently better outcomes for most patients than use of one of these approaches on its own, although there may be exceptions with some subtypes. (Reynolds, et al., 1999) QE = I, SR = C

Severity of depression among psychiatric outpatients is not a reliable discriminator of short term response to either medication or empirically supported psychotherapies. (DeRubeis, et al., 1999) QE = II-2, SR = B

P. Unable to Treat Patient in the Primary Care Setting

OBJECTIVE

To assure appropriate level of care based on local resources available.

ANNOTATION

Many patients with major depressive disorder can be effectively treated in primary care settings. Primary care providers are strongly urged to aim for full symptom remission and to refer without unnecessary delay those patients whose symptoms are not remitting.

Primary care providers vary significantly in skill, comfort, and motivation to treat major depression. Before initiating treatment, the primary care provider should weigh the need for referral to a mental health care specialist. The more specific the referring provider's consultation questions, the more successful the referral/ consultation. Reasons for referral to a specialist include the following: (AHCPR, 1993)

- Patient request for mental health care specialist referral/consultation
- Provider request for diagnostic consultation
- Complicating general medical problems
- Complicating mental disorders ("co-morbidity")
- Severe, recurrent, or psychotic depression
- Suspected need for hospitalization
- Suspected need for involuntary commitment
- Need or patient request for psychotherapy
- Need for light therapy
- Need for electro-convulsive therapy (ECT)
- Questions regarding medication selection, initiation, interactions, or administration
- Provider concerns about patient adherence to treatment
- Symptom breakthrough after a positive acute phase treatment response
- History of poor or partial treatment response.

When weighing the need for consultation, the primary care provider should take into account the common barriers to effective mental health consultation. Potential barriers may include:

- Patient reluctance to see a mental health care specialist
- Feasibility for the patient
- Geographical distance from consultants
- Length of time to consultant availability.

Q. Is Psychotherapy Preferred, Appropriate, and Available?

OBJECTIVE

To determine the best treatment option for the patient.

ANNOTATION

- Psychotherapy for depression is generally appropriate for all forms of depression managed in the primary care setting. Because there are no demonstrated differences in outcome between patients treated with psychotherapy or pharmacotherapy, patient choice should be strongly considered in treatment planning.

- Collaborative management of depressed patients with a mental health specialist, especially those with persistent symptoms, can increase the cost effectiveness of care and may be useful for patients who refuse off-site mental health and consultation. (Katon, 1996; Katon, 1995; Von Korff, et al., 1998; Katon, 1999).

- Utilization of mental health specialists affiliated with a primary care center will facilitate communication, joint management, and more convenience for the patient.

- Availability of a competent psychotherapist is a prerequisite for the psychotherapy option. It has been shown, for example, that the competency of the psychotherapist affects treatment effectiveness (Jacobson & Hollon, 1996). Variability in the quality of administration of all treatments affects the patient's outcome for both medication and psychotherapy.

- Combination of an empirically-supported psychotherapy with medication has not been shown to produce consistently better outcomes for most patients than use of one of these approaches on its own. However, addition of cognitive-behavioral therapy to medication has been shown to reduce risk of relapse (Fava et al., 1994; Rush & Hollon, 1991).

See Appendix 4, Empirically Supported psychoTherapies of MDD.

EVIDENCE

Cognitive-Behavioral Therapy is efficacious for reducing residual symptoms of depression and relapse rates among patients successfully treated with antidepressant drugs. (Fava, et al., 1994; Rush & Hollon, 1991) QE = I; SR = A

Competency of the psychotherapist affects treatment effectiveness. (Jacobson & Hollon, 1996) QE = I; SR = A

Collaborative management of MDD improves symptoms of depression and treatment adherence. (Katon W, et al., 1995) QE = I; SR = B

Collaborative Care of MDD increased depression treatment costs but improved the cost-effectiveness of treatment for patients with major depression. (Von Korff et al., 1998) QE = I; SR = B

Stepped collaborative care improved adherence to antidepressants, satisfaction with care, and depressive outcomes compared with usual care among patients whose depressive symptoms persisted after initiation of antidepressant medication. (Katon W, et al., 1999) QE = I; SR = B

R. Is Pharmacotherapy Appropriate and Is Patient Willing to Take Medications?

OBJECTIVE

To determine whether the patient should receive a pharmacological intervention.

ANNOTATION

Generally patients should receive antidepressant medications for the following indications:

- Moderate or severe symptoms of depression
- Significant impairment in social or occupational functioning due to depression
- Suicidal ideation.

Strong indications for antidepressant medication include:

- Past history of a positive response to medications
- Negative response to psychotherapeutic interventions
- Recurrent depressive episodes
- Family history of depression
- Patient preference for drug therapy.

When determining treatment modality, patient preference should be taken into consideration. However, if the patient does not elect to start antidepressant medications and this is deemed detrimental to the patient's welfare, the clinician should continue discussing all treatment options and monitor the patient for worsening of the symptoms. Educational materials may be helpful for persuading the patient that antidepressant medications can be beneficial.

S. Initiate Pharmacotherapy

OBJECTIVE

To determine and initiate the preferred pharmacological treatment.

ANNOTATION

No antidepressant medication is clearly more effective than another. No single medication results in remission for all patients. Patient factors and drug side effect profiles may favor one class of antidepressants over another for a given individual, but there are no clear differences in efficacy between or within classes. The clinician should consider the medical condition of the patient. In some instances, particularly certain gastrointestinal disorders (chronic diarrhea or peptic ulcer disease) the tricyclic class of antidepressants may be a better first choice. The clinician should determine which medications have been efficacious in the past and at what dosages. Generally medications with favorable side effects profiles should be used. Previously efficacious medications, regardless of class, should be considered as a first choice if medications with favorable side-effects profiles do not help.

Selective Serotonin Reuptake Inhibitors (SSRIs) or venlafaxine are generally first line antidepressants for patients in the primary care setting because of their low toxicity and ease of administration relative to other antidepressants. There is insufficient evidence to recommend one antidepressant over another for all patients.

Prior to declaring treatment failure with any antidepressant, it is important to ensure that an appropriate dose titration and target dose range has been achieved and an adequate response period allowed. Doses should be titrated in order to improve the chance of tolerating the drug. Before assessing the efficacy of an antidepressant, a patient should remain on any given drug for a minimum of four to six weeks. In general, initial doses used for the elderly should be lower than in healthy adults. Adequate treatment response may require titration to a full maintenance dose.

General Considerations

- The choice of medication is based on side effect profiles (see Appendix 5, Pharmacological Therapy of MDD, Table 2), history of prior response, family history of response, type of depression, concurrent medical illnesses, concurrently prescribed medications, and cost of medication.
- Rates of response to antidepressants are reported as high as 60 to 70 percent. However the rate of complete remission may be substantially lower.
- Some depressive target symptoms (e.g. sleep, anxiety, insomnia, decreased appetite, decreased energy, libido) may respond to therapy sooner than the depressed mood resolves.
- Patient and family education about the course and nature of depressive illness, treatment and potential side effects, time course to see symptomatic improvement, and importance of treatment compliance helps to improve treatment adherence and the likelihood of success.
- Antidepressants may precipitate manic episodes in bipolar patients, and may activate latent psychosis in some susceptible patients. Close monitoring for such symptoms may be necessary. Abrupt discontinuation of any antidepressant may result in adverse withdrawal symptoms or return of original depressive symptoms. Discontinuation of antidepressant maintenance therapy should be done with a slow taper. Tapering of the antidepressant should be guided by the elimination half-life of the parent compound and metabolites, and close monitoring of depressive symptoms. For discussion of dosing see Appendix 5, Pharmacological Therapy of MDD.

EVIDENCE

Neither pharmacotherapy nor empirically supported psychotherapy have been shown to be consistently superior in the immediate or long term outcomes. (Rush & Hollon, 1991; Reynolds, et al., 1999) QE=I, SR=A

Medication treatment may lead to faster response, whereas psychotherapy (particularly cognitive behavioral therapy) may reduce risk of relapse. (Fava, et al., 1994; Rush & Hollon, 1991) QE = I, SR = A

Combination of an empirically supported psychotherapy with medication has not been shown to produce consistently better outcomes for most patients than use of one of these approaches on its own, although there may be exceptions with some subtypes. (Reynolds, et al., 1999) QE = I, SR = C

Severity of depression among psychiatric outpatients is not a reliable discriminator of short-term response to either medication or empirically supported psychotherapies. (DeRubeis, et al., 1999) QE = II-2, SR = B

Fluoxetine treatment for MDD is not associated with an increased likelihood of suicidal behavior. QE = II-3, SR = B. (Leon AC, et al., 1999, Warshaw, MG, 1996)

Clinical characteristics can help target patients with MDD at high risk for relapse. Risk factors identified included persistent subthreshold depressive symptoms, chronic mood symptoms, or history of two or more major depressive episodes. QE = II-1, SR = B (Lin, et al., 1998)

Patients with atypical depression features are less responsive to TCAs. QE = II-2; SR =C (unreplicated). (Stewart, et al., 1998)

Sertraline maintenance therapy is well tolerated and prevents recurrence or reemergence of depression in chronically depressed patients. QE = I, SR = B. (Keller, et al., 1998)

Cognitive therapy is an effective acute phase treatment alternative to MAOI antidepressant medications for patients with MDD and atypical features. QE = I, SR = C (unreplicated). (Jarrett, et al., 1999)

Analyses of coroners' data suggest that TCAs are associated with elevated death rates in overdose compared with SSRIs. QE = III, SR =C. (Montgomery SA, 1997)

Presence of personality disorders has generally been linked to poorer outcomes for treatment of MDD. QE = II-1, SR = B. (Thase, 1996)

T. Concern About Patient's Mental Health Persists?

OBJECTIVE

To determine if further mental health care is indicated.

ANNOTATION

Other disorders that present with depressive features may warrant treatment in primary care, but are outside the scope of this guideline. Information on some of the most common of these disorders appears in Appendix 6, Non-MDD Conditions Potentially Requiring Specialty Consultation. Of these disorders, only some are likely to be deemed appropriate for treatment in the primary care setting; the most likely are bereavement and adjustment disorder with depressed mood.

U. Monitor Treatment Every 1 to 2 Weeks. Assess Adherence and Side Effects

OBJECTIVE

To ensure patient is responding to treatment.

ANNOTATION

Patients who are early in a course of treatment or patients who have recently undergone a treatment change require subsequent evaluation of response to the new treatment. Although it is too early to expect a full remission of symptoms, many patients will experience an early improvement in depression symptoms. More importantly, the clinician should assess common antidepressant side effects and discuss the patient's overall treatment adherence and satisfaction. During the visit, the patient may ask questions regarding their condition, symptoms, or care. Providers should seize this opportunity to build rapport, convey hope and encouragement.

Patients may refuse psychotherapy and antidepressant medications for a variety of reasons. Some patients with untreated major depression will recover spontaneously, but a significant number require active intervention to achieve full remission of symptoms and functioning (Wells, 1989). The functional impairment from depression is comparable to impairment from a number of other chronic medical conditions. Depressed patients also tend to use more medical services and are at an increased risk of suicide (Lish, 1996; Caine, 1996).

Side effects – Common short-term side effects affecting adherence to the SSRIs include insomnia, agitation or anxiety, appetite reduction, head pain, nausea, and loose stool. Initiating medication regimens at low doses (e.g., 10 mg of fluoxetine qd, 25 mg of sertraline, or 10 mg of paroxetine) may reduce severity of these side effects, and a qam regimen may ease complaints of insomnia. SSRIs may be augmented with trazodone, generally in doses of 25 to 100 mg, hs, to manage insomnia. It should be noted that of the SSRIs, paroxetine may be more likely to cause drowsiness or asthenia, and for this reason it is frequently administered at bedtime (qhs). Nefazodone and mirtazapine have also been associated with complaints of fatigue or insomnia, and administration at bedtime may be more appropriate for these agents as well.

Sexual dysfunction (reduced libido, delayed orgasm, or decreased vaginal lubrication in women) is the most frequent long-term side effect associated with the SSRIs. Some have suggested that Bupropion or other agents (cyproheptadine, yohimbine, and others) may counteract these side effects although there is little evidence for their efficacy.

Use caution in tapering one medication when substituting another. A discontinuation syndrome when stopping SSRIs and venlafaxine has been observed (Zajecka, Tracy, & Mitchell, 1997). Commonly reported symptoms are dizziness, nausea or vomiting, fatigue, aches, chills, anxiety, irritability and crying spells. Rebound depression may occur. Symptoms generally occur within one to three days of discontinuation. Discontinuation syndrome has not been described for fluoxetine, perhaps because of its very long half-life.

Another caution is the very rare but potentially grave possibility of a "central serotonin syndrome" (sweating, fever, tachycardia, hypertension, altered mental status; more severely hyperpyrexia, cardiovascular collapse, and death) during the transition from one medication to another. The risk of this may be increased when two serotonergic agents are administered together or in close proximity (Lane & Baldwin, 1997; LoCorto, 1997). Some authors recommend waiting for at least five times the half-life of a drug (or its metabolites), before initiating treatment with a second agent (Tollefson & Rosenbaum, 1998).

DISCUSSION

Exploring the patient's understanding of the illness and concerns about treatment is often useful. Many patients have misconceptions that render them unwilling to accept treatment. It may also be useful to talk (with the patient's permission) to the spouse or other support persons important to the patient to enlist their support for treatment.

Occasionally patients present with a desire for electro-convulsive therapy (ECT). Most of these patients have a refractory depression or have had effective treatment with ECT in the past. ECT is a safe and rapidly effective treatment that often can be done on an outpatient basis. Patients who are interested in ECT should be referred to a psychiatrist.

V. Assess Response in 4 to 6 Weeks

OBJECTIVE

To ensure patient remains on treatment with desired outcome.

ANNOTATION

A large body of literature studying the effectiveness of either pharmacotherapy or psychotherapy or both typically report at least a partial remission (50 percent symptom reduction) within four to six weeks of treatment. Full response, defined as minimal or no symptoms, often requires a longer duration of treatment, and full restoration of psychosocial functioning may take several months.

Patients may discontinue treatment at the four to six week interval if either the symptoms are not improving or the symptoms have remitted somewhat despite the natural course of the illness. The four to six week patient visit is an important time to reinforce the need for continued treatment, possible treatment modification, patient education and assessment of adherence.

EVIDENCE

AHCPR and American Psychiatric Association Practice Guidelines for Depression recommend a four to six week reassessment for treatment response. (Schulberg HC, et al., 1998; Shelton RC, 1999) QE = I, SR = B

Rate of response for individuals with MDD who show no improvement by week four will be very low and no better than placebo, and a change in treatment regimen is indicated. (Quitkin 1999) QE = II-2, SR = A

W. Adjust Treatment as Indicated

OBJECTIVE

To manage treatment collaboratively with the patient.

ANNOTATION

When changing treatment, it is most appropriate to engage the patient in the decision and to reconsider available alternatives. Some alternative treatments may include medication (if started on psychotherapy), other medications or psychotherapy (if started on medication), and/or combination therapy. Combination treatment may benefit patients unresponsive to psychotherapy or pharmacotherapy alone (Schulberg, Katon, Simon, & Rush, 1998).

Problems with adherence leading to modification of treatment – Adherence to medications may be lower to drugs requiring bid or tid dosing. Utilization of sustained release preparations enhances compliance with these agents. In general, medications that can be taken on a qd schedule are preferred when adherence to a dosing schedule is an issue. Because of its long half-life, fluoxetine may be the best choice for patients who have trouble adhering to a dosing schedule.

Adherence to psychotherapy appointments and assignments is an important predictor of improvement in the empirically supported psychotherapies. If the patient is not compliant, changes in the therapist or the therapy approach should be considered. Combination therapy may also be considered.

For patients who show particularly poor adherence to initial treatment with medication, psychotherapy should be discussed as an alternate treatment option. Likewise, for patients who show particularly poor adherence to psychotherapy, medication should be discussed as an alternative treatment approach.

EVIDENCE

Combination treatment may benefit patients unresponsive to psychotherapy or pharmacotherapy alone.
(Schulberg, et l., 1998) (small number of trials) QE = I, SR = C

X. Remission?

OBJECTIVE

To assess whether the patient with MDD achieves a full remission of symptoms.

ANNOTATION

Remission is defined as a return to full pre-morbid functioning accompanied by a substantial reduction of depressive symptoms. For research studies, experts typically define remission and improvement as a change in score on standardized rating scales such as the Hamilton Depression Scale (HAM-D). Many efficacy studies cite a 50 percent response rate to define improvement, but a more complete symptom and functional status response is necessary to achieve remission. Expert consensus supports a fairly complete symptom and functional status response before declaring a remission of symptoms.

1. The use of rating instruments is one approach to looking for symptom remission. Measures of use include the Hamilton Depression Rating Scale, PRIME-MD Patient Health Questionnaire (PHQ), Beck Depression Inventory – Click Here , and the Zung Depression Rating Scale (See Appendix 1, Assessment Instruments). In primary care settings, however, often a review of "SIG-E-CAPS" depression symptoms (see below) will suffice. At least one group has presented data suggesting that measuring symptom response based on clinician's global impression may be adequate (Crismon, et al., 1999).

S	Sleep disturbance (insomnia or hypersomnia)
I	Interests (anhedonia or loss of interest in usually pleasurable activities)
G	Guilt and/or low self-esteem
E	Energy (loss of energy, low energy, or fatigue)

C Concentration (poor concentration, forgetful)
A Appetite changes (loss of appetite or increased appetite)
P Psychomotor changes (agitation or slowing/retardation)
S Suicide (morbid or suicidal ideation).

EVIDENCE

Remission defined as the patient no longer meeting the DSM III-R criteria for major depression and having Hamilton Depression Scale scores less than seven for up to three consecutive weeks. (Reimherr FW, et al., 1998) QE = II-2, SR = B

Texas Medication Algorithm Project Report defined remission as equal to or greater than 75 percent global improvement in symptoms. Emphasized goal of symptomatic remission and normalization of function rather than only symptom improvement. (Crismon, et al., 1999) QE = III, SR = B

Remission defined as the total final Hamilton Depression Scale 24 item score equal to or less than seven. (Hirschfeld RMA, et al., 1998) QE = III, SR = B

Danish University *Antidepressant Group defined full remission as seven or less on the 17 item HAM-D*. (Fuglum E, et al., 1996) QE = III, SR = B

Y. Institute Continuation and Maintenance Phase Treatment. Follow-up Including Prevention of Recurrence and Patient/Family Education

OBJECTIVE

To prevent relapse or recurrence of future major depressive episodes.

ANNOTATION

MDD is best conceptualized as a chronic illness resulting in a continuum of outcomes ranging from excellent to poor. Increased rates of recurrence were found in fifty percent of the patients with a single episode of MDD, and the greater the number of episodes the more likely are future depressive episodes. A high percentage of individuals with recurrent major depressive disorder will require indefinite prophylactic antidepressant treatment. Factors increasing the risk of future recurrence include:

- A strong family history of mood disorders
- A history of recurrence within one year after discontinuation of a previously efficacious medication
- One or more suicide attempts
- Onset of the first episode before age 20
- Two or more episodes of major depression in the past two years
- Concurrent dysthymia.

Continuation phase of antidepressant treatment follows the acute phase and begins when the patient has complete remission of depressive symptoms. Continuation phase treatment usually lasts up to nine months and is followed by maintenance phase treatment, an indefinite period of prophylaxis against future depressive episodes.

Continuation Phase Treatment – Priorities of the continuation phase include sustaining the dose of medication resulting in acute phase symptom remission; preventing relapse or recurrence of depressive symptoms; monitoring depressive symptoms and functional status; and building a constructive therapeutic alliance.

In psychotherapy, a maintenance plan should be developed during the course of therapy. The plan should include a summary of learning that occurred during therapy; ways the patient will continue to using lessons from the therapy; a prediction of times of high recurrence risk (e.g., death of a significant other); and coping approaches for such crisis periods. Use of booster sessions and occasional reassessment of depressive symptoms should be considered.

Maintenance Phase Treatment – Following the continuation phase, decisions regarding extended maintenance phase treatment are implemented. Patients who have had three or more episodes of major depression or two or more episodes in combination with another risk factor for recurrence (see list above) should remain on prophylactic antidepressant medication for one or more years after remission of the acute episode at the continuation phase dosage.

Patient/Family Education – Education is important for patients and families concerning risk of relapse and ways to reduce risk and sustain remission status. Information about recurrence risk factors, medications, and early recognition of recurrence should be included.

Module A
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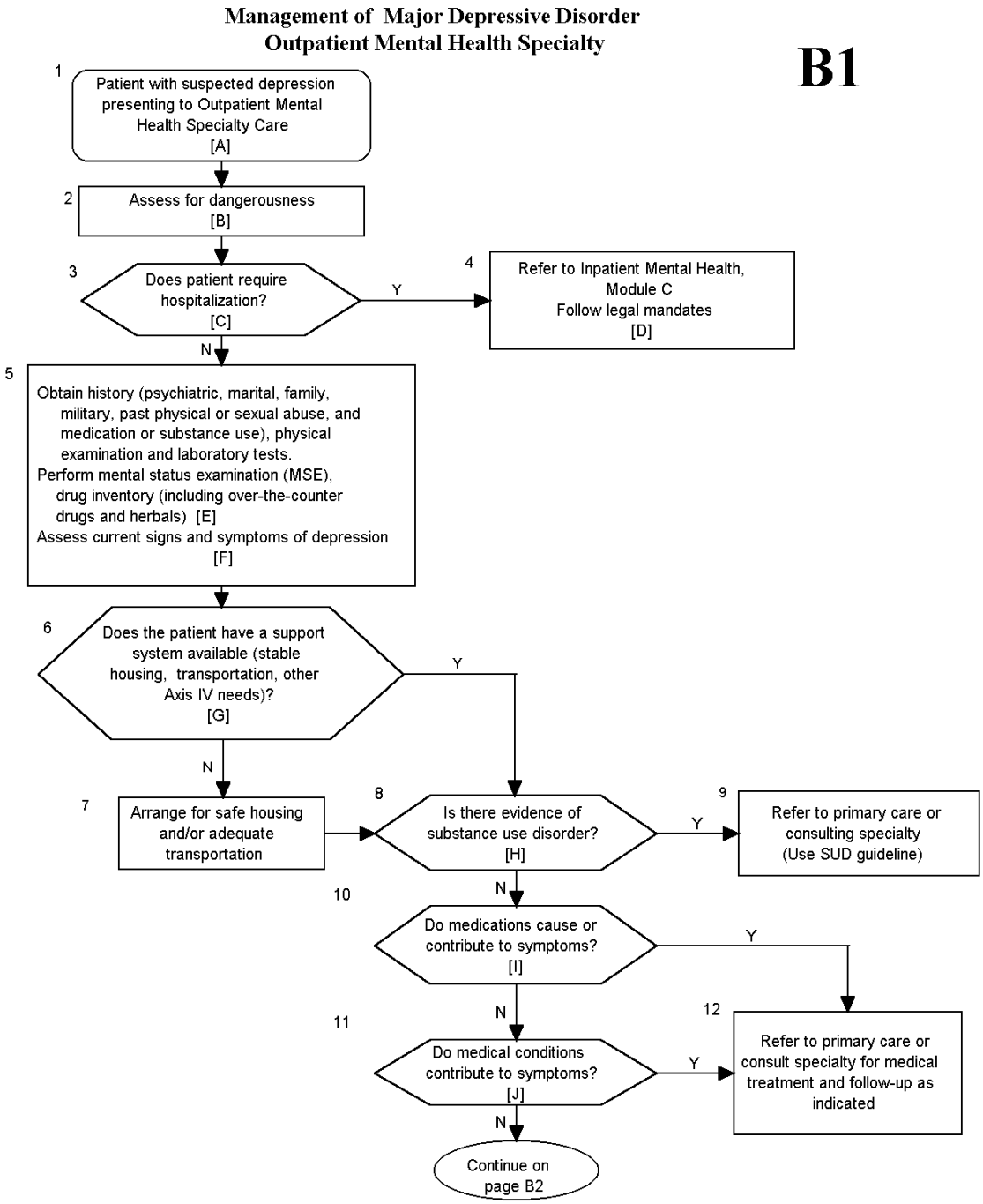
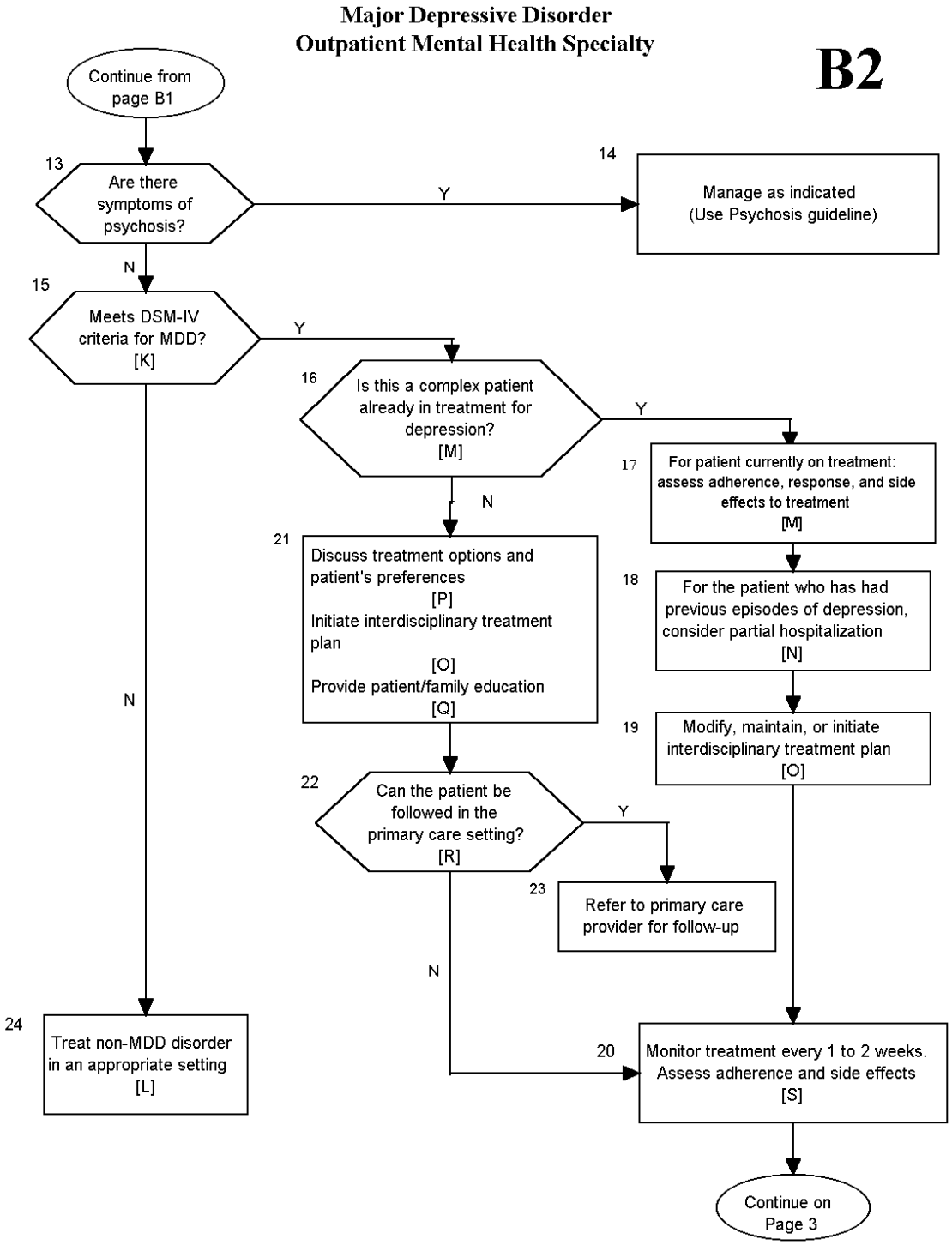
VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER** IN ADULTS IN THE OUTPATIENT MENTAL HEALTH SETTING

ALGORITHMS AND ANNOTATIONS

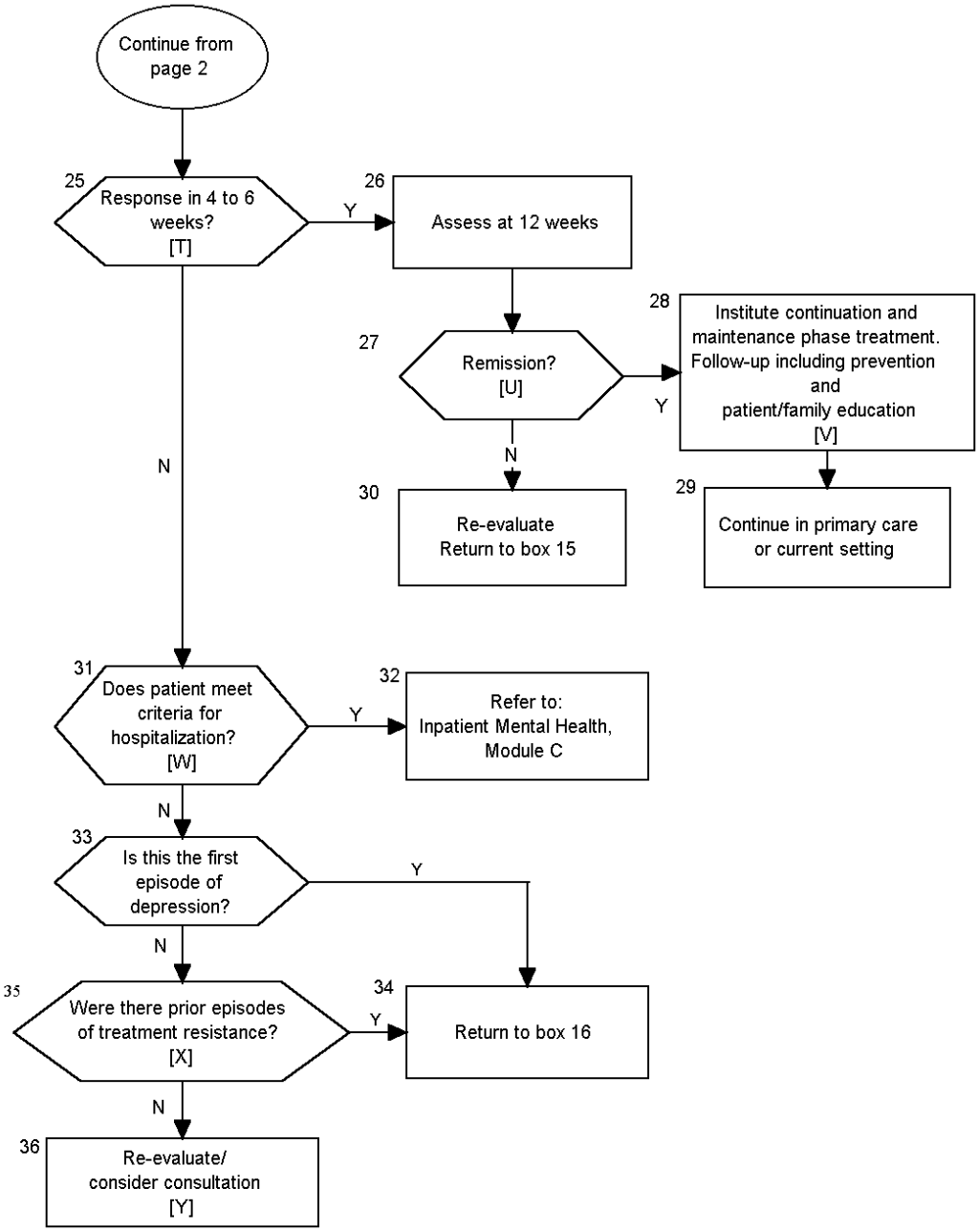
Module B


Management of Major Depressive Disorder
Outpatient Mental Health Specialty
B1
1
Patient with suspected depression presenting to Outpatient Mental Health Specialty Care
[A]
2
Assess for dangerousness
[B]
3
Does patient require hospitalization?
[C]
Y
4
Refer to Inpatient Mental Health, Module C
Follow legal mandates
[D]
N
5
Obtain history (psychiatric, marital, family, military, past physical or sexual abuse, and medication or substance use), physical examination and laboratory tests.
Perform mental status examination (MSE), drug inventory (including over-the-counter drugs and herbals) [E]
Assess current signs and symptoms of depression
[F]
6
Does the patient have a support system available (stable housing, transportation, other Axis IV needs)?
[G]
Y
N
7
Arrange for safe housing and/or adequate transportation
8
Is there evidence of substance use disorder?
[H]
Y
9
Refer to primary care or consulting specialty
(Use SUD guideline)
N
10
Do medications cause or contribute to symptoms?
[I]
Y
N
11
Do medical conditions contribute to symptoms?
[J]
Y
12
Refer to primary care or consult specialty for medical treatment and follow-up as indicated
N
Continue on page B2


Major Depressive Disorder
Outpatient Mental Health Specialty
B2
Continue from page B1
13
Are there symptoms of psychosis?
Y
14
Manage as indicated (Use Psychosis guideline)
N
15
Meets DSM-IV criteria for MDD? [K]
Y
16
Is this a complex patient already in treatment for depression? [M]
Y
17
For patient currently on treatment: assess adherence, response, and side effects to treatment [M]
18
For the patient who has had previous episodes of depression, consider partial hospitalization [N]
19
Modify, maintain, or initiate interdisciplinary treatment plan [O]
N
21
Discuss treatment options and patient's preferences [P]
Initiate interdisciplinary treatment plan [O]
Provide patient/family education [Q]
22
Can the patient be followed in the primary care setting? [R]
Y
23
Refer to primary care provider for follow-up
N
24
Treat non-MDD disorder in an appropriate setting [L]
20
Monitor treatment every 1 to 2 weeks. Assess adherence and side effects [S]
Continue on Page 3

Major Depressive Disorder
Outpatient Mental Health Specialty

B3



Management of Major Depressive Disorder in the Outpatient Mental Health Specialty Setting
Module B

A. Patient with Suspected Depression Presenting to Outpatient Mental Health Specialty Care

DEFINITION

This module targets a large population and aims to provide guidance related to the many ways to access care. The common feature in all presentations is that the patient has reported signs or symptoms of depression, either by a screening instrument or in an interview situation. The patient may or may not have a previously confirmed diagnosis of MDD and may already be receiving treatment for MDD. Entry points include the following:

1. Patients referred from primary care who were diverted to outpatient specialty care at one of various points in the algorithm are noted below:

   MODULE A

   - Box 9 - concerns about mental health persist, although depression symptoms were not elicited by primary care provider
   - Box 12 - positive screen and threat to self or others
   - Box 13 - positive screen and symptom reports of depression, with evidence of psychosis
   - Box 24 - meets DSM-IV criteria for MDD, but case is too complex
   - Box 26 - unable or unwilling to treat patient in primary care
   - Box 33 - positive screen for depression and some symptoms reported, but patient does not meet criteria for MDD; concerns about mental health persist
   - Box 44 - patient has been treated for over 12 weeks without remission and primary care chooses to refer to mental health rather than revising treatment in their setting.

2. Patients coming through mental health walk-in clinic

3. Patients referred from within mental health setting as a result of new emergence of complaints of depression

4. Patients followed up after discharge from inpatient care:

   MODULE C

   - Box 21 (MDD confirmed and treated; GAF and/or lethality improved and now insufficient to justify continued hospitalization, but patient not clearly in remission
   - Box 28 (MDD confirmed and treated, with at least a second course of treatment needed after initial non-response); GAF and/or lethality improved and now insufficient to justify continued hospitalization, but patient not clearly in remission.

B. Assess for Dangerousness

OBJECTIVE

To identify patients that are at high risk to self or others or who have any medical or psychiatric conditions requiring immediate attention.

ANNOTATION

Unstable conditions, whether physiological or psychiatric, represent situations that mandate immediate attention. These include the following:

1. Delirium – Delirium (also known as organic brain syndrome, organic psychosis, acute confusional state, acute brain syndrome and various other names) is a disorder of cognition and consciousness with abrupt onset that is frequently overlooked. This is common in the elderly and medically ill (Farrell KR, 1995).

2. Acute or marked psychosis – "Psychosis" in and of itself, is not a disorder. Rather, psychosis is a symptom which may present in a variety of conditions. Psychotic patients have an impaired sense of reality, which may manifest in several forms (hallucinations, delusions, mental confusion or disorganization). Acute psychosis represents a medical emergency.

3. Severe debilitating depression (e.g., catatonia, malnourishment, severe disability) – While many mild to moderate illnesses may not necessarily present situations mandating immediate attention, the presence of severe depressive symptoms may represent a medical emergency–even in the absence of suicidal ideation.

4. Suicidality – Suicidal behavior is best assessed with the following criteria: presence of active depression or psychosis, presence of substance abuse, past history of suicidal acts, formulation of plan, a stated intent to carry out the plan, feeling that the world would be better off if the patient were dead, availability of means for suicide (firearms, pills, etc.), disruption of an important personal relationship, failure at an important personal endeavor (Simon RI, 1992). The presence of these factors often constitutes a psychiatric emergency and must always be taken seriously. See Appendix 3, Suicidality.

5. Potential for violence – Violence often emerges as a response to perceived threat or marked frustration by the patient from their inability to meet goals by nonviolent means. The specific factors which contribute to violent behavior may include psychiatric, medical, environmental and situational/social engagements. Often, it is a combination of these factors which precipitates and aggravates potential for violence, which may quickly escalate to frank agitation or the carrying out of violent impulses. Whatever the cause, the following situations may serve as warning signs pointing towards a very real threat of violence:

    - Ideation and/or intent to harm others
    - Past history of violent behaviors
    - Severely agitated or hostile
    - Actively psychotic.

    Immediate attention and intervention may be required in order to ward off the potential for escalation of agitation or violent impulses.

6. Unstable urgent medical conditions – Any condition immediately threatening to life, limb, eye sight, or requiring of emergency medical care. Conditions include acute myocardial infarction, respiratory failure, hypertensive crisis, diabetic ketoacidosis, crushing radiating chest pain, etc.

See Appendix 2, Unstable and High Risk Conditions and Appendix 3, Suicidality.

EVIDENCE

Specific factors that contribute to violent behavior include psychiatric, medical, environmental and situational/social. (Hastings EJ, 1997; Thienhaus OJ, 1998; U.S. PSTF, 1996) QE = II-1, SR = B

Insufficient evidence to support routine screening of depression, suicide risk, child abuse or domestic violence. (U.S. PSTF, 1996) QE = II-2, SR = B

Clinicians should maintain a high index of suspicion for depressive symptoms in persons at increased risk of depression, suicide risk, child abuse or domestic violence. (U.S. PSTF, 1996) QE = III, SR = B

C. Does Patient Require Hospitalization?

OBJECTIVE

To determine if the patient meets criteria for appropriate psychiatric hospitalization.

ANNOTATION

Usual reasons for urgent hospitalization include acute suicide risk; acute violence risk due to mental illness; delirium; and acute unstable medical condition.

Specialized treatment only available or often best provided in a hospital include:

- Electro-convulsive therapy (ECT)
- Close monitoring and daily titration of medication with disabling side effects or toxicity
- Constant staff observation as part of an intensive behavioral modification program
- Close monitoring of behavior in an episodic disorder
- Close monitoring of vital signs or need for multiple daily laboratory or electrophysiological testing.

Specific admission criteria must be determined at each setting reflecting local circumstances. However, national uniform standards, such as the Science Allocations International Corporation (SAIC) standards, are strongly recommended. Review of all admissions using standardized utilization review criteria, such as those available from InterQual Medical Necessity Criteria or Science Allocations International Corporation (SAIC) Inpatient Criteria has been recommended by VHA's Under Secretary for Health. The Department of Defense has adopted the use of SAIC admission criteria for CHAMPUS contracts. Thus any facility (VHA or DoD) providing CHAMPUS care is expected to use SAIC criteria for its utilization reviews in accordance with the specifications of its contract. See Appendix 1, Assessment Instruments, for SAIC Criteria for Hospitalization.

D. Refer to Inpatient Mental Health, Module C. Follow Legal Mandates

OBJECTIVE

To ensure patient's safety is maintained during stabilization.

ANNOTATION

If a patient represents a risk to self or others, providers must follow established local, state, and federal guidelines. For VA patients, these procedures should reflect the opinion and guidance of the VA district Council. For DoD patients, these procedures are directed by DoD Directive 6490.1, "Mental Health Evaluation of Members of the Armed Forces", DoD Instruction 6490.4, "Requirements for Mental Health Evaluations of Members of the Armed Forces", and related service regulations/instructions. Regulations/instructions may require a number of notifications (e.g., commanders) which would not be required in a civilian practice. Mental health staff should be prepared not only to manage patients who pose a risk but also be prepared to consult with primary care and other medical specialties on patients who may be encountered in their clinics. Plans for management must reflect the realities of local resources, staffing, and transportation.

If patients represent a risk to others, state or federal laws and/or regulations may require additional notifications. When making notifications, it may be useful to consult a peer and/or medical law consultant for questions on the legal and ethical requirements.

E. Obtain History (Psychiatric, Marital, Family, Military, Past Physical or Sexual Abuse, and Medication or Substance Use), Physical Examination, Laboratory Tests. Perform Mental Status Examination (MSE), Drug Inventory (Including Over-the-Counter Drugs and Herbals)

OBJECTIVE

To develop an appropriate clinical understanding of the patient that can inform subsequent provider decisions.

ANNOTATION

After determining that the patient is stable, the priorities are:

1. Recognizing current symptoms and signs of depression
2. Obtaining a careful psychiatric history looking for past depressive episodes
3. Performing complete physical examination and directed laboratory assessment
4. Remaining attentive to "red flags" that suggest a higher than usual index of suspicion is necessary
5. Estimating anticipated length of treatment
6. Initiating discharge planning.

DISCUSSION

Obtain a Careful Psychiatric History to Identify Past Depressive Episodes – Key elements of the past history of depression include prior antidepressant use, past hospitalization for depression or suicidality, and inability to function in usual life roles. Substance use and misuse may cause or exacerbate depression. Pay special attention to the patient's drug inventory. Over-the-counter and herbal supplements are very commonly used and not prescribed. There may contribute to or alter the patient's sensorium or cause drug interactions with prescribed medications.

There is a high likelihood of depression among individuals with a past or present abuse history. Providers should respectfully ask each patient direct, specific questions about physical or sexual abuse during the history.

"**Red Flags" Suggesting Need for a Higher Than Usual Index of Suspicion** – Certain physiological and psychological conditions or life events may contribute to the development or exacerbation of depression symptoms. These may include, but are not limited to:

- Medically unexplained physical symptoms
- Chronic, debilitating medical condition
- Current substance abuse/use (Rost K, et al., 1993)
- Decrease in sensory, physical, or cognitive function
- Victim of current or past physical or sexual abuse or emotional neglect
- Family history of major depression
- Loss of significant relationship, primary support system, or economic status
- Neurological disorder (e.g., Multiple Sclerosis, Parkinson's Disease, stroke) or history of closed head injury
- Protracted care-giving role for a family member with a chronic, disabling condition
- Spousal bereavement and widowhood

- Symptoms or signs of PTSD.

Physical Examination – A brief, screening physical examination may uncover endocrine, cardiac, cerebrovascular, or neurologic disease that may be exacerbating or causing depressive symptoms. Particularly in the elderly patient, a full Mental Status Examination (MSE) includes cognitive screening assessment that may consist of a standardized instrument such as the Folstein Mini-Mental State Examination (MMSE) (Crum RM, et al., 1993; Cummings JL, 1993; Folstein MF, et al., 1975) (See Psychoses Guideline). If screening is suggestive of cognitive impairment and the patient is not delirious, then a laboratory evaluation to assess for reversible causes of dementia is appropriate. The depression assessment should be continued (Forsell Y, et al., 1993). If delirium is present, consider it an emergency and stabilize the patient before proceeding, then return to the algorithm and continue with depressive assessment, Box 4. Other MSE findings of importance in depression include slow speech, sighing, psychomotor retardation or agitation, downcast eyes, and little or no smiling.

Laboratory Evaluation – Use the history and physical examination findings to direct a conservative laboratory evaluation. There is no test for depression, so testing is directed toward detection of associated general medical conditions. Appropriate laboratory studies to rule out medical disorders that may cause symptoms of depression may include CBC, thyroid studies, chemistry profile, UA, and toxicology screen. For patients over the age of 40, an ECG should be considered.

Diagnostic imaging and neuropsychological, or psychological testing is not a part of the standard laboratory evaluation for depression.

F. Assess Current Signs and Symptoms of Depression

OBJECTIVE

To determine the presence or absence of the cardinal signs and symptoms of major depressive disorder.

ANNOTATION

Core symptoms and signs of depression include:

1. Depressed mood
2. Loss of enjoyment in normally pleasurable activities (anhedonia)
3. Feelings of guilt, hopelessness, and helplessness
4. Fatigue or energy loss
5. Poor concentration or memory problems
6. Persistent appetite changes and weight loss or gain
7. Psychomotor slowing or agitation
8. Morbid thinking to include suicidal ideation and behaviors (Burke WJ, et al., 1992; APA, 1994)
9. Significantly altered sleep (too much or not enough) (DSM-IV).

See Appendix 1, Assessment Instruments, for the DSM-IV Diagnostic Criteria for MDD.

G. Does the Patient Have a Support System Available (Stable Housing, Transportation, Other Axis IV Needs)?

OBJECTIVE

To determine the adequacy of patient's social supports.

ANNOTATION

Without a reasonably stable living situation and a means of transportation to the treatment program, the patient is unlikely to attend treatment and/or comply with a treatment regimen.

Concerns to be addressed may include:

- Need for Case management
- Housing
- Transportation
- Any guidelines specific to the delivery system
- Need to refer to VHA homeless program (VA beneficiaries only).

Housing is usually not a barrier to outpatient treatment for active duty service members. However, if they are in transit and require outpatient treatment, housing may be arranged on a local military facility. Transportation to a treatment facility is the responsibility of the active duty member unless he or she is in a basic training or deployed status and then it becomes the responsibility of the command to provide transportation to an outpatient facility.

If there are problems with housing and transportation for other DoD or VA Medical Beneficiaries, information and assistance is supplied to these patients by the Social Work Service for the purpose of securing adequate services. Case management may be a helpful tool to coordinate services and identify barriers.

H. Is There Evidence of Substance Use Disorder?

OBJECTIVE

To identify patients who require evaluation and treatment according to guidelines for substance use disorder.

ANNOTATION

All patients should be asked about any current or recent use of nicotine, alcohol, or other psychoactive substances (Conners GJ, 1995).

Screening for alcohol may be accomplished using the "CAGE" questions:

C Have you ever attempted to *cut* down on your drinking?
A Have you ever been *annoyed* by other people criticizing your drinking?
G Have you ever felt *guilty* about your drinking?
E Have you ever taken a morning *eye-opener?*

The CAGE is a beneficial mnemonic consisting of questions about alcohol use. One or more positive responses can be considered a positive result to the CAGE test. If the CAGE score is two or more, then more focused assessment for alcohol problems is indicated (Buchsbaum DG, et al., 1991).

See the Substance Use Disorders Guideline for further diagnosis and treatment.

It is useful to start the questioning with the family history of alcohol or drug use, then to follow with a question about the patient's own substance use (e.g., "Have you ever had a problem with drugs or alcohol?"). Note that substance histories relying on quantity of use (e.g., "How much would you say you drink each day?) are notoriously inaccurate. Other systematic screening instruments are available and useful. Descriptions of these instruments may be found in the Guideline on Substance Use Disorders.

Corroboration of the history from significant others is useful, as many problem substance users will convincingly deny their drug use (Conners GJ, 1995; Schorling JB, et al., 1997).

Laboratory tests are not recommended for routine screening of asymptomatic persons (U.S. PSTF, 1996). Patients who screen positive for substance use should be carefully evaluated in accordance with the Substance Use Guideline.

EVIDENCE

Brief self-report screening instruments for alcohol problems may help identify drug problems. (APA, 1995; ASAM, 1996; U.S. PSTF, 1996) QE = II-3, SR = B

I. Do Medications Cause or Contribute to Symptoms?

OBJECTIVE

To identify patients who may be experiencing depressed symptoms from a medication side effect.

ANNOTATION

Many prescriptions or over-the-counter drugs may possibly contribute to depression.

Below is an alphabetical table of medications and evidence ratings linking various medications to increased risk of depression. Although there is little published information on alternative medicines and their relationship to depression, consideration should be given to herbal, nutritional, vitamin and body building supplements, particularly when consumed in large doses.

Table 1. Compounds That Commonly Cause Depression

Drug/Drug Class	QE	SR
ACE inhibitors	II-2	C
Amphetamine withdrawal	I	B
Anabolic Steroids	I	B
Antihyperlipidemics	II-2	C
Benzodiazepines	II-2	C
Cimetidine, Ranitidine	II-2	C
Clonidine	II-2	C
Cocaine withdrawal	I	C
Cycloserine	II-2	C
Digitalis	I	B
Glucocorticoids	I	B
Gonadotropin-releasing agonists	II-2	A
Interferons	II-2	C
Levodopa	II-2	C

Drug/Drug Class	**QE =**	**SR =**
Methyldopa	II-2	C
Metoclopramide	II-2	C
Oral contraceptives	II-2	C
Pimozide	II-2	A
Propanolol (Beta Blockers)	II-2	B
Reserpine	II-1	C
Topiramate	II-2	C
Verapamil (Calcium channel Blockers)	II-2	C

Table adapted from *Drug Safety* 1994;10(3):203-19 and modified using information from Bloch M, et al., 1997; Borras C, et al., 1999; Boumendil E, et al., 1995; Crawford P. 1998; Durelli L, et al., 1996; Ganzini L, et al., 1993; Hallas J, 1996; Metzger ED, et al., 1994; Patten SB, et al., 1993; Patten SB, et al., 1994; VA Medical Advisory Panel (MAP) Guidelines. 1997; VA MAP Addendum 1999; and Warnock JK, et al. 1998.

J. Do Medical Conditions Contribute to Symptoms?

OBJECTIVE

To identify patients who may be experiencing depressed symptoms as a result of an underlying medical condition.

ANNOTATION

Table 2 includes many of the pathobiologies associated with depression. Simultaneous treatment is often required for both the medical problem and psychiatric symptoms. Additionally there is often a strong association between the level of disability from the medical condition and the depressive symptom requiring treatment.

A useful mnemonic for remembering these is $[TIC]^2p^2m^2d^3$. The mnemonic stands for:

- Trauma
- Tumor
- Infection - immune and autoimmune
- Cardiac/vascular
- Congenital/heriditary
- Physiologic - seizure
- Metabolic malignancy
- Degenerative
- Drug toxicity
- Demyelinating.

Patients with chronic pain may also have associated mood disturbance. This may be encountered among individuals suffering conditions such as Chronic Obstructive Pulmonary Disease (COPD) or Asthma or more commonly bone pain with cancer.

Table 2. Pathobiologies Related to Depression

Pathology	Disease
Cardio/vascular	Coronary artery disease Congestive heart failure Uncontrolled hypertension Anemia Stroke Vascular Dementia
Chronic Pain Syndrome	Fibromyalgia, Reflex sympathetic dystrophy, Low back pain (LBP), Chronic pelvic pain Bone or disease related pain
Degenerative	Presbyopia Presbycusis Alzheimer's disease Parkinson's disease Huntington's disease Other Neurodegenerative diseases
Immune	HIV (both primary and infection-related) Multiple Sclerosis Systemic Lupus Erythematosis (SLE) Sarcoidosis
Infection	Systemic Inflammatory Response Syndrome (SIRS) Meningitis
Metabolic/Endocrine Conditions (include renal and pulmonary)	Malnutrition, Vitamin deficiencies Hypo/Hyperthyroidism Addison's Disease Diabetes Mellitus Hepatic disease (cirrhosis) Electrolyte disturbances Acid-base disturbances Chronic Obstructive Pulmonary Disease (COPD) or Asthma Hypoxia
Neoplasm	Of any kind, especially pancreatic or central nervous system (CNS)

K. Meets DSM-IV Criteria for Major Depressive Disorder (MDD)?

OBJECTIVE

To identify patients with the diagnosis of Major Depressive Disorder.

ANNOTATION

At least five symptoms of depression must occur simultaneously, and the symptoms must be present for most of the day, nearly every day, for at least two weeks. To meet formal diagnostic criteria, one of the symptoms present must be either depressed mood or anhedonia (loss of interest). When evaluating a patient for a major depressive episode, the symptoms of depressed mood, loss of interest, psychomotor agitation or retardation, and diminished ability to concentrate can be indicated by either the patient's subjective account or by evidence that

the symptoms are apparent to others. Contacts with family members may be necessary to make an accurate diagnosis.

Note that past manic, mixed manic, or hypomanic episodes must be excluded before the diagnosis is confirmed. In addition, the depressive episode must not be due to Schizoaffective Disorder, Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder not otherwise specified.

See Appendix 1, Assessment Instruments, for the DSM-IV Criteria for MDD.

L. Treat Non-MDD Disorder in an Appropriate Setting

OBJECTIVE

To differentiate patients with other psychiatric disorders requiring specialty mental health care.

ANNOTATION

Other disorders that present with depressive features deserve serious consideration in mental health outpatient settings, but are outside the scope of this guideline. Information on some of the most common of these disorders appears in Appendix 6, Non-MDD Conditions Requiring Specialty Treatment. For information on the treatment of Psychosis and related psychiatric disorders, see Psychoses Guideline.

M. Is This a Complex Patient Already in Treatment for Depression?

OBJECTIVE

To identify those patients who require more involved or specialized management.

ANNOTATION

Complicating factors that may influence treatment decisions include:

1. Current treatment – Any patient currently receiving treatment for depression
2. Provider responsible for coordinating current treatment – Any patient for whom you are not the provider that initiated the current treatment
3. Prior treatment response – Any patient with a history of failed depression treatment or otherwise complicating treatment
4. Comorbid mental health problems - Any patient with a co-existing mental health disorder in need of treatment or otherwise complicating treatment
5. Co-morbid medical problems - Any patient with a co-existing medical condition that has significant impact on the course or treatment of depression
6. Atypical depressive features - Any patient with some combination of depressive symptoms that include hypersomnia, hyperphagia, and/or rejection sensitivity
7. Family or patient history of suicidality - Any patient with either a personal or family history of suicide attempts or suicidal ideas necessitating psychiatric hospitalization
8. Recurrent depressive episodes - Any patient with more than one past depressive episode or a past depressive episode involving severe loss of functioning or other life consequences.

N. For the Patient Who Has Had Previous Episodes of Depression, Consider Partial Hospitalization.

OBJECTIVE

To provide the appropriate level of care to the patient.

ANNOTATION

1. If there is a history of successful MDD treatment, consider reinstituting the previously successful approach
2. If patient requires greater assistance or a higher intensity of care, consider partial hospitalization:
    a. Partial hospitalization, or primary day hospitals are appropriate for patients with a depressive disorder when more support, observation, and intensive efforts than is available through clinic appointments is needed. Day hospitals, where they are available, may run in conjunction with residential care and are available for patients for up to eight hours a day, as an alternative to or an extension of acute hospitalization.
    b. Common indications for partial hospitalization are:
        1) The patient has a DSM-IV disorder with decompensation severe enough to impair daily social, vocational, or educational functioning.
        2) The patient is not an imminent risk for harm to self or others and has sufficient impulse control to be maintained outside of an acute inpatient setting.
        3) The patient has sufficient community-based support to be maintained outside of an acute inpatient setting.
        4) The patient is able to participate in and cooperate with partial hospitalization treatment.
        5) One of the following criteria have been met:
            - The patient has not improved after an adequate trial of outpatient treatment
            - The patient is unlikely to improve with an adequate trial of outpatient treatment
            - The patient is being discharged from an acute inpatient setting but continues to need daily monitoring, support, and therapeutic intervention.

O. Modify, Maintain, or Initiate Interdisciplinary Treatment Plan

OBJECTIVE

To describe a course of clinical action for the various types of complex patients with MDD.

ANNOTATION

The patient should be assigned to a consistent interdisicplinary mental health care team, including members who represent both biomedical and psychosocial perspectives. The interdisciplinary team may include members of the following disciplines depending on the patient's unique health care needs:

1. Psychiatry – management of psychiatric disorders
2. Primary care provider – coordination of the patient's overall health and preventive care
3. Medical specialists other than psychiatry – as indicated by medical co-morbidities
4. Psychology – for behavioral and emotional aspects of care to include psychotherapy, biofeedback, and similar modalities
5. Social work – for coordination of community resources, counseling, and support groups

6. Nursing – health education and training such as for home health care and routine follow-up health care
7. Pharmacist – for the patient on pharmacotherapy, especially those on multiple medications, co-morbid medical conditions requiring pharmacotherapy or interacting with the patient receiving antidepressant therapies
8. Dietary – for education pertaining to nutritional status and dietary aspects of pharmacotherapies (e.g., MAOIs)
9. Occupational therapy – assistance for the patient in need of life skills training
10. Recreational therapy – assistance for the patient in need of employment and/or benefits counseling
11. Vocational rehabilitation – assistance for the patient in need of employment and /or benefits counseling
12. Chaplaincy – assistance for the patient with religious or spiritual concerns or requests.

The interdisciplinary team will discuss the patient's diagnosis, etiological factors, and potential treatment options. Treatment options will also be discussed with the patient. Patient preference will play a major role in deciding what treatment(s) to initiate.

After decisions are made, it is preferable that a specific provider individualizes and coordinates the patient's care. If the patient is hospitalized, the current provider will either continue the care or arrange timely follow-up with another practitioner. The practitioner will establish a close working alliance with the patient, characterized by caring, shared decision-making, and respect for patient privacy. The practitioner will continue to consult with the interdisciplinary team, particularly if the patient does not improve during the first planned course of treatment

DISCUSSION

If the patient is currently being treated for Depression:

1. Assess treatment response – If the patient is responding to current treatment, but the response is only partial, or if the patient is not responding to current treatment, then assess treatment adherence and side effects.

2. Assess treatment adherence – Is the patient attending therapy sessions regularly? If not, why? Is the patient taking prescribed antidepressants or other medicines as directed? If not, why? The patient's answers to these questions will suggest whether a modification of treatment is necessary to achieve a therapeutic response.

3. Assess treatment side effects – Side effects are a common reason for poor adherence to therapy. Undesirable side effects of psychotherapy may include the need to miss work or other important activities and unanticipated effects on important relationships or increases in symptoms.

If the patient has chronic depression or past MDD episodes:

Relapse is not uncommon for individuals previously treated successfully. In a large cohort study of relapse in major depression, 37.1 percent of patients relapsed in the time frame studied. Two major risk factors were associated with relapse:

a. persistence of subthreshold depressive symptoms seven months after the initiation of antidepressant therapy
b. a history of two or more episodes of major depression, or chronic mood symptoms for two years (Lin, et al., 1998).

In such cases, the clinician may want to repeat prior intervention but emphasize continuation and/or maintenance therapy, since a prior history of response (or non-response) to a particular pharmacological agent may indicate the first line choice for further episodes (Janicak, Davis, Preskorn, & Ayd, 1997). With

less certainty, a prior history of good or poor response by a family member to a particular agent may also indicate the best choice of agent for first-degree relatives (Janicak, Davis, Preskorn, & Ayd, 1997). Clinicians, however, should keep in mind that patients with depression that can be characterized as chronic (multiple previous episodes) often do not respond as well to monotherapy, either pharmacotherapy or psychotherapy, as those with single episodes of depression. More severely or chronically depressed patients may respond preferentially to combined treatment (Miller & Keitner, 1996).

If the patient has a personal or family history of suicidality:

This history is necessary to inform the frequency and content of follow-up monitoring. The presence of suicidal ideation or present and past suicidal and parasuicidal behaviors also suggests cautions in pharmacological treatments of choice. Agents of high potential lethality (e.g., TCAs, lithium, MAOIs) should be prescribed only with great caution to patients with current suicidal ideation or a past history of suicidal behavior (especially overdose). In addition, extra vigilance in follow-up should be utilized if, after carefully weighing risks and benefits, such medications are prescribed.

Some patients may express concern that antidepressant drugs, and particularly the SSRIs may "cause" suicidal behavior, as this notion had at one time achieved some currency in the popular press. There is no evidence that treatment with any antidepressant, including the SSRIs, activates suicidal ideation or behavior (Tollefson & Rosenbaum, 1998; Warshaw & Keller, 1996). On the other hand, there is no evidence that antidepressant medication in itself reduces suicidality in patients with histories of suicidal behavior. Leon, et al., (1999) prospectively compared rates of suicidal behavior in patients treated with fluoxetine and other antidepressants to those receiving no treatment. Use of somatic treatments had some protective effect against suicidal behavior, but this difference was nonsignificant when compared to controls. In keeping with the authors' expectations, they found no increase in suicidal behavior among those treated with antidepressants. Montgomery (1997) reviewed the literature on suicide and antidepressants, and reported that there is some evidence that suicide rates actually increased with certain antidepressants, (maprotiline and amitriptyline). Fluoxetine and mianserin were not found to have an effect on suicide rates. Knowledge of the influence of pharmacotherapy on suicide rates must be balanced against other evidence suggesting that patients assigned to psychotherapy also demonstrated an increased rate of suicide.

The SSRIs, particularly fluoxetine and sertraline, [have low lethal dose to effective dose ratio (LD:ED)] ratios, and are rarely lethal if taken alone in overdose, even in large quantity. The presence of Axis II disorders, like Borderline Personality Disorder, increase the risk of suicidal behaviors, and agents of high lethality should be avoided in this population (Dimeff, McDavid, & Linehan, 1999). Close follow-up is mandated; and special psychotherapeutic techniques are recommended in patients presenting with suicidal behavior or other behavior causing self-harm (Linehan, 1993).

If the patient has comorbid psychiatric problems:

Little clear literature is available to guide these decisions, and the clinician should decide based on a complete biopsychosocial work-up, consultation with the interdisciplinary team, and information on issues most distressing to patient and/or what patient is motivated to work on first. If a patient is currently undergoing psychotherapy, close consultation with the psychotherapy provider and clear communication with the patient as to the roles and expertise of each provider optimizes treatment outcome.

Short-term augmentation with benzodiazepines may be helpful in depressed patients with significant anxious features. Such treatment should be time limited. There is no evidence that long-term treatment with benzodiazepines contributes to positive outcome (Smith, Londberg, Glaudin, & Painter, 1998).

The existence of Axis II pathology may complicate treatment of an Axis I disorder, but this has not been systematically investigated. Recent reviews (Crits-Cristoph, 1998; Woo-Ming & Siever, 1998), found a paucity of well-designed trials for either psychological or pharmacological treatment of Axis II problems. Presence of personality disorders has generally been linked to poorer outcomes for treatment of MDD (Crits-Cristoph, 1998; Thase, 1996).

If the patient has co-morbid medical conditions:

Close consultation with the patient's primary care or specialty provider is recommended if medication is the patient's treatment of choice. For patients requiring pharmacotherapy, the clinician must be alert to the presence of relative contraindications as dictated by the medical condition, and, perhaps more importantly, the potential for interaction between psychotropics and medications prescribed by other care givers. There are no known medical conditions that preclude the use of psychotherapy for MDD, although the course of therapy may be complicated by a patient's loss of cognitive function or functional independence. In such cases, a therapist with specific experience in adapting psychotherapy for patients with cognitive or functional impairment will be needed.

If the patient has features of atypical depression:

Though the MAOIs have been represented as the standard of care for depression with atypical features, a recent double-blind, randomized clinical trial found that both cognitive psychotherapy and phenelzine (approximately 64 mg/day) resulted in equivalent improvement (58 percent of patients rated improved in both groups) that was substantially greater than for a pill placebo group (28 percent; Jarrett, Schaffer, McIntire, Witt-Browder, Kraft, & Risser, 1999).

Another recent investigation found that patients with atypical features to their depression (hyperphagia, hypersomnia, leaden paralysis, and rejection sensitivity) are less likely to respond to medications, at least the TCAs (Stewart, Garfinkel, Nunes, Donovan, & Klein 1998). In this re-analysis of the Treatment of Depression Collaborative Research Project data, both Cognitive Behavioral Therapy (CBT) and Interpersonal Therapy (IPT) outperformed a combination of imipramine plus clinical management; CBT was significantly better than imipramine plus clinical management, and there was a trend towards significance for IPT.

For the patient with Post Traumatic Stress Disorder (PTSD):

Post Traumatic Stress Disorder (PTSD) – Some patients may require further diagnostic testing to rule out specific psychiatric disorders such as PTSD that can co-occur with depression and may require additional specialized treatment. See PTSD Guideline.

EVIDENCE

Fluoxetine treatment for MDD is not associated with an increased likelihood of suicidal behavior. (Leon AC, et al., 1999; Warshaw MG, 1996) QE = II-3, SR = B

Clinical characteristics can help target patients with MDD at high risk for relapse. Risk factors identified included persistent subthreshold depressive symptoms, chronic mood symptoms, or history of two or more major depressive episodes. (Lin, et al., 1998) QE = II-1, SR = B

Patients with atypical depression features are less responsive to TCAs. (unreplicated). (Stewart, et al., 1998) QE = II-2; SR =C

Sertraline maintenance therapy is well tolerated and prevents recurrence or reemergence of depression in chronically depressed patients. (Keller, et al., 1998) QE = I, SR = B

Cognitive therapy is an effective acute phase treatment alternative to MAOI antidepressant medications for patients with MDD and atypical features. (unreplicated). (Jarrett, et al., 1999) QE = I, SR = C

Analyses of coroners' data suggest that TCAs are associated with elevated death rates in overdose compared with SSRIs. (Montgomery SA, 1997) QE = III, SR =C

Presence of personality disorders has generally been linked to poorer outcomes for treatment of MDD. (Thase, 1996) QE = II-1, SR = B

P. Discuss Treatment Options and Patient's Preferences

OBJECTIVE:

To guide informed decisions about treatment options.

ANNOTATION

Before initiating any specific treatment(s), the clinician should discuss with the patient (and family, where appropriate) the nature of the disorder. The following treatment options should be discussed and offered, including risks and benefits of each (AHCPR Depression Guideline, Vol. 2, p. 38). Patients should be encouraged to engage in treatment.

There are four broad treatment options for patients with MDD. These are:

1. Pharmacotherapy including other somatic therapies [e.g., electro-convulsive therapy (ECT)]
2. Empirically Supported psychoTherapies (EST)
3. Combined psychotherapy and pharmacotherapy
4. Clinical evaluation of one to three visits

Patients should be educated about the potential consequences of untreated MDD, and encouraged to return.

DISCUSSION

A balanced presentation of the relative benefits and drawbacks of each approach should be provided, to help the patient and provider make a reasoned decision about which approach to select. Points to consider when presenting the options appear below and in Appendix 7, Patient Education.

Pharmacotherapy – There is a wide range of available antidepressant medications for patients to select from (see Appendix 5, Pharmacological Therapy of MDD). The specific medication choice is generally based on side effect profiles, safety in overdose, history of prior response, concomitant medical conditions, family history of response, and type of depression.

Benefits of pharmacotherapy include:

1. Potential of a more rapid initial treatment response
2. Patient's preference for medications over talk therapies.

Risks or drawbacks of pharmacotherapy include:

1. Need to take medications consistently and exactly as prescribed
2. Potential for medication side-effects or interactions with other medications or medical problems
3. Potential for need to take medication for an indefinite or extended period.

Psychotherapy – This is the use of one of the empirically supported psychoTherapies, offered in either one-on-one or group format. See Appendix 4, Empirically Supported psychoTherapy (EST), for a full list of the ESTs and supporting evidence. Generally these approaches aim to help depressed individuals thoughtfully examine their behavior, beliefs, emotions, stressors, and personal relationships in an effort to lead to lasting change in factors that may have contributed to the development of depression. For the purposes of this guideline, psychotherapy is NOT simply unstructured and brief support commonly offered in the context of a primary care office visit.

Benefits of psychotherapy include:

1. Effects may persist beyond the duration of treatment
2. The need to take antidepressant medications or experience medication side-effects may be reduced
3. An opportunity for the patient to make meaningful self-improvements or life changes.

Risks or drawbacks of psychotherapy include:

1. Patients need to come consistently for therapy appointments on a frequent basis for several months at a time
2. A therapist trained in an empirically supported psychotherapy may not be available in every care setting.

Clinical Evaluation – For patients that do not meet criteria for complexity (see Box 16) an extended evaluation (two to three visits) can often identify those patients whose depressive symptoms are transient. Some individuals will have spontaneous remission of symptoms, particularly when symptoms have been precipitated by a life crisis. The main risk of extended clinical evaluation is that MDD may not respond and may worsen without active treatment.

EVIDENCE

Neither pharmacotherapy nor empirically supported psychotherapy have been shown to be consistently superior in the immediate or long term outcomes. (Rush & Hollon, 1991; Reynolds, et al., 1999) QE = I, SR = A

Medication treatment may lead to faster response, whereas psychotherapy (particularly cognitive behavioral therapy) may reduce risk of relapse. (Fava, et al., 1994; Rush & Hollon, 1991) QE = I, SR = A

Combination of an empirically supported psychotherapy with medication has not been shown to produce consistently better outcomes for most patients than use of. (Reynolds, et al., 1999) *one of these approaches on its own, although there may be exceptions with some subtypes.* QE= I, SR = C

Severity *of depression among psychiatric outpatients is not a reliable discriminator of short term response to either medication or empirically supported psychotherapies.* (DeRubeis, et al., 1999) QE = II-B, SR = B

Q. Provide Patient/Family Education

OBJECTIVE

To assist the patient/family in making informed decisions by providing the patient and family information about the disease process, treatment options, and expectations so they may make an informed decision.

ANNOTATION

See Appendix 7, Patient Education.

R. Can the Patient be Followed in the Primary Care Setting?

OBJECTIVE

To state general considerations for determining the extent that the MDD patient can be appropriately managed in the primary care setting.

ANNOTATION

1. The patient, primary care provider, and the remainder of the interdisciplinary team are to collaborate in all decisions regarding the appropriate intensity and setting for follow-up MDD care.

2. Facilitation of primary care-based MDD treatment should involve a detailed plan with parameters for return to specialty mental health care as appropriate for questions, concerns, or intensified need.

There is broad range of training, experience, and comfort with the provision of mental health care among primary care clinicians. All members of the interdisciplinary team, including the patient, must be comfortable with the patient's management in the primary care setting. Examples of MDD patients often amenable to primary care manager (PCM) treatment include:

- Those with their first episode of MDD
- Those well controlled on medication or psychotherapy (maintenance or remission).
- Those with co-morbid medical conditions requiring frequent primary care visits.

EVIDENCE

Clinical characteristics can help target patients with MDD at high risk for relapse. Risk factors identified included persistent subthreshold depressive symptoms, chronic mood symptoms, or history of two or more major depressive episodes. (Lin, et al., 1998) QE = II-1, SR = B

A substantial proportion of PCPs report diagnostic and treatment approaches that are consistent with high-quality depression care. (Williams JW Jr, et al., 1999) QE = II-2, SR = B

S. Monitor Treatment Every 1 to 2 Weeks. Assess Adherence and Side Effects

OBJECTIVE

To assess response to therapy.

ANNOTATION

1. Assess treatment response – If the patient is responding to current treatment, but the response is only partial, or if the patient is not responding to current treatment, then assess treatment adherence and side effects.

2. Assess treatment adherence – Is the patient attending therapy sessions regularly? If not, why? Is the patient taking prescribed antidepressants or other medicines as directed? If not, why? The patient's answers to these questions will suggest whether a modification of treatment is necessary to achieve a therapeutic response.

3. Assess treatment side effects – Side effects are a common reason for poor adherence to therapy. Undesirable side effects of psychotherapy may include the need to miss work or other important activities and unanticipated effects on important relationships or increases in symptoms.

The following problems may be noted during follow-up:

1. Patient is not taking medication as prescribed (e.g., does not obtain refills of medication at appropriate intervals)

2. Patient is not attending psychotherapy appointments consistently

3. Patient expresses dissatisfaction with treatment due to side effects of medications, difficulty following psychotherapy protocol, perceived problems with the assigned therapist, and/or a request for change.

T. Response in 4 to 6 weeks?

OBJECTIVE:

To assess and manage response to therapy.

ANNOTATION

Research studying the effectiveness of pharmacotherapy, psychotherapy, or both suggests a partial remission (50 percent symptom reduction) is common within four to six weeks of treatment. Full response, defined as minimal or no symptoms, often requires a longer duration of treatment; full restoration of psychosocial function may take several months.

DISCUSSION

Quitkin, et al., (1999) evaluated the time to response of 693 depressed patients treated with a variety of antidepressants. Their data indicated that a substantial minority of persons who show no effect at week three will go on to respond by week six of treatment but that the rate of response for those showing no improvement by week four will be very low and no better than placebo. The authors concluded that those patients tolerating adequate doses but not at least minimally improved by week four should have their treatment regimen changed. Both the AHCPR and the American Psychiatric Association Practice Guidelines for Depression recommended a four to six weeks reassessment for response. Schulberg, Katon, Fineman and Rush (1998) noted that recent studies addressing this question emanate primarily from psychiatric settings but that they continue to support the recommendation as originally made.

EVIDENCE

Four to six weeks allows titration to adequate antidepressant therapy and time for response to therapy. (AHCPR Guideline for Depression in the Primary Care Setting, 1993; Am. Psychiatric Guideline for Major Depression, 1993; Schulberg, Katon, et al., 1998) QE = II-3, SR = B

The rate of response for those showing no improvement by week four will be very low and no better than placebo. (Quitkin et al, 1996) QE = II-1, SR = B

U. Remission?

OBJECTIVE

To assess whether the patient with MDD achieves a full remission of symptoms.

ANNOTATION

Remission is defined as a return to full pre-morbid functioning accompanied by a substantial reduction of depressive symptoms. For research studies, experts typically define remission and improvement as a change in score on standardized rating scales such as the HAM-D. Many efficacy studies cite a 50 percent response rate to define improvement, but a more complete symptom and functional status response is necessary to achieve remission. Expert consensus supports a fairly complete symptom and functional status response before declaring a remission of symptoms.

The use of rating instruments is one approach to looking for symptom remission. Measures of use include the Hamilton Depression Rating Scale, PRIME-MD Patient Health Questionnaire (PHQ), Beck Depression Inventory – Click Here , and the Zung Depression Rating Scale (See Appendix 1, Assessment Instruments). In specialty mental health care settings, use of a valid, reliable, and systematic assessment of depression symptoms is recommended.

EVIDENCE

Remission defined as the patient no longer meeting the DSM III-R criteria for major depression and having Hamilton Depression Scale scores less than seven for up to three consecutive weeks. (Reimherr FW, et al., 1998) QE = II-2, SR = B

Texas Medication Algorithm Project Report defined remission as equal to or greater than 75 percent global improvement in symptoms. Emphasized goal of symptomatic remission and normalization of function rather than only symptom improvement. (Crismon, et al., 1999) QE=III, SR=B

Remission defined as the total final Hamilton Depression Scale 24 item score equal to or less than seven. (Hirschfeld RMA, et al., 1998) QE = III, SR = B

Danish University Antidepressant Group defined full remission as seven or less on the 17 item HAM-D. (Fuglum E, et al., 1996) QE = III, SR = B

V. Institute Continuation and Maintenance Phase Treatment. Follow-up Including Prevention and Patient/Family Education.

OBJECTIVE

To prevent relapse or recurrence of future major depressive episodes.

ANNOTATION

MDD is best conceptualized as a chronic illness resulting in a continuum of outcomes ranging from excellent to poor. Increased rates of recurrence were found in fifty percent of the patients with a single episode of MDD, and the greater the number of episodes the more likely are future depressive episodes. A high percentage of individuals with recurrent major depressive disorder will require indefinite prophylactic antidepressant treatment. Factors increasing the risk of future recurrence include:

- A strong family history of mood disorders
- A history of recurrence within one year after discontinuation of a previously efficacious medication
- One or more suicide attempts
- Onset of the first episode before age 20
- Two or more episodes of major depression in the past two years
- Concurrent dysthymia.

Continuation phase of antidepressant treatment follows the acute phase and begins when the patient has complete remission of depressive symptoms. Continuation phase treatment usually lasts up to nine months and is followed by maintenance phase treatment, an indefinite period of prophylaxis against future depressive episodes.

Continuation Phase Treatment – Priorities of the continuation phase include sustaining the dose of medication resulting in acute phase symptom remission; preventing relapse or recurrence of depressive symptoms; monitoring depressive symptoms and functional status; and building a constructive therapeutic alliance.

In psychotherapy, a maintenance plan should be developed as during the course of therapy. The plan should include a summary of learning that occurred during therapy; ways the patient will continue to use lessons from the therapy; a prediction of times of high recurrence risk (e.g., death of a significant other); and coping approaches for such crisis periods. Use of booster sessions and occasional re-assessment of depressive symptoms should be considered.

Maintenance Phase Treatment – Following the continuation phase, decisions regarding extended maintenance phase treatment are implemented. Patients who have had three or more episodes of major depression or two or more episodes in combination with another risk factor for recurrence (see list above) should remain on prophylactic antidepressant medication for one or more years after remission of the acute episode at the continuation phase dosage.

Patient/Family Education – is important for patients and families concerning risk of relapse and ways to reduce risk and sustain remission status. Information about recurrence risk factors, medications, and early recognition of recurrence should be included.

W. Does Patient Meet Criteria for Hospitalization?

OBJECTIVE

To decide whether the patient requires inpatient psychiatric hospitalization.

ANNOTATION

Usual reasons for inpatient hospitalization include acute suicide risk; acute violence risk due to mental illness; or grave disablement due to mental illness (e.g., loss of ability to provide basic personal hygiene, shelter, clothing, or food). See Appendix 1, Assessment Instruments, for SAIC Criteria for Hospitalization.

Sometimes specialized treatment is only available or best provided in a hospital. Examples include:

- Electroconvulsive therapy (ECT)
- Close monitoring and daily titration of medication with disabling side effects or toxicity
- Constant staff observation as part of an intensive behavioral modification program
- Close monitoring of behavior in an episodic disorder
- Close monitoring of vital signs or need for multiple daily laboratory or electrophysiological test.

Specific admission criteria must be determined at each setting reflecting local circumstances. Use of a national uniform standard, such as the SAIC standards (See Appendix 1, Assessment Instruments, for SAIC Criteria for Admission Review are recommended). VHA's Under Secretary for Health has recommended review of all admissions using standardized utilization review criteria (e.g., InterQual Medical Necessity Criteria or SAIC Inpatient Criteria). Department of Defense has adopted the use of SAIC admission criteria for CHAMPUS contracts, such that any facility (including VHA or DoD) providing CHAMPUS care is expected to use SAIC criteria for utilization review in accordance with the specifications of its contract.

X. Were There Prior Episodes of Treatment Resistance?

OBJECTIVE

To assess for the presence of treatment resistant MDD.

ANNOTATION

Treatment-resistant MDD is present if there has been an inadequate response to two or more adequate trials of depression treatment (Guscott & Grof, 1991). An adequate trial of antidepressant medication must be at least six weeks of treatment at an adequate daily dosage (Preskorn, et al., 1992). The diagnosis of MDD should be reconsidered/reverified and the possibility of a coexisting medical or psychiatric problem should be excluded. The following treatment modalities may be considered for individuals with treatment resistant MDD:

1. Psychotherapy is a useful augmentation strategy for treatment refractory MDD.
2. The clinician should attempt to augment treatment if there has been a partial response to one antidepressant. This can be accomplished by adding tri-iodothyronine (T3), 25 to 50 micrograms in one daily dose to the existing medication regimen. Baseline thyroid function tests (T4, TSH) are not predictive of response but provide a means of ensuring that TSH levels are no more than partially suppressed during T3 therapy.
3. An alternative strategy is to add lithium carbonate, 600 to 900 mg per day, to the existing medication regimen. The dosage is titrated to therapeutic serum levels. Lithium augmentation may be less efficacious for patients with multiple depressive episodes in a year compared to individuals with less frequent episodes.
4. Trazodone, 50 to 100 mg at night, is sometimes used to improve sleep among depressed patients, particularly those on an SSRI. Sometimes this allows higher doses of SSRI when insomnia is a dose-limiting side effect. Trazodone is preferable to benzodiazepines or other sedative-hypnotics for chronic sleep disturbance accompanying depression.
5. Bupropion may be used with SSRIs, particularly among patients complaining of fatigue or sexual dysfunction.
6. Anticonvulsants (e.g., carbamazepine) may be useful with conventional antidepressants, particularly among patients with patients with multiple depressive episodes in a year or those with prominent impulsivity, irritability, and/or anxiety.
7. Changing the class of antidepressant may help. Patients with atypical depression characterized by unrelenting mood reactivity, rejection sensitivity, hypersomnia, 'leaden paralysis', or increased appetite respond well to MAO inhibitors. Combination MAOI-TCA therapy is risky and requires an experienced psychopharmacologist. If response is achieved, consideration should be given to tapering and discontinuing the TCA.
8. ECT is useful for treatment-refractory MDD. If ECT is successful, it should be followed by maintenance therapy using an antidepressant or maintenance ECT.

EVIDENCE

Patients with atypical MDD are preferentially responsive to MAOIs. (Liebowitz M, et al., 1988) QE = I, SR = B

T3 increases the rapidity of TCA response by approximately 25 percent. (Nemeroff CB, 1991) QE = I, SR = C

A significant percentage of patients with antidepressant treatment resistant MDD respond to ECT. (Prudic J, et al., 1996) QE = II-2, SR = C

Y. Re-evaluate/Consider Consultation

OBJECTIVE

To monitor patient response to treatment and manage any needed adjustments.

ANNOTATION

AHCPR Clinical Practice Guidelines for treating depression in primary care recommend consultation when the clinician feels they lack sufficient knowledge or experience to manage a patient's medication or if two or more

attempts at acute phase medication treatment have failed or resulted in partial response. Consultation options in the mental health specialty setting include a local clinical case conference, psychological testing, specialized psychopharmacology clinic or pharmacist, or referral to a specialized mood disorders program.

Failure to display at least a partial remission (25 to 50 percent symptom reduction) at this point should evoke concern regarding:

1. Adherence – poor adherence is commonly due to adverse effects of treatment, patient misunderstanding about treatment, or other causes.
2. Concurrent medical illness – this may impede clinical response, especially if the medical condition is poorly controlled or compensated
3. Co-morbid psychiatric disorders
4. Co-morbid substance use disorder
5. Exacerbating psychosocial stressors
6. Error in Diagnosis.

Module B
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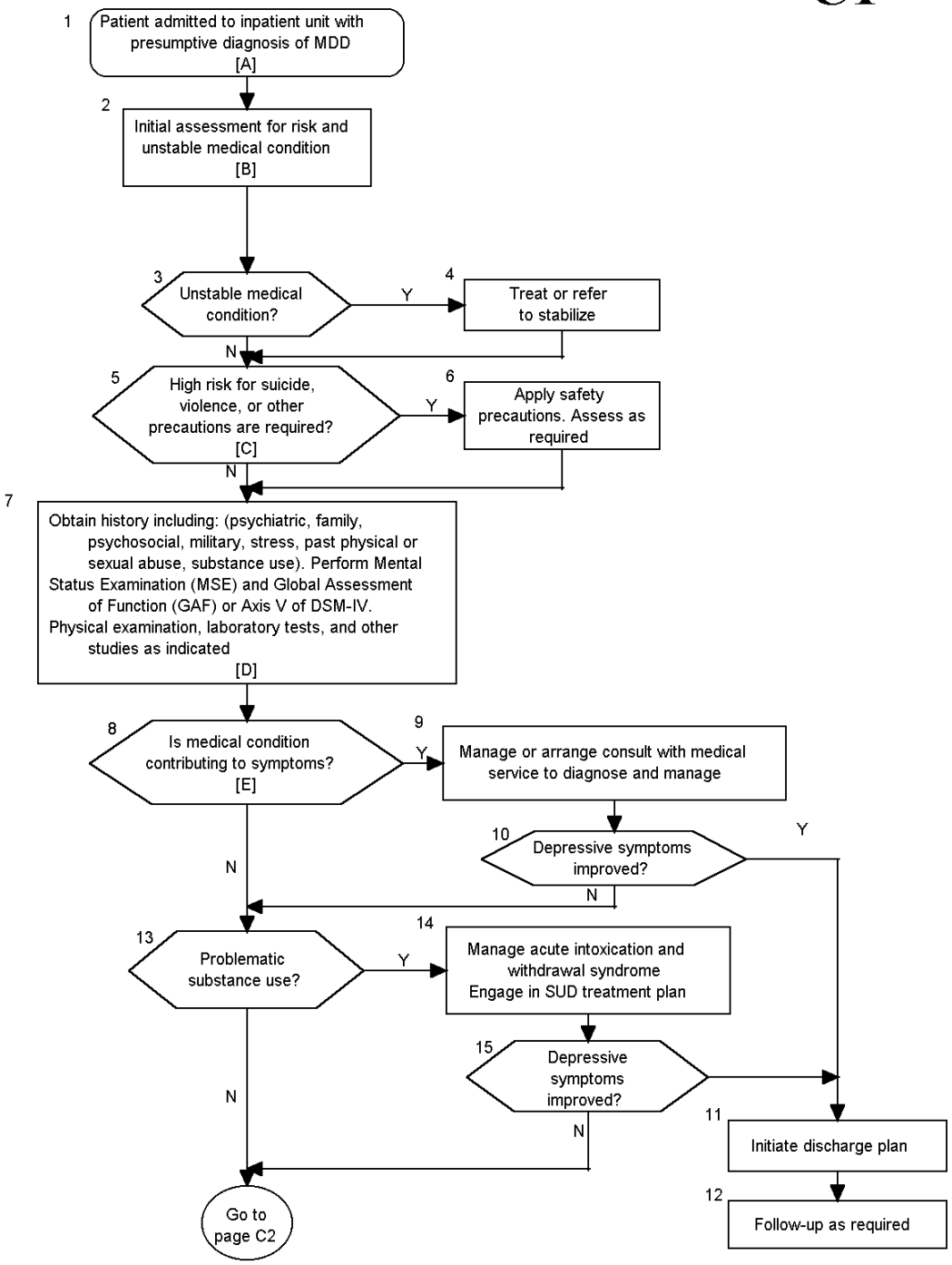
VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER** IN ADULTS IN THE INPATIENT SETTING

ALGORITHMS AND ANNOTATIONS

Module C

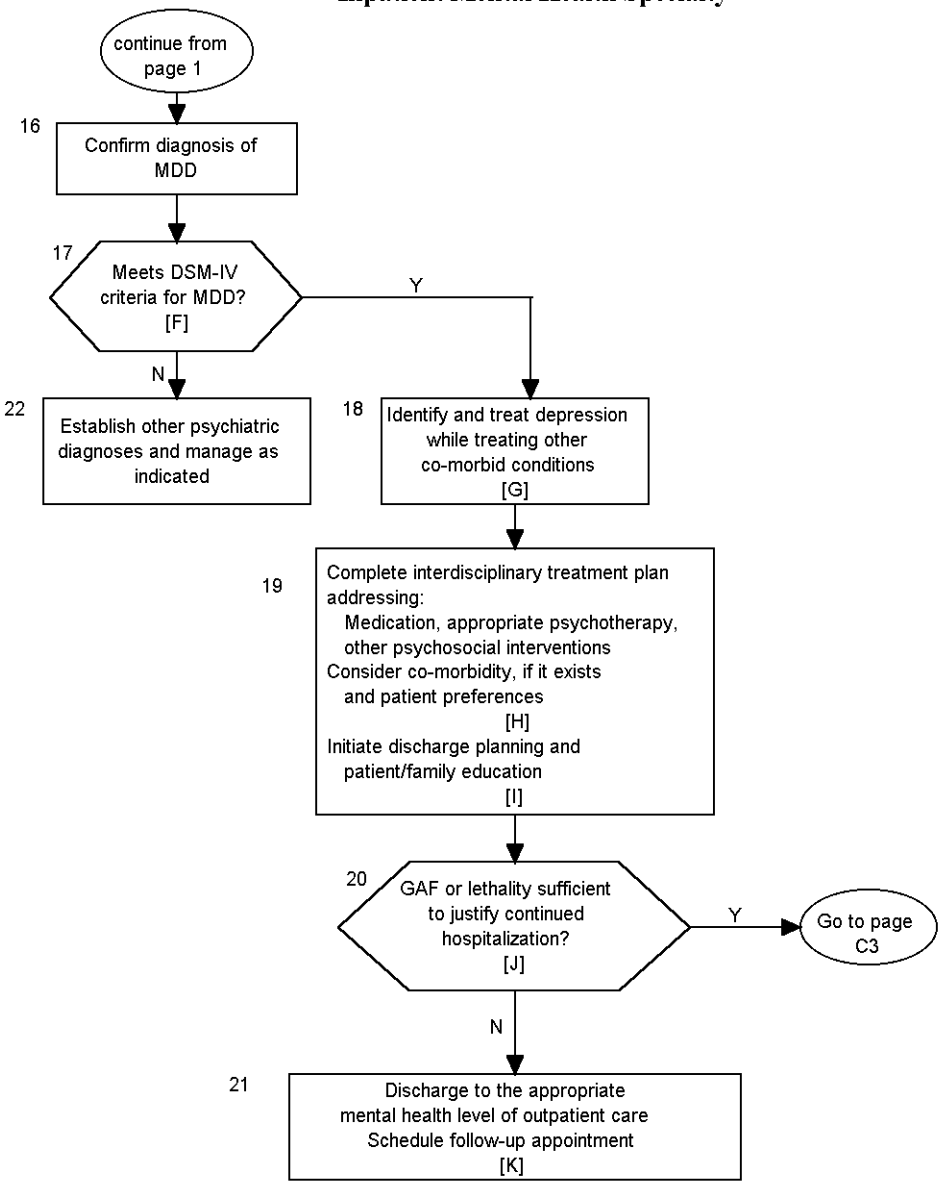
Major Depressive Disorder
Inpatient Mental Health Specialty

C1



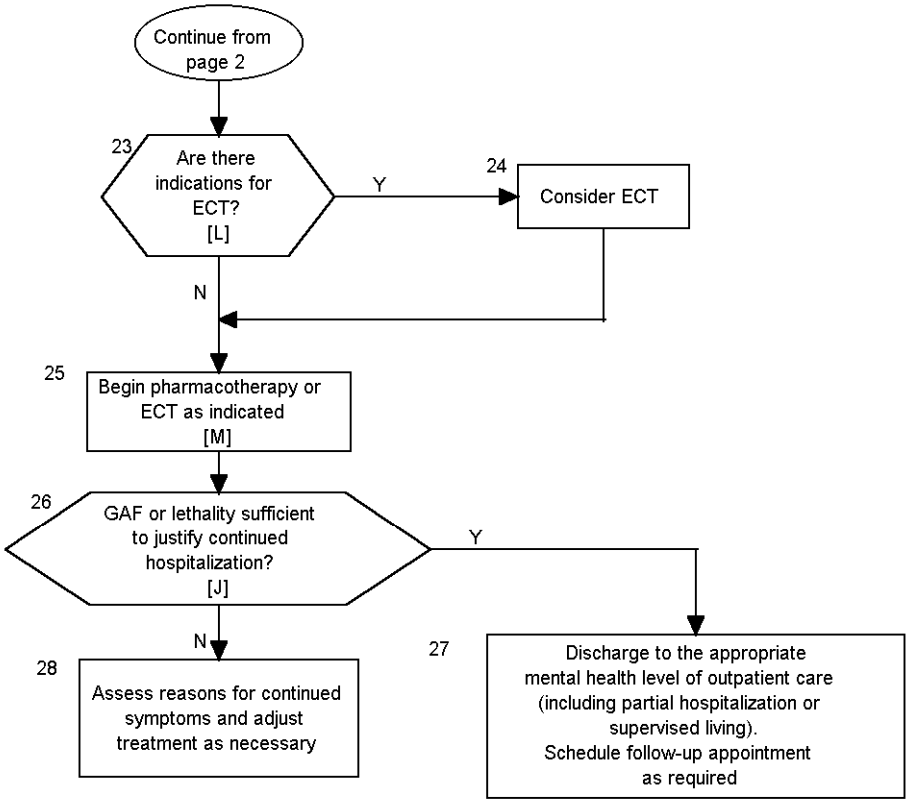
Major Depressive Disorder
Inpatient Mental Health Specialty

C2



Major Depressive Disorder
Inpatient Mental Health Specialty

C3



MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS IN THE INPATIENT MENTAL HEALTH SETTING
Module C.

A. Patient Admitted to Inpatient Unit with Presumptive Diagnosis of MDD

DEFINITION

This module applies to any patient newly admitted to inpatient psychiatric care for purposes of intensifying care or providing a more restrictive management setting. This is generally a relatively high-risk patient for whom effective psychiatric care is essentially unmanageable in a lower level of care.

B. Initial Assessment for Risk and Unstable Medical Condition

OBJECTIVE

To assess the newly admitted inpatient for factors that may acutely alter the required treatment setting or intensity.

ANNOTATION

Newly admitted psychiatric patients should be considered unstable until an initial assessment can be obtained. The patient should first be assessed for psychiatric or medical instability. Assessment of dangerousness includes acute risk of harming self or others. Assessment of medical instability should focus on medical conditions that will necessitate rapid consultation with either a medical or surgical consultant and/or precipitate transfer to a medical or surgical inpatient service.

Refer to Appendix 2, Unstable and High Risk Conditions, for information about potential dangerousness and/or urgent medical conditions.

C. High Risk for Suicide, Violence, or Other Precautions Are Required?

OBJECTIVE

To implement the least restrictive strategies that will ensure patient safety.

ANNOTATION

Assess treatment setting and patient for factors related to maintaining patient safety. Patients are to be admitted to the least restrictive treatment setting, indiscriminate use of "closed admitting wards" is discouraged. Potential for self-harm and harm to others must be reassessed upon admission even if a very recent pre-admission assessment was completed.

Special observation is a common nursing activity in psychiatric units and may employ intensified observation and assessment of high-risk patients. The indication, intensity and duration of special observation should be based upon the individual needs of the patient within parameters established by local facility policy, national hospital guidelines, and medical and legal standards.

D. Obtain History Including (Psychiatric, Family, Psychosocial, Military, Stress, Past Physical or Sexual Abuse, and Substance Use). Perform MSE and GAF or Axis V of DSM-IV, Physical Examination, Laboratory Tests, and Other Studies as Indicated

See Annotation E from Module B. Functional Status Assessment Instruments such as the GAF and SF-36 provide a means of determining the patient's ability to perform certain activities and/or respond to therapy at the time. These instruments also provide a baseline from which to measure improvement in functionality.

E. Is Medical Condition Contributing to Symptoms?

OBJECTIVE

To identify patients who may be experiencing depressed symptoms as a result of an underlying medical condition.

ANNOTATION

Many prescription or over-the-counter medicines can cause or compound symptoms of depression. Many pathobiologies may cause or compound symptoms of depression. For more detail see Module B Annotation J.

Table 1. Compounds That Commonly Cause Depression

Drug/Drug Class	QE =	SR =
ACE inhibitors	II-2	C
Amphetamine withdrawal	I	B
Anabolic Steroids	I	B
Antihyperlipidemics	II-2	C
Benzodiazepines	II-2	C
Cimetidine, Ranitidine	II-2	C
Clonidine	II-2	C
Cocaine withdrawal	I	C
Cycloserine	II-2	C
Digitalis	I	B
Glucocorticoids	I	B
Gonadotropin-releasing agonists	II-2	A
Interferons	II-2	C
Levodopa	II-2	C
Methyldopa	II-2	C
Metoclopramide	II-2	C
Oral contraceptives	II-2	C
Pimozide	II-2	A
Propanolol (Beta Blockers)	II-2	B
Reserpine	II-1	C
Topiramate	II-2	C
Verapamil (Calcium channel Blockers)	II-2	C

Table adapted from *Drug Safety* 1994,10(3):203-19 and modified using information from Bloch M, et al., 1997; Borras C, et al., 1999; Boumendil E, et al., 1995; Crawford P. 1998; Durelli L, et al., 1996; Ganzini L, et al., 1993; Hallas J, 1996; Metzger ED, et al., 1994; Patten SB, et al., 1993; Patten SB, et al., 1994; VA Medical Advisory Panel Guidelines. 1996, Unpublished; and Warnock JK, et al. 1998.

F. Meets DSM-IV Criteria for Major Depressive Disorder (MDD)?

See Appendix 1, Assessment Instruments, for the DSM-IV Criteria for MDD.

G. Identify and Treat Depression While Treating Other Co-morbid Conditions

OBJECTIVE

To determine treatment for depressed patient with co-morbid conditions

ANNOTATION

Depression may appear in conjunction with other DSM-IV, Axis 1, 2, or 3 diagnoses.

See Appendix 6, Non-MDD Conditions Potentially Requiring Specialty Consultation for some examples of co-morbid disorders. Also consider other DSM-IV and ICD-10 conditions in conjunction with depression and related disorders.

H. Complete Interdisciplinary Treatment Plan Addressing: Medication, Appropriate Psychotherapy, Other Psychosocial Interventions. Consider Co-morbidity if it exists, and Patient Preferences.

OBJECTIVE

To describe a course of clinical action for the various types of complex patients with MDD.

ANNOTATION

The patient should be assigned to a consistent interdisicplinary mental health care team, including members who represent both biomedical and psychosocial perspectives. The interdisciplinary team may include members of the following disciplines depending on the patient's unique health care needs:

1. Psychiatry – management of psychiatric disorders
2. Primary care provider – coordination of the patient's overall health and preventive care
3. Medical specialists other than psychiatry – as indicated by medical co-morbidities
4. Psychology – for behavioral and emotional aspects of care to include psychotherapy, biofeedback, and similar modalities
5. Social work – for coordination of community resources, counseling, and support groups
6. Nursing – health education and training such as for home health care and routine follow-up health care
7. Pharmacist – for the patient on pharmacotherapy, especially those on multiple medications, co-morbid medical conditions requiring pharmacotherapy or interacting with the patient antidepressant therapies
8. Dietary – for education pertaining to nutritional status and dietary aspects of pharmacotherapies (e.g., MAOIs)
9. Occupational therapy – assistance for the patient in need of life skills training
10. Recreational therapy – assistance for the patient in need of employment and/or benefits counseling
11. Vocational rehabilitation – assistance for the patient in need of employment and /or benefits counseling
12. Chaplaincy – assistance for the patient with religious or spiritual concerns or requests.

The interdisciplinary team will discuss the patient's diagnosis, etiological factors, and potential treatment options. Treatment options will also be discussed with the patient. Patient preference will play a major role in deciding what treatment(s) to initiate.

After decisions are made, it is preferable that a specific provider individualizes and coordinates the patient's care. If the patient is hospitalized, the current provider will either continue the care or arrange timely follow-up with another practitioner. The practitioner will establish a close working alliance with the patient, characterized by caring, shared decision-making, and respect for patient privacy. The practitioner will continue to consult with the interdisciplinary team, particularly if the patient does not improve during the first planned course of treatment

DISCUSSION

If the patient is currently being treated for Depression:

1. Assess treatment response – If the patient is responding to current treatment, but the response is only partial, or if the patient is not responding to current treatment, then assess treatment adherence and side effects.

2. Assess treatment adherence – Is the patient attending therapy sessions regularly? If not, why? Is the patient taking prescribed antidepressants or other medicines as directed? If not, why? The patient's answers to these questions will suggest whether a modification of treatment is necessary to achieve a therapeutic response.

3. Assess treatment side effects – Side effects are a common reason for poor adherence to therapy. Undesirable side effects of psychotherapy may include the need to miss work or other important activities and unanticipated effects on important relationships or increases in symptoms.

If the patient has chronic depression or past MDD episodes:

Relapse is not uncommon for individuals previously treated successfully. In a large cohort study of relapse in major depression, 37.1 percent of patients relapsed in the time frame studied. Two major risk factors were associated with relapse:

a. persistence of subthreshold depressive symptoms seven months after the initiation of antidepressant therapy
b. a history of two or more episodes of major depression, or chronic mood symptoms for two years (Lin, et al., 1998).

In such cases, the clinician may want to repeat prior intervention but emphasize continuation and/or maintenance therapy, since a prior history of response (or non-response) to a particular pharmacological agent may indicate the first line choice for further episodes (Janicak, Davis, Preskorn, & Ayd, 1997). With less certainty, a prior history of good or poor response by a family member to a particular agent may also indicate the best choice of agent for first-degree relatives (Janicak, Davis, Preskorn, & Ayd, 1997). Clinicians, however, should keep in mind that patients with depression that can be characterized as chronic (multiple previous episodes) often do not respond as well to monotherapy, either pharmacotherapy or psychotherapy, as those with single episodes of depression. More severely or chronically depressed patients may respond preferentially to combined treatment (Miller & Keitner, 1996).

If the patient has a personal or family history of suicidality:

This history is necessary to inform the frequency and content of follow-up monitoring. The presence of suicidal ideation or present and past suicidal and parasuicidal behaviors also suggests cautions in pharmacological treatments of choice. Agents of high potential lethality (e.g., TCAs, lithium, MAOIs) should be prescribed only with great caution to patients with current suicidal ideation or a past history of

suicidal behavior (especially overdose). In addition, extra vigilance in follow-up should be utilized if, after carefully weighing risks and benefits, such medications are prescribed.

Some patients may express concern that antidepressant drugs, and particularly the SSRIs may "cause" suicidal behavior, as this notion had at one time achieved some currency in the popular press. There is no evidence that treatment with any antidepressant, including the SSRIs, activates suicidal ideation or behavior (Tollefson & Rosenbaum, 1998; Warshaw & Keller, 1996). On the other hand, there is no evidence that antidepressant medication in itself reduces suicidality in patients with histories of suicidal behavior. Leon, et al., (1999) prospectively compared rates of suicidal behavior in patients treated with fluoxetine and other antidepressants to those receiving no treatment. Use of somatic treatments had some protective effect against suicidal behavior, but this difference was nonsignificant when compared to controls. In keeping with the authors' expectations, they found no increase in suicidal behavior among those treated with antidepressants. Montgomery (1997) reviewed the literature on suicide and antidepressants, and reported that there is some evidence that suicide rates actually increased with certain antidepressants (maprotiline and amitriptyline). Fluoxetine and mianserin were not found to have an effect on suicide rates. Knowledge of the influence of pharmacotherapy on suicide rates must be balanced against other evidence suggesting that patients assigned to psychotherapy also demonstrated an increased rate of suicide.

The SSRIs, particularly fluoxetine and sertraline, [have low lethal dose to effective dose ratio (LD:ED)], and are rarely lethal if taken alone in overdose, even in large quantity. The presence of Axis II disorders, like Borderline Personality Disorder, increase the risk of suicidal behaviors, and agents of high lethality should be avoided in this population (Dimeff, McDavid, & Linehan, 1999). Close follow-up is mandated; and special psychotherapeutic techniques are recommended in patients presenting with suicidal behavior or other behavior causing self-harm (Linehan, 1993).

If the patient has comorbid psychiatric problems:

Little clear literature is available to guide these decisions, and the clinician should decide based on a complete biopsychosocial work-up, consultation with the interdisciplinary team, and information on issues most distressing to patient and/or what patient is motivated to work on first. If a patient is currently undergoing psychotherapy, close consultation with the psychotherapy provider and clear communication with the patient as to the roles and expertise of each provider optimizes treatment outcome.

Short-term augmentation with benzodiazepines may be helpful in depressed patients with significant anxious features. Such treatment should be time limited. There is no evidence that long-term treatment with benzodiazepines contributes to positive outcome (Smith, Londberg, Glaudin, & Painter, 1998).

The existence of Axis II pathology may complicate treatment of an Axis I disorder, but this has not been systematically investigated. Recent reviews (Crits-Cristoph, 1998; Woo-Ming & Siever, 1998) found a paucity of well-designed trials for either psychological or pharmacological treatment of Axis II problems. Presence of personality disorders has generally been linked to poorer outcomes for treatment of MDD (Crits-Cristoph, 1998; Thase, 1996).

If the patient has co-morbid medical conditions:

Close consultation with the patient's primary care or specialty provider is recommended if medication is the patient's treatment of choice. For patients requiring pharmacotherapy, the clinician must be alert to the presence of relative contraindications as dictated by the medical condition, and perhaps more importantly, the potential for interaction between psychotropics and medications prescribed by other care givers. There are no known medical conditions that preclude the use of psychotherapy for MDD, although the course of therapy may be complicated by a patient's loss of cognitive function or functional independence. In such cases, a therapist with specific experience in adapting psychotherapy for patients with cognitive or functional impairment will be needed.

If the patient has features of atypical depression:

Though the MAOIs have been represented as the standard of care for depression with atypical features, a recent double-blind, randomized clinical trial found that both cognitive psychotherapy and phenelzine (approximately 64 mg/day) resulted in equivalent improvement (58 percent of patients rated improved in both groups) that was substantially greater than for a pill placebo group (28 percent; Jarrett, Schaffer, McIntire, Witt-Browder, Kraft, & Risser, 1999).

Another recent investigation found that patients with atypical features to their depression (hyperphagia, hypersomnia, leaden paralysis, and rejection sensitivity) are less likely to respond to medications, at least the TCAs (Stewart, Garfinkel, Nunes, Donovan, & Klein 1998). In this re-analysis of the Treatment of Depression Collaborative Research Project data, both Cognitive Behavioral Therapy (CBT) and Interpersonal Therapy (IPT) outperformed a combination of imipramine plus clinical management; CBT was significantly better than imipramine plus clinical management, and there was a trend towards significance for IPT.

For the patient with Post Traumatic Stress Disorder (PTSD):

Post Traumatic Stress Disorder (PTSD) – Some patients may require further diagnostic testing to rule out specific psychiatric disorders such as PTSD that can co-occur with depression and may require additional specialized treatment. See PTSD Guideline.

EVIDENCE

Fluoxetine treatment for MDD is not associated with an increased likelihood of suicidal behavior. (Leon AC, et al., 1999; Warshaw MG, 1996) QE = II-3, SR = B

Clinical characteristics can help target patients with MDD at high risk for relapse. Risk factors identified included persistent subthreshold depressive symptoms, chronic mood symptoms, or history of two or more major depressive episodes. (Lin, et al., 1998) QE = II-1, SR = B

Patients with atypical depression features are less responsive to TCAs. (unreplicated). (Stewart, et al., 1998) QE = II-2; SR =C

Sertraline maintenance therapy is well tolerated and prevents recurrence or reemergence of depression in chronically depressed patients. (Keller, et al., 1998) QE = I, SR = B

Cognitive therapy is an effective acute phase treatment alternative to MAOI antidepressant medications for patients with MDD and atypical features. (unreplicated). (Jarrett, et al., 1999) QE = I, SR = C

Analyses of coroners' data suggest that TCAs are associated with elevated death rates in overdose compared with SSRIs. (Montgomery SA, 1997) QE = III, SR =C

Presence of personality disorders has generally been linked to poorer outcomes for treatment of MDD. (Thase, 1996) QE = II-1, SR = B

I. Initiate Discharge Planning and Patient/Family Education

Appendix 7, Patient Education

J. Global Assessment of Function (GAF) or Lethality Sufficient to Justify Continued Hospitalization?

OBJECTIVE

To determine if the patient is safe to discharge to a less restrictive level of care.

ANNOTATION

The clinician should reassess whether the patient meets all of the following criteria for discharge to a less restrictive environment:

- Stabilization and/or improvement of symptoms
- Level of functioning allowing maintenance care in a less restrictive setting
- No acute manifestations of intent to harm self or others
- Support level allows active participation in aftercare.

See Appendix 1, Assessment Instruments, and Appendix 2, Unstable and High Risk Conditions for more information.

K. Discharge to the Appropriate Mental Health Level of Outpatient Care. Schedule Follow-up Appointment.

OBJECTIVE

To ensure appropriate level and continuity of care following discharge from the inpatient psychiatric setting.

ANNOTATION

Discharge planning serves as a vehicle to guide the patient/family to a successful termination of inpatient care, constructive re-integration into the community and staging for the implementation of a plan of continued recovery. Patient and family participation and education as well as continuity of care are the cornerstones of its effective application. The plan is interdisciplinary in nature (physician, psychologist, nurse, social worker, nutritionist, etc.) and identifies specific criteria for successful completion of inpatient care. Criteria will vary based on the goals of the setting, age and level of impairment. This critical activity proceeds throughout the hospitalization and requires timely and thoughtful preparation.

Discharge planning focuses on meeting the patient's assessed needs in critical domains of care. The plan is developed with the patient and family and should address the continuing physical, social, emotional, and psychological care requirements. It also attends to aspects of care that include:

- Patient and family education on aspects of all health care and high risk behaviors
- Substance abuse
- Functional status for self care, independent living and its compatibility with living arrangements
- Safe, decent, affordable, stable, and secure a domicile
- Family support for patient's recovery
- Constructive social activity that is consistent with continuing care goals
- Viable source of income that supports community re-entry
- Venue for continued or future employment that utilizes patient's skills
- Capacity to locate and access needed services as disruptive events impact on patient's stability.

In preparation for the patient's discharge, the patient and family should be provided education on the following:

- The course, prognosis, and causes of depression
- Factors that will exacerbate depression
- Strategies for adaptive coping
- Techniques for relapse prevention

- Medical and psychosocial follow-up plans
- Instructions regarding discharge medications and their risks and benefits.

Whenever a patient is discharged from the inpatient setting, appropriate patient information is communicated as a formulated discharge plan to ensure continuity of health care. The discharge plan consists of relevant information, including:

- The reason for treatment
- Date of admission and discharge
- Clinically significant findings
- Patient's physical and psychosocial status at admission and discharge
- Summary of care provided including progress made toward patient care goals
- Strengths, abilities, needs, and preferences of the patient
- Reason for hospital discharge
- Community resources or referrals provided or recommended to the patient and/or family
- Any specific instructions given to the patient and/or family.

Instructions for care after discharge are given not only to the patient and family, but also to the clinician responsible for coordinating the patient's medical care.

L. Are There Indications for ECT?

OBJECTIVE

To determine if the patient is a candidate for ECT.

ANNOTATION

Primary ECT – ECT may be justified as primary therapy for MDD if any of the following are present:

1. Psychotic features
2. Catatonic stupor
3. Severe suicidality
4. Food refusal leading to nutritional compromise
5. A history of prior good response.

ECT is justifiable as a first line therapy for the following indications:

1. Need for rapid, definitive treatment response on either medical or psychiatric grounds
2. Risks of other treatments outweigh the risks of ECT
3. A history of poor drug response
4. Patient preference.

Secondary ECT – Secondary use of ECT may be justified for any of the following:

1. Major Depression accompanied by:

    a) Documented antidepressant treatment failure after an adequate trial (medication, dosage, and time frame must be recorded in the medical record)
    b) Intolerable side effects of antidepressant medications (e.g., seizures, blood dyscrasia, second- and third-degree heart block, severe hypotension, severe anxiety).

2. Mania accompanied by:

    a) Documented failure to respond to pharmacological mood stabilizers (lithium, carbamazepine, valproic acid)
    b) Intolerable side effects to mood stabilizers (e.g., blood dyscrasia, dermatitis).

3. Psychosis with acute neuroleptic malignant syndrome
4. Schizophrenia and other functional psychoses
5. History of favorable response to ECT.
6. Indications for secondary use include:

    - Treatment failure
    - Unavoidable adverse effects using alternative treatments
    - Deterioration of patient's condition such that first criterion is met.
    - Informed Consent is required for all ECT.

See Appendix 8, Electro-convulsive Therapy.

M. Begin Pharmacotherapy or ECT as Indicated

OBJECTIVE

To describe somatic therapies for the inpatient with MDD.

ANNOTATION

See Appendix 5, Pharmacological Management of MDD; and Appendix 8, Electro-convulsive Therapy

Module C
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VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER** IN ADULTS

APPENDICES

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Appendices

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    2. CES-D Center for Epidemiological Studies – Depression scale - (5 items) (modified for geriatrics)
    3. Zung Depression Rating Scale
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    5. MOS Medical Outcomes Study - depression questions (4 items)
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MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Appendix 1. Assessment Instruments

- **Symptoms of Depression - Screening Instruments**

Multiple screening tools are now available that are potentially easy to use in primary care settings. The following tools are reproduced for consideration in local settings; they are arranged from shortest to longest. Information on sensitivity and specificity of each screener are provided:

1. PRIME MD Primary Care Evaluations of Mental Disorders – Depression questions (2 items).
2. CES-D Center for Epidemiological Studies – Depression scale - (5 items)
3. Zung Depression Rating Scale (21 items)
4. Beck Depression Inventory – Click Here
5. MOS Medical Outcomes Study - depression questions (4 items)
6. Ham-D Hamilton Depression Scale (21 items)

1. Primary Care Evaluation of Mental Disorders: PRIME MD - depression questions (2 questions)

Question	Yes or No
1. During the past month, have you often been bothered by feeling down, depressed, or hopeless?	
2. During the past month, have you often been bothered by little interest or pleasure in doing things?	

2. Center for Epidemiological Studies – Depression Scale (CES-D)

5-item brief version developed as screening instrument for patients of all ages and 60 or over:

For each of the following, please indicate how often you felt that way **during the past week**, using the following ratings *(Total score of **4** or more is a **positive** depression screen)*:

Score for questions 1 - 4 only

Rarely or none of the time (less than one day)	0
Some or a little of the time (1 to 2 days)	1
Moderately or much of the time (3 to 4 days)	2
Most or almost all the time (5 to 7 days)	3

Item #	Question	Score
1.	I felt that I could not shake off the blues even with help from my family or friends	0 1 2 3
2.	I felt depressed	0 1 2 3
3.	I felt fearful	0 1 2 3
4.	My sleep was restless	0 1 2 3

Score for question 5 only

Most of the time	0
Moderately or much of the time	1
Some of the time	2
Rarely	3

5.	I felt hopeful about the future.	0 1 2 3

This screening instrument is derived from the CES-D (Lewinsohn, et al., 1997).

3. Zung Self-Rating Depression Scale (21 items)

Patient Name_____Age_____ Sex_____ Date_____

INSTRUCTIONS:

Read each sentence carefully. For each statement, check the bubble in the column that best corresponds to how often you have felt that way during the past two weeks. For statement 5 and 7, if you are on a diet, answer as if you were not.

Please check a response for each of the 20 items.	None OR a Little of the Time	Some of the Time	Good Part of the Time	Most OR All of the Time
1. I feel downhearted, blue, and sad	[ ]	[ ]	[ ]	[ ]
2. Morning is when I feel the best	[ ]	[ ]	[ ]	[ ]
3. I have crying spells or feel like it	[ ]	[ ]	[ ]	[ ]
4. I have trouble sleeping through the night	[ ]	[ ]	[ ]	[ ]
5. I eat as much as I used to	[ ]	[ ]	[ ]	[ ]
6. I enjoy looking at, talking to, and being with attractive women/men	[ ]	[ ]	[ ]	[ ]
7. I notice that I am losing weight	[ ]	[ ]	[ ]	[ ]
8. I have trouble with constipation	[ ]	[ ]	[ ]	[ ]
9. My heart beats faster than usual	[ ]	[ ]	[ ]	[ ]
10. I get tired for no reason	[ ]	[ ]	[ ]	[ ]
11. My mind is as clear as it used to be	[ ]	[ ]	[ ]	[ ]
12. I find it easy to do the things I used to do	[ ]	[ ]	[ ]	[ ]
13. I am restless and can’t keep still	[ ]	[ ]	[ ]	[ ]
14. I feel hopeful about the future	[ ]	[ ]	[ ]	[ ]
15. I am more irritable than usual	[ ]	[ ]	[ ]	[ ]
16. I find it easy to make decisions	[ ]	[ ]	[ ]	[ ]
17. I feel that I am useful and needed	[ ]	[ ]	[ ]	[ ]
18. My life is pretty full	[ ]	[ ]	[ ]	[ ]
19. I feel that others would be better off if I were dead	[ ]	[ ]	[ ]	[ ]
20. I still enjoy the things I used to do	[ ]	[ ]	[ ]	[ ]

4. Beck Depression Inventory – Click Here

BDI *(continued)*

Beck Depression Inventory – Click Here

Beck, Ward, & Mendelson, 1961

Screening criterion: score of 10 or higher.

5. Medical Outcomes Study Depression Questionnaire

Recommended screening instrument for patients age under age 60:

This four-item screener recommended is also part of the evaluation package and has empirical support demonstrating its specificity and sensitivity (Rost, Burnam, Smith, 1993). It may be administered as a paper and pencil measure, as a computer assessment package, or assessed by the clinician.

Medical Outcomes Study: MOS Depression Questionnaire

Item	Question	Response /Score	
A.	In the past year, have you had two consecutive weeks or more during which you felt sad, blue, or depressed, or when you lost all interest or pleasure in things that you usually cared about or enjoyed?	YES NO	
B.	Have you had two years or more in your life when you felt depressed or sad most days even if you felt okay sometimes?	YES NO	
C.	Have you felt depressed or sad much the time in the past year?	YES NO	
D.	How much of the time in the past week did you feel depressed?	less than one day one or two days three or four days more than four days	Score 0 1 2 3
		1, 2, OR 3 – positive screen	

Positive Screen: the patient must indicate yes on question A OR yes on both questions B AND C, AND score 1, 2, or 3 on question D to be positive.

NOTE: If the answers to both questions A and C are NO, then the patient does not meet screening criteria for MDD even question D scores one or more. (currently depressed). Another diagnosis, such as dysthymia, may be appropriate but is outside the scope of this algorithm. Similarly, if the answer to question D is "less than one day" then the patient does not meet the screening criteria for MDD even if one or more of the earlier answers are "yes."

If the patient screening criteria for MDD is positive, then move on to a more intensive assessment on the algorithm. (Whooley, et al., 1997)

Evidence supports the sensitivity and specificity of the MOS Depression questions as a screening instrument for MDD in community and medical settings. (Rost K, Burnam MA, Smith GR, 1993) QE = II-2, SR = B

6. The Hamilton Rating Scale For Depression (clinician administered)

Patient's Name _____

Date of Assessment _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

---

1 DEPRESSED MOOD (Sadness, hopeless, helpless, worthless

_____
0= Absent
1= These feeling states indicated only on questioning
2= These feeling states spontaneously reported
3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2 FEELINGS OF GUILT

_____
0= Absent
1= Self reproach, feels he has let people down
2= Ideas of guilt or rumination over past errors or sinful deeds
3= Present illness is a punishment. Delusions of guilt
4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3 SUICIDE

_____
0= Absent
1= Feels life is not worth living
2= Wishes he were dead or any thoughts of possible death to self
3= Suicidal ideas or gesture
4= Attempts at suicide (any serious attempt rates 4)

4 INSOMNIA EARLY

_____
0= No difficulty falling asleep
1= Complains of occasional difficulty falling asleep—i.e., more than ½ hour
2= Complains of nightly difficulty falling asleep

5 INSOMNIA MIDDLE

_____
0= No difficulty
1= patient complains of being restless and disturbed during the night
2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6 INSOMNIA LATE

_____
0= No difficulty
1= Waking in early hours of the morning but goes back to sleep
2= Unable to fall asleep again if he gets out of bed

Hamilton Rating Scale For Depression (*continued*)

7 WORK AND ACTIVITIES

_____
0= No difficulty
1= Thoughts and feeling of incapacity, fatigue or weakness related to activities; work or hobbies
2= Lost of interest in activity; hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3= Decrease in actual time spent in activities or decrease in productivity
4= Stop working because of present illness

8 RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

_____
0= Normal speech and thought
1= Slight retardation at interview
2= Obvious retardation at interview
3= Interview difficult
4= Complete stupor

9 AGITATION

_____
0= None
1= Fidgetiness
2= Playing with hands, hair, etc.
3= Moving about, can't sit still
4= Hand wringing, nail biting, hair-pulling, biting of lips

10 ANXIETY (PSYCHOLOGICAL)

_____
0= No difficulty
1= subjective tension and irritability
2= worrying about minor matters
3= Apprehensive attitude apparent in face or speech
4= Fears expressed without questioning

11 ANXIETY SOMATIC: Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

_____
0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

12 SOMATIC SYMPTOMS (GASTROINTESTINAL)

_____
0= None
1= Loss of appetite but eating without encouragement from others. Food intake about normal
2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

Hamilton Rating Scale For Depression (*continued*)

13 SOMATIC SYMPTOMS GENERAL

_____ 0= None
1= Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2= Any clear-cut symptom rates 2

14 GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____ 0= Absent
1= Mild
2= Severe

15 HYPOCHONDRIASIS

_____ 0= Not present
1= Self-absorption (bodily)
2= Preoccupation with health
3= Frequent complaints, requests for help, ect.
4= Hypochondriacal delusions

16 LOSS OF WEIGHT

_____ A. When rating by history:
0= No weight loss
1= Probably weight loss associated with present illness
2= Definite (according to patient) weight loss
3= Not assessed

17 INSIGHT

_____ 0= Acknowledges being depressed and ill
1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2= Denies being ill at all

18 DIURNAL VARIATION

_____ Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none
0= No Variation
1= Worse in A.M.
2= Worse in P.M

B. When Present, mark the severity of the variation. Mark “None” if NO variation
0= None
1= Mild
2= Severe

19 DEPERSONALIZATION AND DEREALIZATION (Such as: Feelings of unreality; Nihilistic ideas)

_____ 0= Absent
1= Mild
2= Moderate
3= Severe
4= Incapacitating

_____ 20 PARANOID SYMPTOMS
0= None
1= Suspicious
2= Ideas of reference
3= Delusion of reference and persecution

_____ 21 OBSESSIONAL AND COMPULSIVE SYMPTOMS
0= Absent
1= Mild
2= Severe

Total Score_____

Adapted from Hedlung and Vieweg, (1979). The Hamilton rating scale for depression, Journal of Operational Psychiatry,10(2), 149-165.

- **Functional Status Measures**

1. Global Assessment of Function (GAF)

The following 0 to 100 scale (100 = maximum functioning) is the metric recommended by the American Psychological Association for measuring functional impairment due to mental disorders (DSM-IV).

Code	(**Note:** Use intermediate codes when appropriate, e.g., 45, 68, 72.)
100 91	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.
90 81	Absent or minimal symptoms (e.g., mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., an occasional argument with family members).
80 71	If symptoms are present, they are transient and expected reactions to psychosocial stressors (e.g., difficulty concentrating after family argument); no more than slight impairment in social, occupational, or school functioning (e.g., temporarily falling behind in schoolwork).
70 61	Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.
60 51	Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peers or coworkers).
50 41	Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) OR any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).
40 31	Some impairment in reality testing or communications (e.g., speech is at times illogical, obscure, or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).
30 21	Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communications or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day; no job, home, or friends).
20 11	Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or mute).
10 1	Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.
0	Inadequate information.

This rating of overall psychological functioning on a scale of zero to 100 was implemented by Luborsky in the Health-Sickness Rating Scale (Luborsky L: Clinicians Judgments of Mental Health. Archives of General Psychiatry 7:407-17. 1962)). Spitzer and colleagues developed a revision of the Health-Sickness Rating Scale

called the Global Assessment Scale (GAS): A Procedure for Measuring Overall Severity of Psychiatric Disturbance. Archives of General Psychiatry 33: 766-71. 1976). A modified version of the GAS was included in DSM-III-R as the Global Assessment of Functioning (GAF) Scale.

2. SF-36 Quality of Life

The Short Form 36 (SF-36) is a research tool used for quantifying functional status. It is offered here to illustrate useful questions for assessing functioning in potentially depressed patients. Generally, the need for computerized scoring precludes its routine clinical use.

Instructions:
This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:	Excellent [ ]	Very good [ ]	Good [ ]	Fair [ ]	Poor [ ]
2. Compared to one year ago, how would you rate your health in general now?	Much better now [ ]	Somewhat better now [ ]	About the same now [ ]	Somewhat worse now [ ]	Much worse [ ]

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	[ ]	[ ]	[ ]
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[ ]	[ ]	[ ]
Lifting or carrying groceries	[ ]	[ ]	[ ]
Climbing **several** flights of stairs	[ ]	[ ]	[ ]
Climbing **one** flight of stairs	[ ]	[ ]	[ ]
Bending, kneeling, or stooping	[ ]	[ ]	[ ]
Walking **more than a mile**	[ ]	[ ]	[ ]
Walking **several blocks**	[ ]	[ ]	[ ]
Walking **one block**	[ ]	[ ]	[ ]
Bathing or dressing yourself	[ ]	[ ]	[ ]

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
Cut down on the **amount of time** you spent on work or other activities	[ ]	[ ]
Accomplished less than you would like	[ ]	[ ]
Were limited in the **kind** of work or other activities	[ ]	[ ]
Had **difficulty** performing the work or other activities (for example, it took extra effort)	[ ]	[ ]

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
Cut down on the **amount of time** you spent on work or other activities	[ ]	[ ]
Accomplished less than you would like	[ ]	[ ]
Didn't do work or to her activities as **carefully** as usual	[ ]	[ ]

(SF-36 Quality of Life continued)

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
[ ]	[ ]	[ ]	[ ]	[ ]

7. How much bodily pain have you had during the past 4 weeks?

None	Very Mild	Mild	Moderate	Severe	Very Severe
[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the hope and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
[ ]	[ ]	[ ]	[ ]	[ ]

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
Did you feel full of pep?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Have you been a very nervous person?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Have you felt so down in the dumps that nothing could cheer you up?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Have you felt calm and peaceful?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Did you have a lot of energy?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Have you felt downhearted and blue?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Did you feel worn out?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Have you been a happy person?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]
Did you feel tired?	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

10. During the past 4 weeks, how much time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	[ ]	[ ]	[ ]	[ ]	[ ]
b) I am as healthy as anybody I know	[ ]	[ ]	[ ]	[ ]	[ ]
c) I expect my health to get worse	[ ]	[ ]	[ ]	[ ]	[ ]
d) My health is excellent	[ ]	[ ]	[ ]	[ ]	[ ]

SF-36 Manual

Scoring available and more information at www.SF-36.com

1. DSM-IV Diagnostic Criteria for MDD

The following criteria are from the DSM-IV Criteria for establishing the diagnosis of Major Depressive Disorder (MDD).

Diagnostic Criteria for Major Depressive Episode (from DSM-IV, page 327)

A major depressive episode is not always indicative of major depressive disorder. Other causes of a Major Depressive Episode besides MDD include, for example, Bipolar Disorders. (See criteria below.)

A. At least five of the following symptoms have been present during the same 2-week period, nearly every day, and represent a change from previous functioning. At least one of the symptoms must be either (1) depressed mood or (2) loss of interest or pleasure:

    1. Depressed mood most of the day, nearly every day, as indicated by self or others
    2. Markedly diminished interest or pleasure in all, or almost all, activities
    3. Significant weight loss or weight gain (5 %/mo.) or loss/gain in appetite nearly every day.
    4. Insomnia or hypersomnia nearly every day
    5. Psychomotor agitation or retardation nearly every day (as noted by others).
    6. Fatigue or loss of energy nearly every day
    7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
    8. Diminished ability to think or concentrate or indecisiveness nearly every day
    9. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. Symptoms are not better accounted for by a Mixed Episode, Mood Disorder Due to a General Medical Condition, a Substance-Induced Mood Disorder, or Bereavement (normal reaction to the death of a loved one)

D. Symptoms are not better accounted for by a Psychotic Disorder (e.g., Schizo-affective Disorder).

Diagnostic Screening Criteria for Major Depressive Disorder

Patients suffering from a Major Depressive Episode who also meet all of the following criteria should be diagnosed with MDD.

1. Presence of either a single (296.2) or recurrent (296.3) Major Depressive Episode(s), respectively. (See definition below.)
2. The major depressive episode(s) is/are not better accounted for by Schizo-affective Disorder and is/are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.
3. There has never been a Manic Episode (DSM-IV, page 327), a Mixed Episode (DSM-IV page 335), or a Hypomanic Episode (DSM-IV page 338). **Note**: This exclusion does not apply if all of the manic-like, mixed-like or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.

American Psychiatric Association. 1994.

1. SAIC Criteria for Admission

SAIC psychiatric admission criteria are abstracted as follows:

Admission is indicated if #1 and (#2 or #3 or #4) of the A. Severity of Illness criteria are met **and both** of the B. Treatment Need criteria are met.

1. Severity of Illness

A. A DSM-IV diagnosis or diagnoses are present and complete on all five axes, and there is evidence of significant associated social impairment, occupational impairment, or subjective suffering.

B. The patient is a danger to him/herself such as might be indicated by one or more of the following:

- High lethality or high-intent suicide attempt in past two weeks
- Recent suicide gesture in patient with history of high lethality or high intent suicide attempts
- Suicidal ideation with a plan, in the presence of command hallucinations, delusions of guilt or impending death, intractable pain, feelings of desperation or hopelessness, or other known precipitant of suicide
- Persistent acts of serious self-mutilation
- Medical emergencies influenced by mental illness
- Inability to provide for own basic needs of food, shelter, or medical care as the result of a mental illness.
- Bizarre behavior due to a psychotic disorder that endangers patient, his reputation, assets, or relationships.

C. The patient is a danger to others as a result of a mental disorder that is likely to improve by hospitalization, for example, as evidenced by one or more of the following:

- Threats of harm against a specific individual when associated with a delusional thought pattern or persistent anger or agitation
- Threats of harm against an unidentified person(s)
- Threatening behavior with a lethal weapon or possession of a lethal weapon in a state of severe emotional disturbance
- Escalating threatening language or behavior in a patient with a history of assaultive or aggressive behavior
- Significant damage to property.

D. The patient has a serious mental disorder causing significant impairment of social, familial, vocational, or educational functioning that would benefit from the intensity of acute treatment, such as:

- Depressed mood with disabling vegetative symptoms.
- Exacerbation of acute schizophrenia with severe disordered thinking and perception
- Marked deterioration in personal hygiene as a result of an acute psychiatric disorder
- Complete withdrawal from work, school, or social situations due to an acute psychiatric disorder
- Adequate trial of outpatient treatment resulting in failure. Examples of outpatient failures are:
  - Six weeks of outpatient therapy, including medication and psychotherapy, for an affective or psychotic disorder
  - Noncompliance with treatment as a complication of affective or psychotic disorder

- Socially disruptive behavior that alienates the social support necessary for outpatient treatment success
- Severe primary psychiatric illness worsened by substance abuse
- Unstable, unsupportive, or hostile living situation that significantly interferes with outpatient treatment success
- Medical condition or physical disability that prevents regular participation in outpatient treatment.

2. Treatment Needs

A. Intensive, short term intervention (at least four hours per day for three to five days per week) is needed to achieve the individualized treatment goals

B. An assessment including 1) evaluation of medical, emotional, behavioral, social, recreational, vocational, legal, and nutritional needs and resources, and 2) a review of the psychiatric history, presenting symptoms, mental status examination, and diagnostic impressions has been completed

C. A treatment plan identifying treatment goals, interventions, and the patient's strengths, resources, and limitations has been completed

D. The patient requires one of the following:

- Crisis stabilization to avert hospitalization
- Transitional treatment following a period of acute inpatient care because he/she cannot be safely maintained in the community with outpatient treatment
- The patient requires more intensive services than outpatient treatment to increase his/her level of independent functioning, but does not require acute inpatient treatment.

E. An identified licensed clinical staff member is responsible for coordination of treatment

F. The initial treatment plan for depressive disorders includes <u>diagnosis – specific elements</u> such as the following:

3. Depressive Disorder

A. The treatment plan has the following three prioritized objectives:

- Reduction of signs and symptoms of the depression
- Restoration of occupational and psychosocial functioning
- Reduction of the likelihood of relapse.

B. The treatment plan includes patient or family education about treatment, side effects of treatment, and likelihood of treatment success

C. If the patient has severe depression, antidepressant medication is included in the treatment plan unless an appropriate rationale for not using medication is provided.

Treatment that is only available or is best provided in a hospital, such as:

- Electro-convulsive therapy (ECT)
- Closely monitoring and daily titration of medication with disabling side effects or toxicity

- Constant staff observation as part of an intensive behavioral modification program
- Close monitoring of behavior in an episodic disorder
- Close monitoring of vital signs or need for multiple daily laboratory or electrophysiological tests.

(Mental Health Quality Monitoring Screens and Utilization Review Criteria. 1995)

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Appendix 2. Unstable and High Risk Conditions

Delirium – Delirium (also known as organic brain syndrome, organic psychosis, acute confusional state, acute brain syndrome and various other names) is a common disorder of cognition and consciousness of abrupt onset. Delirium is easily overlooked and a harbinger of a poor outcome. The elderly, demented, or chronically ill are at elevated risk of delirium. The cognitive and behavioral disturbances characterizing delirium often mimic the signs and symptoms of MDD, dementia, psychotic disorders, and impulse control disorders. These disturbances are generally caused by direct physiological consequences of a general medical condition, medication or substance, or due to substance intoxication or withdrawal. Often a combination of these etiologies is responsible.

Failure to recognize delirium or misdiagnosis of the same is a serious problem. First, correction of the mental status changes requires correction of the underlying medical cause. Second, the presence of delirium is a predictor of mortality and morbidity. Other consequences include a delay in the administration of appropriate therapy and increased risk for prolonged hospitalization or institutionalization. Delirium may be approached as follows:

1. Maintain Index of Suspicion

   The following have been identified as risk factors for the development of delirium:

   - Age greater than 65, with or without past psychiatric history (though absence of past or family psychiatric history can be quite valuable in terms of diagnosis)
   - History of significant substance abuse
   - Advanced general medical condition, especially if it is worsening
   - Poor nutritional status
   - Conditions that predispose to sensory deprivation (blindness, deafness, sleep disturbances, etc.)
   - History of neurological disease or insult (dementia, traumatic brain injury, etc.)
   - Heightened susceptibility to infection
   - Multiple medications (especially with significant anti-muscarinic properties).

2. Assess For Core Cross-Sectional Features:

   These are the essential presenting features of delirium, which may be divided into disorders of consciousness, cognition (and attention), and behavior. They reflect the criteria put forth in the most recent *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).*

   a. Disorder of consciousness.

      The delirious patient suffers from diminished awareness and attentiveness to his/her environment. This may be reflected in **disorientation** to time and/or place. Only the most seriously ill may be disoriented to person. Delirious patients are easily distracted, and are thus prone to **transient shifts of attention** to environmental stimuli. Finally, transient **somnolence** (arousable, but cannot keep train of thought) or **stupor** (vigorous stimulation required for arousal) may be apparent either upon presentation or by history.

   b. Disorder of cognition.

      Memory disturbances may be readily apparent, with short-term memory being more severely affected and long-term memory being relatively prescribed (although this may not always be the case). This phenomenon may stem, from specific deficits in registration, retention and recall. These may be assessed using standardized tools such as the Mini-Mental Status Examination (MMSE).

Misidentification of unfamiliar objects as being familiar and other **perceptual disturbances** such as visual, gustatory, olfactory or tactile hallucinations (as opposed to auditory hallucinations characteristic of schizophrenia), as well as hypnagogic or hypnapompic hallucinations, may be present. Although delusions can be a feature of delirium, they tend not to be as fixed across time, or as systematized as though associated with intrinsic psychotic disorders. The aforementioned distractibility usually leads to problems with tasks that depend on a certain degree of sustained concentration; and may cause difficulties with **problem solving**.

Speech can also be affected by the patient's inability to maintain attention. Clear streams of thought cannot be maintained, resulting in fragmented, halting or incoherent speech. In tandem with memory disturbances, this can lead to a pattern of speech marked by no apparent connection from topic to topic.

c. Disorder of behavior.

Combinations of the above deficits in cognition and consciousness may lead to fragmented and unpredictable behaviors, shifting between states of heightened agitation and marked quiescence (variable psychomotor activity), along with rapidly alternating emotional symptoms. Sleep disturbances are profound, often with complete reversal of the normal sleep/wake cycle, or nocturnal exacerbations of any of the previously mentioned disturbances of consciousness, cognition or behavior ("sundowning").

3. Assess For Longitudinal Features

The symptoms of delirium typically **emerge abruptly**, or may manifest more insidiously, erupting over hours to only a few days. Afterwards, the symptoms themselves persist in a **fluctuating course**, characterized by a "waxing and waning" pattern, often with brief periods of luscency. Night-time **exacerbations** are common. Other times, symptoms can follow a more stable course, presenting a true diagnostic challenge.

Clarify the Underlying Cause and Provide Appropriate Treatment. See Module A, Box 5.

Severe Psychotic Symptoms – "Psychosis," in and of itself, is not a disorder. Rather, it is a symptom which may present in a variety of conditions. Psychotic patients have an impaired sense of reality, which may manifest in several ways (hallucinations, delusions, mental confusion or disorganization).

There are many causes of psychosis, including primary psychiatric illness; drug-induced psychoses (e.g., therapeutic agents, **alcohol**, illegal drugs); withdrawal from CNS depressants; poisoning (carbon monoxide, Belladonna alkaloids, etc.), and selected medical conditions.

Psychotic symptoms become severe when the patient's sense of reality becomes so impaired that there is potential for self-harm or harm to others. These dangerous behaviors, or the potential for such behaviors, often stem from paranoid **ideations** or responses to internal stimuli (e.g., auditory hallucinations). A mental health consultation or referral is almost always indicated.

Severe Depression – The clinical presentation of depressed patients is marked by considerable variation, not only in the expression of various neurovegetative symptoms themselves, but also in the magnitude of severity of these symptoms. While many mild to moderate illnesses may not necessarily present as situations mandating immediate attention, the presence of severe depressive symptoms may represent a situation entirely to the contrary—even in the absence of suicidal ideation.

It is important to first recognize that what appears to be a severely depressed patient may actually be a patient harboring an unstable organic pathology. Suspicion is raised in the setting of 1) no personal or family history of psychiatric illness; 2) discernible alteration or sudden change in consciousness or cognitive status; or 3) elderly; 4) demented; 5) post-operative; or 6) multiple medications or medical problems; or 7) metabolic abnormality.

If no organic etiology is apparent, there still remains the question of an severe and unstable depression. Specific situations which place the patient at added risk to self, even in the absence of suicidal ideation, include the following:

- Severe neurovegetative disturbance in the form of anorexia/severe weight loss
- Anhedonia or lethargy which has progressed to the inability to provide adequate self-care
- Presence of psychotic features
- Severe agitation
- Refusal of medication
- Catatonia.

The presence of any of the aforementioned items may be an indication for mental health consultation or referral.

The Potentially Violent/Agitated Patient – Violence often emerges as a response to perceived threat or from marked frustration caused by the inability to meet goals by nonviolent means. The specific factors that contribute to violent behavior include psychiatric, medical, environmental, and situational/social. Often it is a combination of factors that precipitates and aggravates the potential for violence. Violence may quickly escalate to frank agitation or the carrying out of violent impulses. Whatever the cause, the following situations may serve as warning signs pointing towards a threat of violence:

- Ideation and/or intent to harm others
- Past history of violent behaviors
- Severely agitated or hostile
- Actively psychotic.

Immediate attention and intervention may be required in order to stave off the potential for escalation of agitation or violent impulses. The assessment of the potentially violent patient has three primary tasks: assessing the cause, assessing the intent, and establishing control of an acute situation.

1. Assessing the Cause

   Though the causes of violent behaviors are numerous, they can be grossly subdivided into three main categories. This classification scheme suggests not only a pathway for further evaluation, but also suggests which forms of treatment may be more effective. The categories are as follows:

   Organic mental disorders, Psychotic disorders, Non-psychotic, non-organic disorders.

   - Organic Mental Disorders

     The differential diagnosis under this section closely mirrors that of delirium, see Annotation for Box 4.

     The primary culprits include:

     a. Infections (systemic or CNS)
     b. Substance withdrawal (CNS depressants)
     c. Substance intoxication (alcohol and other CNS depressants, phencyclidine and other CNS stimulants, hallucinogens, inhalants, anticholinergic medications, steroids)
     d. Hypoxia (any cause)
     e. Hypertension
     f. Hypoglycemia
     g. Hypo- or hyper-natremia

h. Acid-base disturbances
i. Hypo- or hyper-thyroidism
j. Severe hepatic or renal disease
k. CNS pathologies (seizures, tumors or other space-occupying lesions, encephalitis, meningitis, intracranial bleed, dementing illness, NPH, MS, CVA/infarct)
l. Traumatic brain injury
m. Deficiency state (B_{12}, folate)
n. Toxin exposure (heavy metals, insecticides)
o. Drugs that cause delirium.

- Psychotic disorders

  In assessing the potentially violent patient, it is most useful to concentrate on the presence or absence of delusions (especially paranoid delusions), hallucinations (especially command-type hallucinations), catatonic excitement, mania (with or without psychotic features); or major depressive disorder with psychotic features.

- Non-psychotic, non-organic disorders

  These include disorders of impulse control, Axis II pathologies and violent behavior that may be present in various syndromes of mental retardation.

2. Assessing the Intent

   Assessment of violent intent is quite challenging unless it is actively endorsed by the patient via direct questioning. Most studies concerned with the prediction of violent behavior have focused on demographic aspects and risk factor identification. Such studies may accurately reflect violent behaviors in the particular groups studied; however, their usefulness in predicting an individual patient's behaviors is less so. Some basic risk factors for violence are listed below:

   - Threat is well-planned
   - Means to harm others are readily available
   - Past history of violence to others, especially in the immediate past
   - Past history of dangerous impulsive behaviors
   - History of having suffered from child abuse
   - Alcohol or other substance abuse
   - Psychosis
   - Escalating level of agitation.

3. Establishing Control of an Acute Situation

   See Module A, Box 4.

Threat To Self/Suicidality – See Appendix 3, Suicidality.

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Appendix 3. Suicidality

The potential threat of self-harm and violence and the assessment of the potentially violent patient have been introduced in Module A, Box 4. Please refer to that particular section for the aforementioned discussion regarding the potentially violent patient. In this annotation, a more detailed recommendation for assessing the potentially suicidal patient will be offered.

Suicidality – Suicidality is a topic relevant to all health care providers. It is highly prevalent, representing one of the leading causes of mortality in the United States. It is the leading cause of violent death in this country. Up to one-third of people in the general population report having had suicidal ideation during some point in their life. As many as two-thirds of patients who commit suicide visited their physician within one month of their death.

The primary challenge to the provider is prediction of suicide, or assessment of degree of intent. Numerous epidemiological studies have afforded us a great deal of knowledge in terms of risk factor identification, especially for completed suicide. From this data, several means of assessing suicide potential (some formal, others not so regimented) have been developed and employed, with varying degrees of success and inconsistent results. Prediction of suicide in the individual patient remains among the most formidable of clinical challenges. Expression of suicidal ideation (or intent) warrants aggressive intervention, likely in the form of referral or consultation with a mental health provider.

Evaluation of the Potentially Suicidal Patient – The evaluation itself consists of three main parts:

1. Eliciting suicidal ideation or intent
2. Gathering data on risk factors for completed suicide
3. Weighing items one and two to assess safety.

1. Eliciting Suicidal Ideation or Intent

   Ideally, eliciting suicidal ideation or intent involves a free and honest exchange of information between patient and clinician. Unfortunately, this is not always so. Familiarity with the existing epidemiological and demographic data concerning suicide (see below) is useful in generating an index of suspicion. From there, *direct questioning* regarding suicidal ideation/intent may be initiated. There are no data demonstrating an increased rate of suicide attempts or completions following questioning about suicide. Avoid rushing this part of the history or putting it off.

   Despite the lack of reliable measures of suicide risk among individuals, a basic assessment should (Goldberg, 1987):

   a. Determine presence/absence of delirium, psychosis, or depression.
   b. Elicit patient's statements about his/her suicidality
   c. Elicit patient's own ideas concerning what would help attenuate or eliminate suicidal ideation/intent
   d. Attempt to gather collateral data from a third party in order to confirm the patient's story
   e. A suggested sequence of suicide questions to ask is:

      – Are you discouraged about your medical condition (or social situation, etc.)?
      – Are there times when you think about your situation and feel like crying?
      – During those times, what sorts of thoughts go through your head?
      – Have you ever felt that if the situation did not change, it would not be worth living?
      – Have you reached a point that you've devised a specific plan to end your life?
      – Do you have the necessary items for completion of that plan readily available?

f. Formulate acute and chronic management plan. Encourage active patient participation in negotiating a plan for follow-up.

- What epidemiological risk factors are present (may have to inquire about each one individually)?
- What other psychiatric conditions are present (besides the ones mentioned above)?
- What is the level of psychological defense functioning?
- Has there been a will made recently?
- Is there talk of plans for the future?
- What is the makeup and condition of the patient's social support system? How can they be contacted?
- Is there active suicidal ideation? "How strong is (your) intent to do this?"
- "Can you resist the impulse to do this?" "Do you tend to be impulsive?"
- "Have you ever rehearsed how you would kill yourself?"
- "Have any family members or people close to you ever killed themselves?"

1. Risk Factors for Completed Suicide

The causes of suicide are multifactorial. The risk for suicide increases with the accumulation of risk factors in an individual. Clinician should be alert for suicide risk in patients with a sad or depressed mood, suicidal ideation and one or more of the following risk factors.

There is no accepted standard screening instrument for suicidal risk. Recent publications including the VA Education Module, "Prevention of Suicide: Everyone's Concern", and the article by Hirschfeld and Russell provide examples of brief, thorough screening tools.

Patients with evidence of intent for suicide should be offered mental health counseling and possibly hospitalization (U.S. PSTF, 1996)

Patients with definite intent (suicidal/homicidal ideation, intent, and/or plan) to harm self or others require voluntary or involuntary emergency psychiatric treatment (DHHS pub. no. 95-3061, 1995; APA, 1993)

The endorsement of suicidal ideation or intent represent obvious risk factors for suicide completion, especially if intent exists with an active plan for carrying it out. Other identified risk factors are listed below:

- **Presence of psychiatric illness –** Greater than 90 percent of adults who successfully complete suicide have some form of psychiatric illness. A symptom triad of mood symptoms, aggressiveness and impulsivity has been described as representing a major contribution to risk of suicide completion. The presence of hopelessness has been similarly classified.

- **Serious medical illness –** This is especially true of disorders marked by a debilitating course. Even so, suicide in this particular population rarely occurs in the absence of a psychiatric condition.

- **Means for suicide completion readily available** – Refers to immediate accessibility of firearms or other highly lethal modality.

- **Psychosocial disruption** – Includes recent separation, divorce, loss of job, retirement, bereavement, or other perceived negative life event (including living alone).

- **History of previous suicide attempts** – One percent of suicide attempters will go on to completion each year, and 10 to 20 percent will eventually succeed at some point.

- **Active substance abuse**

- **Impulsivity or history of poor adaptation to life stress**
- **Family history of completed suicide**
- **Male sex** - though females attempt suicide three times as frequently as males, 75 percent of completed suicides are by males.
- **Advanced age –** Higher rates of suicide completed and suicide attempts reported in patients greater than age 60. Age generally becomes a risk factor beginning at age 45. This is a gross generalization of a complex body of data.
- **Caucasian race** – Risk is highest for Caucasians.

1. Evaluating the available data.

   If suicide risk is present, a stratification system is useful in terms of formulating a strategy for intervention. One such system includes the following divisions: (1) imminent (suicide may be attempted within the next two days); (2) short-term (days to weeks); and (3) long term.

   Imminent Risk – Suspect if patient endorses suicidal intent, an organized plan is presented, lethal means are available, signs of psychosis (especially command hallucinations) are present, extreme pessimism is expressed (despair, hopelessness, etc.), or several additional risk factors for suicide are present.

   - Management suggestions – Immediate action is required. Hospitalize or commit. DO NOT leave the patient alone.

   Short-Term Risk – Suspect if: Several risk factors for suicide present, but no suicidal behaviors present.

   - Management suggestions:

     a. With patient's permission, involve family member of other person close to patient and advise them of the situation.
     b. If potentially lethal means of suicide completion are available, initiate steps to make these items inaccessible.
     c. Stay in contact with the patient (telephone calls, more frequent office visits, etc.). Frequently re-evaluate risk.
     d. Treat psychiatric conditions as appropriate, including substance abuse/dependence (may require consultation from mental health professional). Close follow-up will help to improve compliance and continue risk assessment.
     e. Consider hospitalization as appropriate.

   Long-Term Risk – The therapeutic goal is to eliminate or improve modifiable suicide risk factors. This may involve treatment of psychiatric illness (through biological means or through psychotherapy), treatment of substance abuse, etc. Frequent reassessment is still a useful guideline, and acute situations mandating psychiatric referral or hospitalization may arise. Thus, all of the aforementioned management suggestions should be considered even here.

   The clinician should be reminded that the assessment of suicidal potential is far from exact, and that the above text serves only as one of many suggested approaches. In any case, the provider should adopt a systematic approach, such as the one offered above, in order to more comfortably assess and manage the potentially suicidal patient.

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Appendix 4. Empirically Supported psychoTherapies (ESTs) of MDD

1. Several depression specific psychotherapies are effective alternatives to medication. This does not mean that any intervention described as "psychotherapy" has equal effectiveness as the medications with documented efficacy. For example, there is no evidence that long-term psychodynamic treatment is an effective intervention for depression. At the other end of the spectrum, there is also no evidence that brief, supportive counseling is an effective intervention; in fact, a recent study demonstrates that it is not as effective as antidepressant medication (Malt, Robak, Madsbu, Bakke, & Loeb, 1999). The specific forms of short-term, structured psychotherapies with established efficacy for treatment of major depression are:

    - Cognitive therapy
    - Behavior therapy
    - Interpersonal therapy
    - Brief dynamic therapy
    - Marital psychotherapy.

These therapies are described in Appendix 1, Assessment Instruments, in a format appropriate to present to patients when describing treatment options.

Referral should be made to a therapist experienced in the use of at least one of these psychotherapies for the treatment of major depression. Referral for psychotherapy may be made to one of the following, depending on local resources:

- Mental health professional on primary care team
- Mental health specialty service
- Contract community mental health provider.

Depending on local resources and individual patient preference, therapy may be provided in individual, group, or couples format.

Other relevant psychosocial interventions that have been clinically described as beneficial, although not established empirically as treatments for major depressive disorder, include spiritual counseling, family therapy, and grief therapy. These interventions, as well as ancillary services such as vocational therapy, financial/money management or other tangible socioeconomic assistance, and contact with a relevant special interest national association/organization for connection to local support resources, should be considered as needed. Referral for these services should be made to therapist(s) experienced in the use of such interventions with depressed patients. Depending on local resources, referral may be made to an appropriate member of the primary care team, other VAMC or DoD services, or contract community providers.

There is some evidence that religious belief has a protective effect that counters depression in some patients.

EVIDENCE

Cognitive therapy: (Antonuccio, Danton, & DeNelsky 1995; Jacobson & Hollon 1996; Persons, Thase, & Crits-Christoph 1996; Rush et al., 1993; Scogin & McElreath 1994; Teri, Gallagher-Thompson, & Thompson 1994; Zeiss & Breckenridge, 1998) QE = I, SR = A

Behavioral therapy: (Antonuccio, Danton, & DeNelsky 1995; Jacobson & Hollon 1996; Persons, Thase, & Crits-Christoph 1996; Rush et al. 1993; Scogin & McElreath 1994; Teri, Curtis, Gallagher-Thompson, & Thompson 1994; Zeiss & Breckenridge, 1998) QE = I, SR = A

Interpersonal therapy: (Rush, et al., 1993; Niederehe, 1994). QE = I, SR = A.

Brief psychodynamic therapy: (Persons, Thase, & Crits-Christoph 1996; Rush et al., 1993; Scogin & McElreath 1994; Niederehe 1994) QE = II-1, SR = C

Marital therapy: (Prince & Jacobson, 1995; Rush, et al., 1993) QE = II-1, SR = C

Religious belief: QE = (Koenig et al., 1992; Pressman, et al., 1990) II-2, SR = B

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Appendix 5. Pharmacological Therapy

A. Phases of Treatment

Psychopharmacological treatment of depression has three phases: acute, continuation, and maintenance. The acute phase of treatment begins when the patient is diagnosed with major depressive disorder and an antidepressant is started and ends once there is a complete remission of depressive symptoms. Typically the acute phase of treatment lasts up to four months. The continuation phase of therapy begins once the patient has complete remission of depressive symptoms and lasts up to nine months. A decision must then be made regarding the need for extended maintenance treatment with medication. In general, patients who have had three or more episodes of major depression and patients who have had two episodes of major depression and one or more additional risk factors (strong family history of mood disorders, history of recurrence after discontinuation of efficacious medication, one or more suicide attempts, onset of first episode before age 20, two or more episodes of major depression in the last year, or concurrent dysthymia) should remain on a maintenance antidepressant medication for one or more years. More information on maintenance and continuation treatment may be found in the annotation for box W, Module B.

Generall**y** patients continue on the same antidepressant throughout the continuation and maintenance phases that was efficacious during acute phase therapy. To sustain remission during the continuation phase of therapy, it is important to encourage patients to remain on the maximal dose of antidepressant required to achieve remission during acute phase treatment.

B. Pharmacological Treatment Steps during the Acute Phase of Treatment

1. Is medication the appropriate treatment?

   Generally a patient should receive antidepressant medications if he or she has:

   - Moderate or severe symptoms of depression
   - Significant impairment in social or occupational functioning
   - Suicide ideation.

   Strong indications for antidepressant medication include:

   - Past history of positive response to medications
   - Negative response to psychotherapeutic interventions
   - Recurrent depressive episodes
   - Family history of depression.

   Other considerations include patients who are pregnant or breastfeeding and the presence of various diagnostic subtypes that may be more likely to respond to psychotherapeutic intervention (see Modules A and B).

   Patient preference should be respected when considering antidepressant treatment. Educational materials may be helpful for persuading ambivalent patients that antidepressant medications can be beneficial.

2. Choice of antidepressant medication

   Many effective agents are available for major depressive disorder. Although no one antidepressant medication is clearly more effective than another or results in remission for all patients, there are patient factors and drug side effect profiles that may favor one class of antidepressants over another for a given individual. The clinician should determine which

medications have been efficacious in the past and at what dosages. Generally medications with favorable side effect profiles should be used. However, previously efficacious medications, regardless of class, should be considered as a first choice if medications with favorable side effect profiles have not been efficacious in the past.

The choice of medication is based on side effect profile (See Table 1: Side Effect Profiles of Antidepressants), history of previous response, family history of response, type of depression, co-morbid medical conditions, concurrently prescribed medications, and cost.

SSRIs or venlafaxine are generally considered first line antidepressants for most patients in the primary care setting because of their ease of administration and low toxicity in overdose relative to other antidepressants. Although differences in drug characteristics may influence the selection of a specific SSRI for a given patient, there is insufficient evidence to prefer any one SSRI for all patients on the basis of efficacy or side effect profile.

General considerations concerning antidepressant therapy include:

- Rates of response to antidepressants are reported as high as 60 to 70 percent. However, the rate of complete remission may be substantially lower.
- Doses should be titrated in order to improve the chance of tolerating the drug. In general, doses used for the elderly should be lower than in healthy adults.
- Some depressive target symptoms (e.g., anxiety, insomnia, decreased appetite, decreased energy, libido) may respond to therapy sooner than the depressed mood resolves.
- Patient and family education about the course and nature of depressive illness, treatment and potential side effects, time course to see symptomatic improvement, and importance of treatment compliance helps to improve treatment adherence and the likelihood of success.
- Antidepressants may precipitate manic episodes in bipolar patients, and may activate latent psychosis in other susceptible patients. Close monitoring for any such symptoms may be necessary.

3. Follow-up during the acute phase of treatment

   Follow-up is extremely important during the first month of treatment, as it has been shown that up to 50 percent of patients will stop their antidepressant in the first month. The various reasons for non-compliance include side effects (especially unexpected ones), lack of response, and illness-related parameters such as memory impairment, motivation and apathy, social and cultural influences, and patient perception of the importance and appropriateness of drug treatment.

   Patients should be seen to monitor clinical status and side effects at one week (optimally) and no later than 2 weeks after antidepressant is started. Patients may be contacted by telephone if necessary. Compliance and patient outcomes are improved if the physician educates the patient about side effects and is available to take telephone calls. If there is a response to a particular antidepressant after two weeks of treatment, the patient should be re-assessed at four weeks and at six weeks after initiation of antidepressant treatment. Thereafter, the patient should ideally be monitored monthly throughout the acute phase of treatment.

4. Changing antidepressant medications if no response is noted

   Common causes of nonresponse to antidepressant medication treatment include: insufficient dose, inadequate trial length, incorrect diagnosis, medical illness, interactions with concomitant medications, or poor compliance with treatment.

   a. Nonresponse through the second week of therapy, at least with SSRIs, appears predictive of subsequent nonresponse. However, antidepressant medications should be changed only after it

has been established that patients are not responsive after four to six weeks of treatment at therapeutic serum concentrations, at therapeutic doses, or at the maximum dose the patient tolerates if therapeutic dose precipitates bothersome side effects.

b. The second medication trial should use a different class of antidepressant. In patients with a partial response to a second medication, augmentation with either lithium or liothyronine may be tried. Combination therapies may be tried, but are not suggested until efforts to institute single drug therapy have failed. In rare instances experienced psychopharmacologists may combine an MAOI with a non-MAOI antidepressant.

c. Abrupt discontinuation of any antidepressant may result in an abstinence or rebound syndrome or a return of original depressive symptoms. Discontinuation should be performed via a slow taper that is guided by the elimination half-life of the parent compound and its metabolites. Depressive symptoms should be monitored closely.

Table 1. Side Effect Profiles of Antidepressants

	Adverse Effects				
0 = none **+ = slight** **++ = moderate** **+++ = high** **++++ = very high** **+++++ = highest**	**Anti-Cholinergic Effects**	**Sedation**	**Orthostatic Hypotension**	**Cardiac Conduction Abnormalities**	**Weight Gain**
SSRIs					
Citalopram (Celexa®)	0/+	0/+	0/+	-	-
Fluoxetine (Prozac®)	0/+	0/+	0/+	-	-
Paroxetine (Paxil®)	0/+	0/+	0	-	+
Sertraline (Zoloft®)	0/+	0/+	0	-	-
TCAs					
Amitriptyline (Elavil,® generics)	++++	++++	+++	++++	++++
Desipramine (Norpramin,® generics)	+	+	+	+++	+
Doxepin (Sinequan,® generics)	+++	++++	++	++	++++
Imipramine (Tofranil,® generics)	+++	+++	+++	++++	++++
Nortriptyline (Pamelor,® Aventyl,® generics)	++	++	+	+++	+
Protriptyline (Vivactil,® generics)	+++	+	++	++++	-
Trimipramine (Surmontil®)	++++	+++	+++	++++	++++
Dual Mechanism					
Bupropion (Wellbutrin®)	0/+	0/+	0/+	+	-
Mirtazepine (Remeron®)	+	++++	+++	-	++++
Nefazodone (Serzone®)	0/+	++	+	+	+
Venlafaxine (Effexor®)	0/+	+	0	+	-
MAOIs					
Isocarboxazid (Marplan®)					
Phenelzine (Nardil®)	+	+	++(1)	+	+++
Tranylcypromine (Parnate®)	+	+	+(1)	+	++
Other Antidepressants					
Amoxapine (Asendin,® generics)	+++	++	+	++	++
Maprotiline (Ludiomil,® generics)	++	++	+	++	++
Trazodone (Desyrel,® generics)	0/+ (2	++++	++	+	++

(1) Orthostatic symptoms often appear several days to weeks after treatment is started with MAOIs.
(2) Anticholinergic side effects (e.g., dry mouth) may be due to a system other than an anticholinergic mechanism.

Table 1 is adapted from PBM-MAP, August 1997; Hebel SK ed. *Antidepressants*. In: Olin Br. (Ed). *Drug Facts and Comparisons.* St. Louis, MO: Facts and Comparisons Inc., 1996; 262k; and Scott MA, Shelton P, Gattis W. Therapeutic options for treating major depression, and the role of venlafaxine. *Pharmacotherapy* 1996;16(3):352-65

C. Specific Antidepressant Medications

For this appendix antidepressants available in the U.S. are classified as SSRIs (citalopram, fluoxetine, paroxetine, sertraline); TCAs (amitriptyline, doxepin, imipramine, nortriptyline, protriptyline, trimipramine); dual mechanism antidepressants (bupropion, mirtazepine, nefazodone, venlafaxine); monoamine oxidase inhibitors (MAOIs; phenelzine, tranylcypromine); and other antidepressants (amoxapine, maprotiline, trazodone). The following entries for each drug class describe its mechanism of action, side effect profile, drug interactions, dosing, and therapeutic blood levels (if applicable).

1. Selective Serotonin Reuptake Inhibitors (SSRIs) (Refer to Tables 2, 3, and 4)
   The mechanism of action of the SSRIs is selective inhibition of serotonin (5HT) uptake, with limited affinity for receptors associated with other neurotransmitters. The efficacy of SSRIs is similar to that of TCAs, but the SSRIs are generally accepted to have a more favorable adverse effect profile. SSRIs have a wide therapeutic index, are significantly less lethal than other antidepressants when taken in overdose, and are preferred for most patients at significant suicide risk. Due to their low toxicity and ease of administration, SSRIs are generally considered first line antidepressants in the primary care setting.

   There are presently four FDA approved agents for MDD: citalopram, fluoxetine, paroxetine and sertraline. Fluvoxamine is approved only for the treatment of obsessive-compulsive disorder (OCD) and is not discussed in these guidelines.

   The elimination half-life and incidence of side effects varies among SSRIs. The most common side effects include: nausea, insomnia, sedation, headache, dizziness, fatigue, sexual dysfunction, anorexia, sweating, dry mouth, constipation (especially with paroxetine), tremor, nervousness, anxiety (especially with fluoxetine), and diarrhea & loose stools (especially with sertraline). Citalopram, which was recently introduced to the United States, appears to have similar side effects to the other three agents. In many cases side effects can be managed with lower doses and/or concomitant medication. Also, tolerance can develop to some, but not all side effects.

   The combination of SSRIs and other antidepressant medications, particularly those with a primarily serotonergic mechanism, should be used cautiously due to rare cases of serotonin syndrome. Mental status changes, myoclonus, hyperreflexia, diaphoresis, shivering, diarrhea, and incoordination characterize serotonin syndrome.

   SSRIs may precipitate or exacerbate anxiety and sleep disturbance in some patients. Anxiety may be minimized by introducing the agent at a low dose and titrating to a therapeutic dose. Insomnia may also be effectively treated by the addition of diphenhydramine or trazodone at bedtime. There are case reports of the precipitation of serotonin syndrome when trazodone and paroxetine are co-prescribed.

   Vivid dreams, nightmares, tremors, dizziness, nausea, and occasionally even disorientation characterize the abstinence syndrome associated with abrupt discontinuation of SSRIs. The dose should be gradually tapered, especially in SSRIs with shorter elimination half-lives and/or no active metabolite.

Table 2. Dosing Table For SSRIs

AGENT	DOSE[1]	ELDERLY DOSE	COMMENTS
Citalopram	**initial:** 20 mg/d **range:** 20 – 40 mg/d **max:** 60 mg/d	**initial:** 20 mg/d **range:** **max:** 40 mg/d if indicated	• No dose adjustment necessary for mild to moderate renal impairment • For patients with hepatic impairment and in the elderly use 40 mg/d only if patient does not respond to 20 mg/d
Fluoxetine	**initial:** 20 mg/d **range:** 20 – 40 mg/d **max:** 80 mg/d	**initial:** 10 mg/d	• Administer doses > 20 mg on a once (am) or twice (am, noon) daily schedule
Paroxetine	**initial:** 20 mg/d **range:** 20 – 50 mg/d **max:** 50 mg/d	**initial:** 10 mg/d **range:** **max:** 40 mg/d if indicated	• Use elderly dosing for debilitated patients • Dose usually in the morning • Titrate in increments of 10 mg/d in 1 week intervals
Sertraline	**initial:** 50 mg/d **range:** 50 – 200 mg/d **max:** 200 mg/d	**initial:** 25 mg q am **range:** 75 – 100 mg/d **max:** 200 mg/d	• In elderly patients, titrate in increments of 25 mg/d every 2-3 days • Administer doses in the morning or evening

(1) range refers to usual therapeutic range.

Table 2: Dosing Table for SSRIs adapted from: Hebel SK ed. Antidepressants. In: Olin Br. (Ed.) *Drug Facts and Comparisons*, St. Louis, Missouri: Facts and Comparisons Inc., 1996 and Semla TP, Beizer JL, Higbee MD. *Geriatric Dosage Handbook. 2nd edition 1995-1996.* APhA: Lexi-comp Inc., 1995;301-302, 535-536, 643-44.

Table 3. SSRI Drug Interactions [1-2]

PRECIPITANT DRUG	OBJECT DRUG	EFFECT	DESCRIPTION
Azole antifungals	***Citalopram***	increase	May increase plasma levels of citalopram
Fluoxetine Sertraline	**Benzodiazepines**	increase	Clearance of BZDs is decreased. BZD levels and drug effects may increase
Fluoxetine	Buspirone	decrease & increase	Effects of buspirone may be decreased. Paradoxical worsening of OCD has occurred although combination has been used to potentiate antidepressant action of fluoxetine
Fluoxetine	*Carbamazepine*	increase	Serum CBZ levels may be increased which may result in toxicity
Carbamazepine	Citalopram	decrease	Carbamazepine may increase the clearance of citalopram
Cimetidine	Paroxetine Citalopram	increase	Cimetidine increases concentration of paroxetine and citalopram
Macrolides *Clarithromycin* Erythromycin	Fluoxetine Citalopram	increase	Clarithromycin added to fluoxetine has been reported to result in delirium. Erythromycin may increase citalopram plasma levels. Use caution when using SSRIs with macrolide antibiotics
Fluoxetine Sertraline	Clozapine	increase	Elevated clozapine levels have occurred; closely monitor
Cyproheptadine	Fluoxetine Paroxetine	decrease	Effect of fluoxetine may be decreased or reversed; combination has been used to treat fluoxetine induced sexual dysfunction
Dextromethorphan	Fluoxetine	increase	Hallucinations have occurred during concurrent use
Fluoxetine Sertraline	Phenytoin	increase	Fluoxetine and sertraline may increase hydantoin levels
Omeprazole	Citalopram	increase	Omeprazole inhibits CYP2C19, therefore possibly reducing the clearance of citalopram
Fluoxetine All SSRIs	Haloperidol *Lithium*	increase increase	May increase serum concentrations; may impair memory and attention Although a case report suggests that lithium levels may be increased by fluoxetine, neurotoxicity is probably caused by a pharmacodynamic interaction. Lithium is often used to potentiate antidepressant response to SSRIs
Fluoxetine Sertraline	Loratadine	increase	Plasma levels of the non-sedating antihistamine loratadine may be increased; effects on cardiac conduction are unknown. Terfenadine and astemizole have been withdrawn from the market
MAOIs	*All SSRIs*	increase	Serious sometimes fatal, reactions have occurred (e.g., rigidity, hyperthermia, myoclonus, autonomic instability, rapid vital sign fluctuations) as well as mental status changes (e.g., agitation, delirium, coma). Refer to Table 11 for drug interaction and washout period
Citalopram	Metoprolol	increase	No clinically significant effects on blood pressure or heart rate. May lose cardioselectivity of metoprolol
Paroxetine	*Phenytoin*	decrease	Paroxetine decreases phenytoin levels

PRECIPITANT DRUG	OBJECT DRUG	EFFECT	DESCRIPTION
Phenytoin *L-tryptophan*	Paroxetine SSRIs	decrease increase	Phenytoin decreases half-life of paroxetine Concurrent use may result in CNS toxicity (e.g., headache; dizziness; agitation; aggressiveness; worsening OCD) and peripheral toxicity (e.g., nausea and vomiting)
ALL SSRIs Fluoxetine	***TCAs*** *Valproate*	increase increase	Plasma TCA levels may be increased which may result in toxicity. The combination may potentiate antidepressant response for SSRIs due to a pharmacodynamic interaction, but drug combination may warrant a psychiatry consult Serum valproate levels may be increased which may result in toxicity
All SSRIs	*Warfarin*	increase	A pharmacodynamic interaction (increased bleeding diathesis in the face of unaltered PT) may occur with paroxetine. Concurrent use of sertraline and warfarin result in a relatively small increase in PT and delayed normalization of PT. Fluoxetine alone may increase bleeding time

(1) SSRIs = selective serotonin reuptake inhibitors; BZDs = benzodiazepines; OCD= obsessive compulsive disorder; CBZ = carbamazepine; PT= prothrombin time; MAOIs = monoamine oxidase inhibitors; **Bold** = serious drug interaction; *Italics* = moderate; Regular = minor
(2) Does not include drug interactions with fluvoxamine

Table 3: SSRI Drug Interactions: adapted from PBM-MAP, August 1997; Hebel SK ed. Antidepressants. In: Olin Br. (Ed.). Drug Facts and Comparisons**.** St. Louis, Missouri: Facts and Comparisons Inc.,1999; Drug Interactions & Updates. Hansten PD, Horn JR eds.; 1996: 480, 490, 491, 721, 725, 726, 729, 744, 815, 818, 857, 858, 883; Drug Interaction Facts by Facts and Comparisons, July 1996: 94a, 344a, 382, 622b-622c, 623, 742

2. Tricyclic Antidepressants (TCAs) (Refer to Tables 4, 5, and 6)

TCAs inhibit reuptake of norepinephrine and/or serotonin at the presynaptic neuron, but are predominately adrenergic reuptake inhibitors. TCAs appear to be equally efficacious but have major differences in their side-effect profile. Contraindications to TCAs include:

- Hypersensitivity to any tricyclic drug (cross-reactivity may occur within a chemically related group such as TCAs)
- Acute recovery phase following myocardial infarction (MI).

TCAs should be avoided for patients with the following clinical conditions unless consultation from an appropriate specialist guides therapy:

- Angle-closure glaucoma or increased intraocular pressure
- History of urinary retention or uretheral spasm
- Cardiovascular disease (CVD) including coronary heart disease (CHD) with ECG abnormalities, conduction abnormalities including bundle branch block, paroxysmal tachycardia and/or orthostatic hypotension
- Patients at risk for suicide
- Patients with cognitive impairment (anticholinergic effects may slow cognition or cause delirium)
- Concomitant use of TCAs and MAOIs.

The most common side effects of the TCAs include anticholinergic effects (dry mouth, blurred vision, increased intraocular pressure, constipation, urinary retention); cardiovascular (orthostatic hypotension, syncope, tachycardia, arrhythmias), CNS (sedation, confusion); weight gain (especially with amitriptyline and doxepin); and sexual dysfunction. TCAs can also decrease seizure threshold.

TCAs may be considered first line agents for certain patients. In general, the secondary amine TCAs (i.e., nortriptyline, desipramine) have equal efficacy and fewer side effects than the parent tertiary amines (i.e., amitriptyline, imipramine).

TCAs should be used cautiously in the elderly. If the use of TCAs is necessary, nortriptyline and desipramine should be considered first. Due to increased side effects (e.g., CNS, anticholinergic, cardiovascular) associated with amitriptyline, imipramine and doxepin, the primary care physician should avoid the use of these agents in elderly patients.

With the exception of clomipramine, the available TCAs are listed in Table 1 and Table 5. Clomipramine is approved only for the treatment of obsessive-compulsive disorder (OCD) and is not discussed in these guidelines. Patients with obsessive-compulsive disorder should be referred to a psychiatrist.

Therapeutic response and dosing with a TCA may vary among patients due to both pharmacokinetic (e.g., enzyme induction by smoking), and pharmacodynamic (e.g., increased sensitivity in the elderly) differences.

The clinical value of tricyclic plasma concentrations remains controversial. Of the various TCAs, plasma levels for desipramine, imipramine, and nortriptyline are best established. Although amitriptyline has been extensively studied, no clear relationship between response and plasma level has emerged. The use of therapeutic blood levels can be of value in particular clinical instances such as in patients who do not respond to or comply with therapy, patients on combination therapy, elderly patients, or patients with suspected drug toxicity. (See Table 6: Therapeutic Blood Monitoring of TCAs)

Table 4. Dosing Table for TCAs [a-c]

AGENT	DOSE		ELDERLY DOSE		COMMENTS
Amitriptyline	initial range max	50-100 mg hs 50-200 mg/day 300 mg/daye	Not recommended for use in the elderly		
Desipramine	range	75-200 mg/day titrate as tolerated (or per levels)	initial range	lower doses 25-150 mg/day	Serum levels are associated with efficacy Therapeutic level 125 - 300 ng/mL
Doxepin	initial range max	75 mg/day 75-150 mg/day 300 mg/day	Not recommended for use in the elderly		Higher doses, (up to 300 mg/day) are generally for more severe anxiety or depression Antianxiety activity is seen rapidly
Imipramine	range	75-200 mg/day titrate as tolerated (or per levels)	Not recommended for use in the elderly		Serum levels are associated with efficacy Therapeutic level 200-350 ng/mL parent and metabolite (desipramine)

Table 4. Dosing Table for TCAs [a-c]

AGENT	DOSE		ELDERLY DOSE		COMMENTS
Nortriptyline	initial range	25 mg tid 75-200 mg/day titrate as tolerated (or per levels)	initial range	lower doses 30-50 mg/day in divided doses	Serum levels are associated with efficacy Therapeutic level 50 - 150 ng/mL
Protriptyline	initial range max	15-40 mg/day in 3-4 divided doses titrate as tolerated 60 mg/day	initial range	5 mg tid gradually	FDA approved for obstructive sleep apnea Monitor cardiovascular system closely at 20 mg/d
Trimipramine	initial range max	75 mg/day in divided doses 50-150 mg/day 200 mg/day	initial range max	50 mg/day? decrease gradually 100 mg/day	

[a] Adapted from: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1996: 262j-263;

[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. APhA: Lexi-comp Inc., 1995.

[c] TCAs = tricyclic antidepressants

[d] range refers to usual therapeutic range

[e] max dose of 300 mg/day should be reserved for severely ill patients

Table 5. Therapeutic Drug Monitoring of TCA [sa-c]

- Therapeutic plasma levels for desipramine, imipramine, and nortriptyline can be used to guide treatment for patients that do not respond to or comply with therapy, for individuals on combination therapy, in elderly patients, or when ruling out toxicity
- Therapeutic plasma levels should be drawn after 1 week of therapy, when the majority of patients will be in steady state
- Draw blood sample 10-12 hours after the last dose to ensure that absorption and distribution of the drug are complete
- Nortriptyline plasma levels demonstrate a curvilinear concentration-response relationship and therefore the dose should be adjusted to obtain levels within a therapeutic range window (50-175 ng/mL); levels above the upper limit are associated with a declining (but not necessarily toxic) response
- Imipramine (plus metabolite desipramine) plasma levels demonstrate a linear concentration-response relationship and therefore the upper limit is a function of toxicity rather than reduced efficacy (200-350 ng/mL); raising serum levels above threshold may convert nonresponders into responders; monitor for signs and symptoms of toxicity
- The relationship between response and plasma desipramine levels is less clear; in general a minimum levels of 125 ng/ mL should be obtained if tolerated; levels over 300 ng/mL may increase the risk of toxicity

[a] DeVane LC, Jarecke RC. (1992). Chapter 33: Cyclic Antidepressants. pharmacokinetics, Principles of therapeutic drug monitoring, 3rd ed., Evans WE, Schentag JJ, Jusko WJ, eds.Vancouver, WA: Applied Therapeutics, Inc. 1-47.

[b] Preskorn SH, Burke MJ, Fast GA. Therapeutic Drug Monitoring: Principals and Practice. (1993). Psychiatric Clinics of North America. 16(3):611-645.

[c] Charney D, Miller H, Licinio J, Salomon R. (1995). Chapter 28: Treatment of depression. From: Schatzberg A, Nemeroff C, ed. Textbook of psychopharmacology. American psychiatric press; 575-601.

Table 6. TCA Drug Interactions [(1)]

PRECIPITANT DRUG	DRUG	OBJECT EFFECT	DESCRIPTION
TCAs	Anticholinergics	Increase	Combined use may result in excessive anticholinergic effect
Barbiturates	TCAs	Decrease	May decrease TCA serum levels; additive central and respiratory effects
Bupropion	TCAs	Increase	May increase TCA serum levels
Carbamazepine TCAs	TCAs Carbamazepine	Decrease Increase	May require larger TCA doses (especially imipramine). Monitor for altered TCA response if CBZ therapy is started or discontinued. CBZ levels may be increased.
Cimetidine	TCAs	Increase	May increase TCA serum levels, with increased anticholinergic symptoms. May require lower TCA doses
TCAs	**Clonidine**	Increase	Adding a TCA to clonidine may antagonize the hypotensive effect of clonidine. Dangerous elevations in BP and hypertensive crises have occurred in patients receiving concurrent TCAs. Use caution or avoid coadministration.
Ethanol	TCAs	Increase	Combined use may increase impairment in psychomotor skills, especially during the 1st week of treatment.
TCAs	Guanethidine	decrease	May antagonize antihypertensive effects; avoid combination if possible
TCAs	Levodopa	Decrease	May delay absorption and decrease bioavailability of levodopa; hypertensive episodes have occurred with combination
MAOIs	*TCAs*	Increase	Serious sometimes fatal, reactions have occurred (e.g., rigidity, hyperthermia, myoclonus, autonomic instability, rapid vital sign fluctuations) as well as mental status changes (e.g., agitation, delirium, coma). Refer to Appendix 11 for drug interaction and washout period
Neuroleptics[(2)] Phenothiazines	TCAs	Increase	In combination, monitor for increased toxicity and altered therapeutic response

Table 6. TCA Drug Interactions (continued)

PRECIPITANT DRUG	DRUG	DRUG	DESCRIPTION
TCAs	Quinolones **Gatifloxacin** **Grepafloxacin** **Moxifloxacin** **Sparfloxacin**	Increase	May increase risk of life-threatening cardiac arrhythmias, including torsades de pointes; grepafloxacin was withdrawn from the market as of October 1999. Drug interactions with the recently approved quinolones moxifloxacin and gatifloxacin are unknown, but the drugs are known to cause QT prolongation in some patients
Rifamycins	TCAs	decrease	TCA levels may be decreased
All SSRIs	*TCAs*	increase	May increase TCA serum level, resulting in toxicity. Use combination cautiously. Start with lower TCAs doses; fluoxetine toxic effects may persist for several weeks after the discontinuation of fluoxetine
Smoking	TCAs	increase	May increase metabolic biotransformation of the TCAs
Sympathomimetics	TCAs	Increase & decrease	Pressor response to direct-acting sympathomimetics is potentiated; dysrhythmias have occurred. Pressor response to indirect-acting sympathomimetics is decreased.
Valproic acid	TCAs	increase	May increase plasma concentrations and side effects of TCAs

(1) TCAs = tricyclic antidepressants; CBZ = carbamazepine; BP = blood pressure; MAOIs = monoamine oxidase inhibitors; SSRIs = selective serotonin reuptake inhibitors; **Bold** = serious drug interaction; *Italics* = moderate; Regular = minor
(2) Neuroleptics include butaperazine, chlorpromazine, fluphenazine decanoate, trifluoperazine

Adapted from: PBM-MAP, August 1997; Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1999: 893; Drug Interactions & Updates. Hansten PD, Horn JR, eds.; 1996:191, 335, 473-74, 476, 479-81, 487-88, 530, 796; Drug Interaction Facts by Facts and Comparisons, July 1996: 179, 742, 745, 748-49; Final Draft Package Insert for Moxifloxacin (Avelox®). Bayer Corporation: West Haven, Connecticut. December 1999; Prescribing Information for Gatifloxacin (Tequin®). Bristol-Myers Squibb: Princeton, New Jersey. December 1999.

3. Dual mechanism antidepressants (Refer to Tables 7 & 8)

Bupropion – Bupropion is a weak reuptake blocker of 5HT and norepinephrine compared with TCAs, and has some effect of dopamine reuptake. Like most antidepressants, the neurochemical basis of its antidepressant mechanism is not known. Unlike the TCAs, the side effects of bupropion do not include anticholinergic effects. In addition, bupropion has little cardiovascular effects, sedation, and sexual dysfunction potential. Bupropion is contraindicated in patients with seizure disorders or diagnoses of bulimia or anorexia nervosa due to increased risk of seizures. The reported incidence of seizures is lower with the new sustained release preparation. Due to a low toxicity profile, it may be considered a good alternative for elderly patients with no history of seizure disorder.

The daily dose of bupropion should not exceed 450 mg/day for immediate release and 400 mg/day for sustained release. A single daily dose should also not exceed 150 mg for immediate release or 200 mg as a single dose due to the potential for dose-related seizures.

Nefazodone – Nefazodone is structurally related to trazodone. Nefazodone blocks $5HT_2$ receptors postsynaptically and inhibits 5HT reuptake presynaptically. It also blocks norepinephrine reuptake presynaptically and demonstrates antagonism of a $_1$-adrenergic receptors. Side effects are dose related. The most common side effects associated with nefazodone include: somnolence, dizziness, dry mouth, nausea, headache, impaired vision, and constipation.

Nefazodone is an inhibitor of cytochrome P450 III A4 isozyme. Caution should be used when prescribing with drugs that inhibit and/or are metabolized by cytochrome P450 isozymes due to potential interactions. Prior to initiating nefazodone, the washout period after discontinuing an SSRIs should generally be 4 to 5 days for paroxetine and sertraline, and several weeks for fluoxetine. If the clinical situation dictates, a shorter washout period may be used. In these cases, the starting dose of nefazodone should be modified, (i.e. 50 mg daily) and then titrated to response as tolerated.

Venlafaxine -- Venlafaxine is similar to the TCAs in that it inhibits both NE and 5HT uptake; it has little effect on adrenergic, cholinergic or histaminergic receptors. The most common side effects associated with venlafaxine include: nausea, somnolence, insomnia, dizziness, abnormal ejaculation, headache, nervousness, dry mouth, anxiety, asthenia, and sweating.

Venlafaxine treatment has been associated with sustained hypertension. The incidence of increased blood pressure was highest (13 percent) with doses > 300 mg/day. Patients on venlafaxine for > 1 week should have their dose tapered prior to discontinuation to avoid withdrawal symptoms. If a patient has been on this agent [3] 6 weeks, slowly discontinue venlafaxine over 2 weeks.

Venlafaxine is partly metabolized by cytochrome P450 II D6 and, therefore, the potential exists for enzyme inhibitors to reduce the metabolism of the drug when taken concomitantly.

Mirtazapine -- Mirtazapine is a tetracyclic compound unrelated to tricyclic antidepressants. It works by inhibiting presynaptic a 2-adrenoreceptors, which results in an increase in both noadrenergic and serotonergic neurotransmission. It is also a potent antagonist of 5HT2 and 5HT3 receptors. Mirtazepine may also possess anxiolytic activity.

Adverse effects include: drowsiness, somnolence, fatigue, increased appetite, dry mouth, headache, constipation and weight gain; agranulocytosis has been reported (rare). Few drug interactions have been reported. Mirtazapine may have additive effects on cognitive and motor performance when given with alcohol and diazepam, and should be used cautiously when combining with other central nervous system depressants. (Refer to Table 8: Dual Mechanism Antidepressant Drug Interactions)

Mirtazapine should be reserved for patients who are non-responsive to other antidepressants due to potential troubling adverse effects (e.g., sedation, weight gain). The possibility of agranulocytosis or neutropenia should also be considered.

Tables 7. Dosing Table for Dual Mechanism Antidepressants[a,b]

AGENT	DOSEc		ELDERLY DOSE		COMMENTS
Bupropion (immediate release/ sustained release)	initial range max	75-100 mg bid/ 150 mg qd in am increase per response to 300 mg/d in 3 divided doses for immediate release or 150 mg bid for sustained release 450 mg/d immediate release or 400mg/d sustained release	initial range	50 - 100 mg/d immediate release increase as tolerated, some patients may respond to 150 mg/d divided doses	Do not exceed dose increase of 100 mg/d in a 3 day period Immediate release doses of 300 mg/d should be given in 3 divided doses Immediate release doses of 450 mg/d should be given in 3-4 divided doses Use cautiously in patients with renal or hepatic impairment Adequate therapeutic response may not be evident for 4 weeks
Nefazodone	initial range	200 mg/d in 2 divided doses 300 - 600 mg/d in 2 divided doses	initial range	100 mg/d in 2 divided doses increase to 100 mg bid; titrate slowly	Titrate 100 - 200 mg/d in 2 divided doses at 1or more week after initiation Lower initial doses reduce adverse effects
Venlafaxine	initial range max	75 mg/d in 2 - 3 divided doses 150 mg/d in 2 - 3 divided doses 375 mg/d in 3 divided doses	initial	may start on 25 mg bid	Administer with food Titrate in increments of 75 mg/d at 4 or more day intervals For severely depressed, may increase dose to 375 mg/d in 3 divided doses No dose adjustment is necessary for the elderly, but use care individualizing doses In patients with hepatic impairment decrease dose 50% In patients with renal impairment (GFR 10 - 70 mL/min):decrease dose 25% In patients on dialysis decrease dose 50%
Mirtazapine	initial range max	15 mg hs 15-45 mg 45 mg	Elderly patients may require lower doses		Increase dose at intervals of no less than 1-2 weeks

[a] Adapted from Antidepressants. In: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,1996
[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. APhA: Lexi-comp Inc., 1995; 733-734.
[c] range refers to usual therapeutic range

Table 8. Dual Mechanism Antidepressant Drug Interactions [a-d]

PRECIPITANT DRUG	OBJECT DRUG	EFFECT	DESCRIPTION
Carbamazepine	Bupropion	decrease	Although this interaction is not well documented, it would be prudent to monitor for altered bupropion response if CBZ is initiated, discontinued, or changed in dosage
Bupropion	Levodopa	increase	A higher incidence of adverse experiences occurs with concurrent use of these agents. Use small initial doses and small gradual dose increments of bupropion
Nefazodone	Benzodiazepines	increase	Substantial and clinically important increases in plasma concentrations of alprazolam and triazolam have occurred. decrease initial dose of alprazolam by 50%, decrease initial dose of triazolam by 75% when coadministered with nefazodone. Lorazepam was not affected
Nefazodone	Haloperidol	increase	Haloperidol clearance was decreased by 35% with no significant increase in peak plasma concentrations or time to peak
MAOIs	Bupropion Nefazodone Venlafaxine Mirtazapine	increase	
Nefazodone	Astemizole Cisapride Terfenadine	increase	Plasma levels of astemizole, cisapride, and terfenadine may be increased, resulting in QT prolongation or torsades de pointes, sometimes fatal. Do not use concurrently. Plasma levels of loratadine may also be increase although the cardiac conduction effects are unknown
Nefazodone	Digoxin	increase	Cmax, Cmin and AUC of digoxin were increased by 29%, 27%, and 15% respectively in one study. Monitor digoxin levels

[a] Adapted from Antidepressants. In: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,1996

[b] Drug Interaction Facts by Facts and Comparisons, July 1996: 622b.

[c] MAOIs = monoamine oxidase inhibitors

d = object drug increased; =object drug decreased; Bold = serious drug interaction; Italics = moderate; Regular = minor

4. Monoamine oxidase inhibitors (MAOIs) (Refer to Tables 9, 10, and 11)

MAOIs inhibit the enzyme monoamine oxidase, preventing the breakdown of NE, 5HT, and dopamine. MAOIs are useful for atypical depression (DSM-IV depression with atypical features). Criteria for atypical depression include reactive mood disturbance, prominent anxiety, histrionic features, phobic features, marked fatigue, reversed neurovegetative features, insomnia combined with hypersomnolence, adequate premorbid personality, psychosomatic complaints and/or hypochondriasis.

MAOIs should not be considered first-line for treatment of major depression due to adverse effects and potentially severe drug-drug and drug-food interactions. Fatal hypertensive crisis has occurred with concomitant use of tryptophan or tyramine. These crises usually occur within several hours after ingestion of a contraindicated substance.

Serotonin syndrome has also occurred with combination tryptophan or tyramine and MAOI use, and is characterized by mental status changes (myoclonus), hyperreflexia, tachycardia, fever, diaphoresis, shivering, diarrhea, and/or incoordination.

The most common side effects of the MAOIs include: orthostatic hypotension, restlessness, insomnia, sexual dysfunction, constipation, nausea, diarrhea, dry mouth, edema, anorexia, dizziness, weight gain (especially with phenelzine), headache, and vertigo.

Primary care providers should not prescribe MAOIs (phenelzine, tranylcypromine, isocarboxazid) unless they have a expertise/experience with these medications.

Table 9. Dosing Table for MAOIs[a,b]

AGENT	DOSE		COMMENTS
Phenelzine	initial range	15 mg tid (titrate to at least 60 mg/d) 15-60 mg/d	Reserve for treatment resistant patients Adequate therapeutic response may take at least 4 weeks Increase dosage up to 90 mg/d may be necessary to obtain sufficient MAO inhibition
Tranylcypromine	initial range max	10 mg bid 30 mg/d in divided doses 60 mg/d	Adequate therapeutic response may be as soon as 48 hours or may take as long as 3 weeks Titrate dose in increments of 10 mg/d at 1-3 week intervals

[a] Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,1996: 264s-264x.
[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. AphA: Lexi-comp Inc., 1995; 553-54, 707-8.

Table 10. MAOI Drug Interaction [a-e]

PRECIPITANT DRUG	OBJECT DRUG	EFFECT	DESCRIPTION
MAOIs	Antidepressants	increase	Refer to Table 4 for drug interaction and washout period
MAOIs	Dextromethorphan	increase	Hyperpyrexia, hypotension and death have been associated with this combination
MAOIs	levodopa f	increase	Hypertensive reactions occur if levodopa is given to patients receiving MAOIs
Lithium	MAOIs	increase	Two fatal cases of malignant hyperpyrexia have been reported in patients taking these two agents; causation has not been clearly established. Avoid combination if possible; but if administered, observe closely for neuroleptic malignant syndrome
MAOIs	Meperidine	increase	Coadministration may result in agitation, seizures, diaphoresis and fever, progress to coma, apnea, and death. Adverse reactions are possible for weeks after MAOI withdrawal. Avoid this combination; administer other narcotic analgesics with caution
MAOIs	Oral hypoglycemics/ insulin	increase	Excessive hypoglycemia may occur when MAOIs are administered to patients with DM. Warn patients on oral hypoglycemics about possible hypoglycemic reactions when MAOI therapy is started. Monitor for deteriorating glycemic control when MAOI is stopped
MAOIs	Sympatho-mimetics	increase	The MAOIs’ potentiation of indirect or mixed-acting sympathomimetic substances (including anorexiants), may result in severe headache, HTN, and hyperpyrexia, possibly resulting in hypertensive crisis. Avoid coadministration. Direct-acting agents appear to interact minimally, if at all
MAOIs	L-tryptophan	increase	Coadministration may result in hyperthermia, hyperventilation, increased tone, hyperreflexia, confusion, disorientation, shivering, myoclonic jerks, agitation, amnesia, delirium, hypomanic signs, ataxia, ocular oscillations, Babinski signs, hyperkinesis, and disinhibition. Symptoms appear to resolve upon discontinuation of one or both drugs

[a] Adapted from Antidepressants. In: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,1996
[b] Drug Interactions & Updates. Hansten PD, Horn JR eds.; 1996: 383, 486, 491, 579-581, 585-586, 817, 840
[c] Drug Interaction Facts by Facts and Comparisons, July 1996: 244, 416, 446, 488, 680.
[d] MAOIs = monoamine oxidase inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; DM = diabetes mellitus; HTN = hypertension
e = object drug increased; =object drug decreased; Bold = serious drug interaction; Italics = moderate; Regular = minor
[f] drug interaction is not seen with combination levodopa/carbidopa

Table 11. Recommended Washout Periods with MAOIs

DRUG	WASHOUT PERIOD WITH AN MAOI
TCAs	Allow 14 days after stopping an MAOI and before starting medication
SSRIs	Allow 14 days after stopping an MAOI and before starting medication Allow 14 days after stopping sertraline and paroxetine and 5 weeks (due to long half-lives) after stopping fluoxetine before starting an MAOI; in rare cases fluoxetine (plus metabolite) may persist after 5 weeks
Dual Mechanism Bupropion Nefazodone Venlafaxine Mirtazapine	Allow 14 days after stopping an MAOI and before starting treatment with bupropion or mirtazapine Allow 14 days after stopping an MAOI and before starting nefazodone or venlafaxine Allow 7 days after stopping medication and before starting an MAOI
Other Antidepressants Amoxapine Maprotiline Trazodone	Allow 14 days after stopping an MAOI and before starting medication It is not known whether interactions will occur. Although, trazodone has been used safely in combination with MAOIs, caution is still warranted

Adapted from Antidepressants. In: Hebel Sk ed. Drug facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1996

TCAs = tricyclic antidepressants; SSRIs = selective serotonin reuptake inhibitors; MAOIs = monoamine oxidase inhibitors
Plasma levels may be a useful guide to reduce the possibility of a drug-drug interaction

5. Other antidepressants (Refer to Table 12)

Amoxapine **–** Amoxapine is structurally a TCA, but unlike the TCAs, it inhibits the reuptake of norepinephrine (NE), inhibits $5HT_2$ receptors and is an agonist of $5HT_{1A}$ receptors. Amoxapine and/or its metabolites also have postsynaptic dopamine receptor blocking action.

Amoxapine use should be reserved *to psychiatry* due to its potential to cause parkinsonian effects, tardive dyskinesia, and rarely neuroleptic malignant syndrome.

Maprotiline – Maprotiline is a selective inhibitor of NE reuptake and is similar to the TCAs. It should be reserved as a second-line agent due to the potential for seizures at both therapeutic doses and in overdose.

Trazodone – Trazodone weakly blocks 5HT and is a $5HT_2$ partial agonist. The neurochemical basis of its antidepressant mechanism is not fully understood. Unlike the TCAs, it is free from anticholinergic side effects, but still retains the potential to cause orthostasis and a high degree of sedation. Although rare, trazodone has been associated with priaprism.

Trazodone may enhance the CNS depressant response to ethanol, barbiturates, and other CNS depressants. There have been case reports of serotonin syndrome with co-administration of trazodone and paroxetine. It is unknown at this time if this is a class effect with all SSRIs.

Trazodone is not considered a first line agent for major depression, but rather is often used as a hypnotic in patients on SSRIs.

Table 12. Dosing Table for Other Antidepressants [a,b]

AGENT	DOSEc		ELDERLY DOSE		COMMENTS
Amoxapine	initial range max	50 mg bid or tid 200-300 mg/day 400-600 mg/day if no history of seizures	initial range	25 mg bid or tid; if tolerated 100-150 mg/day	For the adult dosage, may dose to 100 mg bid or tid in first week For the elderly, may increase to 50 mg bid or tid in first week For the elderly, the maintenance dose usually yields adequate control but some may need higher doses Classified as Category C, has been known to be teratogenic
Maprotiline	initial range max	75 mg/d as a single or divided doses 150 mg/d 225 mg/d	initial range	25 mg/d single or divided dose 50-75 mg/d	<small>Maintain initial dose for 2 weeks due to </SMALL>long half-life Titrate in 25mg increments Adequate therapeutic response may not be evident for 1 week, usually 2-3 wks
Trazodone	initial range max	150 mg/d increase as tolerated 600 mg/d in divided doses	initial range	25 - 50 mg q hs 75 - 150 mg/d	Titrate in 50 mg/d increase q 3-4 days Dose major portion of daily dose q hs due to sedation Adequate therapeutic response may not be evident until the 1st or 2nd weeks

[a] Adapted from Antidepressants. In: Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc.,1996
[b] Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook. 2nd edition 1995-1996. APhA: Lexi-comp Inc., 1995; 46-47, 98-99, 432-433, 709.
[c] range refers to usual therapeutic range

6. Psychostimulants

Methylphenidate HCl -- Methylphenidate is believed to work as a mild cortical stimulant with CNS actions similar to the amphetamines, although the exact mechanism of action is not known. Although not currently FDA approved, some success has been reported in the treatment of depression in elderly, medically ill, and treatment-resistant patients.

Methylphenidate should be used CAUTIOUSLY in patients with an element of agitation or a history of substance abuse. Common adverse effects include nervousness and insomnia, which may be controlled by decreasing dose and/or omitting the afternoon or evening dose.

The dosage of methylphenidate needs to be individualized. The average dose is 20 to 30 mg/d, but may be increased to as much as 60 mg/d in 2 to 3 divided doses. The medication should preferably be taken 30 to 45 minutes before meals.

Drug interactions include guanethidine (may be dose dependent), MAOIs (increased methylphenidate levels may be seen up to several weeks after discontination of MAOIs), and TCAs (pharmacologic effects of TCAs may be altered by methylphenidate). Other pharmacokinetic reactions are likely, but have not been studied.

REFERENCES

American Psychiatric Association. 1993; Brown TM, et al. 1996; Charney D, et al.1995; Ciraulo D, et al. 1995; Ciraulo DA, et al. 1990; Cohen LJ, 1997; Depression Guideline Panel.1993; Diagnostic and Statistical Manual of Mental Disorders, 1994; Ellingrod VL, et al. 1995; Ereshefsky L.1995; Finley PR. 1994; Glassman AH, 1994; Hirschfeld RMA. 1994; Jessen LM. 1996;Kehoe WA, et al. 1996; Messiha FS.1993; Nemeroff CB. 1994; Pies RW, et al.1995; Pollak PT, et al. 1995; Preskorn SH, et al. 1993; Preventive Services Task Force. 1997; Scott MA, et al. 1996; Small GI. 1991; The Medical Letter. 1996; von Moltke LL. 1993; Wilcox SM, et al. 1994; Montgomery SA, et al. 1995; Bougerol T, et al.1997; Ekeselius L.1997; Greenblatt DJ, et al. 1998.

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Appendix 6. Non-MDD Conditions Potentially Requiring Specialty Consultation

A number of other psychiatric disorders associated with or characterized by depression treatment are not directly addressed in this algorithm but are treatable, can significantly complicate MDD treatment, and may require specialty consultation. These include:

- Dysthymia
- Subsyndromal depression, seen particularly in the elderly in primary care settings;
- Bereavement
- Adjustment disorder with depressed mood
- Personality disorders with depressive symptoms
- Bipolar I and II
- PTSD
- Other.

1. **Dysthymia,** defined in DSM-IV and characterized by chronic depressed mood and a small but significant number of additional symptoms of depression, is often an unrecognized or under-diagnosed disorder that is not treated. It is often a co-morbid diagnosis with major depression (double depression). Studies of double depression a well as pure dysthymia have shown that various psychotherapeutic interventions and antidepressant medications including tricyclic-antidepressants, SSRIs, and monoamine oxidase inhibitors are more effective than placebo in alleviating the symptoms of dysthymia.

   When using antidepressant medication, it is important to use the maximum tolerated dose of medication. Sequential trials of more than one class of antidepressant for an adequate duration as recommended. However, approximately 50 percent of dysthymic patients do not respond to antidepressant mediation, and for some the side effects are intolerable. The decision to give a trial of antidepressant medication is based on several clinical considerations. These include a family history of antidepressant treatment response, a past history of positive response to medications, a negative response to psychotherapeutic interventions, the possibility that the patient has a subthreshold depression, as well as patient preference.

   Randomized, controlled trial studies have demonstrated effectiveness in utilizing psychoeducational and cognitive approaches to assist the patient in identifying stressors and learning techniques to manage mood disturbance, including dysthymic presentations. Education with family members may also be effective. Interventions have been shown to be effective in improving mood and reducing depressive symptoms immediately post-treatment and follow-up research for up to three years after treatment has shown generally sustained gains (Scogin & McElreath 1989). Thus, treatment by a mental health specialist with cognitive-behavioral therapy expertise should be considered in intervention for dysthymia and other depressive symptomatology not meeting criteria for MDD.

2. **Subsyndromal depression** is an accepted variant of Depression NOS in DSM-IV (though established since its publication and not listed in it), representing a constellation of depressive symptoms that do not meet full diagnostic criteria yet have a demonstrable impact on a patient's level of disability. This entity is of particular concern in those with chronic medical disorders and in the elderly, due to confusion between somatic symptoms of the disorders per se and the neurovegetative symptoms of depression.

3. **Bereavement** is defined in DSM-IV as a V code, i.e. not a disorder per se but possibly a focus of treatment. Intense periods of grief typically follow the loss of a loved one or of some aspect of the self (e.g., vision, independent function in activities of daily living; a valued role). Bereavement usually follows a predictable course of gradual improvement without intervention, although this may take up to a year or more. Generally, depression would not be considered as a diagnosis unless at least two months have passed since a significant loss, even if all symptoms of MDD are present.

4. **Adjustment disorder with depressed mood** is a commonly seen diagnosis, well-defined in DSM-IV in terms of response to an identifiable stressor, without development of symptoms sufficient for any Axis 1 diagnosis. Little research is available to guide decision-making concerning when to treat and when problems will resolve without treatment for this diagnosis. An extended evaluation (two to three visits) during which symptoms are monitored may usefully identify those who will remit fully with clinical management alone.

   Some common stressors related to increased risk for Adjustment disorder with depressed mood are protracted care giving role for family member with chronic disabling condition, loss of significant relationship or primary support system, or sudden negative change in economic status. In addition to trials of medication or psychotherapy, other approaches which have been clinically described as beneficial include spiritual counseling, referral for tangible socioeconomic assistance, contact with a relevant special intererst national association for connection to local support resources, family therapy, and vocational therapy.. Referral for these services should be made to therapist(s) experienced in the use of such interventions with depressed patients. Depending on local resources, referral may be made to an appropriate member of the primary care team, other VAMC services, or contract community providers.

5. **Individuals with Personality disorders with depressive symptoms are frequently seen in health care settings.** Treatment of depressive symptoms in patients with such Axis II pathology has not been systematically investigated. Recent reviews (Crits-Cristoph, 1998; Woo-Ming & Siever, 1998), found a paucity of well-designed trials for either psychological or pharmacological treatment of Axis II problems. Presence of personality disorders has often, but not always, been linked to poorer outcomes (Crits-Cristoph, 1998; Thase, 1996).

6. **Bipolar I & II (mania/hypomania).** Individuals sometimes present with primarily depressive symptoms, but who on further examination/history-taking are discovered to also either acutely or chronically manifest evidence of manic or hypomanic symptoms. This subset of patients may manifest a distinct period of persistently elevated, expansive, or irritable mood, lasting through at least four days, that is clearly different from the usual nondepressed mood and is observable by others. During this period of abnormal mood at least three of the following symptoms have been present to a significant degrees and have persisted:

   - Inflated self esteem or grandiosity
   - Decreased need for sleep
   - Pressure to keep talking
   - Flight of ideas or subjective experience that thoughts are racing
   - Distractibility
   - Increase in goal-directed activity or psychomotor agitation
   - Excessive involvement in pleasurable activities that have a high potential for painful consequences.

   These symptoms are not severe enough to cause marked impairment in social or occupational functioning or require hospitalization and have no psychotic features. Symptoms are not secondary to a substance or general media condition.

   A past history of mania or hypomania will exclude a patient from a diagnosis of major depressive episode, but patients presenting with depressive symptoms and such a history should be referred to a mental health professional because of the need for treatment and the risk that routine antidepressant medication might precipitate an unnecessary and potentially dangerous manic episode.

7. PTSD – Patients with PTSD usually have a history of exposure to traumatic stress (e.g., may be combat related) or trauma. This diagnosis requires the use of several assessment tools and specialized treatment. (See the PTSD module of the Psychoses guideline).

8. **Other considerations** - Patients with dementia are at particular risk of suffering from depression yet failing to meet full diagnostic criteria. Strong consideration should be given to active treatment of such conditions.

MANAGEMENT OF MAJOR DEPRESSIVE DISORDERS IN THE PRIMARY CARE SETTING
Appendix 7. Patient Education

To ensure that patients newly diagnosed with major depressive disorder (MDD) are provided with core competency education the provider will present information to the patient that incorporates the basic concepts of diagnosis, prognosis and treatment options as well as outside resources.

The clinician may present content from the following guidance verbally with reinforcement of the major topics as appropriate. Alternatively, the clinician my wish to print the following patient education sections as a patient handout. The questions addressed in the handout are:

1. Who gets Depressed?
2. What is depression?
3. How will I know if I am depressed?
4. What should I do if I have these symptoms?
5. What should I do if I have these symptoms
6. How will treatment help me?
7. What type of treatment will I get?
8. Who may provide mental health treatment?
9. Who should see a mental health specialist?
10. How will my health care provider know if I have depression?
11. Are there different forms or types of depression?
12. How is depression usually treated?
13. How long will I take medication?

MANAGEMENT OF MAJOR DEPRESSIVE DISORDERS IN ADULTS
Self-Management and Education – Patient Handout

1. Who gets Depressed?

Major depressive disorder, or depression as it is commonly referred, is a medical illness that can affect anyone. It affects over 11 million people every year, with twice as many women as men generally affected.

2. What is depression?

Since depression is a medical condition, like diabetes or heart disease, it is more than just of feeling of sadness or being "down in the dumps". It affects your day to day life by impacting your thoughts, ideas, actions and physical well being. Some common causes may include: certain medical conditions, some medications, drugs or alcohol, family history or other psychiatric conditions. It may result from certain life events, such as the loss of a loved one, or by stress. Depression is not the result of a weakness or a fault, it is a medical illness that can be effectively treated.

3. How will I know if I am depressed?

People who are depressed generally experience one or more of the following symptoms almost daily, over a period of at least two weeks:

- Loss of interest in things previously enjoyed
- Feeling sad, blue, or down in the dumps.

4. You may also experience at least three of the following symptoms:

- Feeling restless, slowed down or unable to sit still
- An increase or decrease in appetite or weight
- Thoughts of death or suicide
- Difficulty thinking, concentrating, remembering or making decisions
- Sleeping too much or too little
- Feeling tired all the time, or loss of energy.

Other symptoms you may experience include:

- Headaches
- Aches and pains
- Digestive problems
- Feeling hopeless or pessimistic
- Being anxious or worried.

5. What should I do if I have these symptoms?

Many times people will suspect that something is wrong but will hesitate to find help or feel guilty or responsible for their symptoms. Sometimes they are not aware that help is available or don't know what treatment might be available. If you think there may be a problem there are health care providers that can help you learn if professional treatment would be beneficial. These health care providers may include your family physician, local clinic, health maintenance organization (HMO), or local health department. They can help you find out if there is a physical cause for your symptoms, treat the symptoms or refer you to a mental health specialist for evaluation or treatment.:

6. *How will treatment help me?*

Treatment will help you by reducing the pain and the suffering of the depression. It will remove your symptoms and return you to your normal life and help you to feel better. Treatment is aimed at complete remission of symptoms and staying well afterward. Early treatment is often more beneficial and some people feel much better and return to regular daily activities in just a few weeks.

7. What type of treatment will I get?

As with any illness, sometimes more than one type of treatment may be tried to find the best response for you. It is important not to get discouraged since many options exist, and generally an effective treatment can be found for each person that will result in significant improvement and recovery. The primary treatments for depression include antidepressant medication, psychotherapy or antidepressant medication combined with psychotherapy. Other forms of treatment include light therapy and electro-convulsive (ECT) therapy.

8. Who may provide mental health treatment?

Depression, depending upon the symptoms, may be treated by general health care providers as well as specialized mental health providers. General health care providers include the following: physicians, physician assistants, and nurse practitioners. The general health care provider you see may refer you to a mental health specialist such as: a psychiatrist, a psychologist, a social worker, or a psychiatric nurse specialist.

9. Who should see a mental health specialist?

Although many people are successfully treated for depression by their primary care provider, there are times when it may be necessary for a referral to a specialized mental health provider. Some common reasons for a specialty type of referral may include the need for a combination of treatments, or for very severe or persistent symptoms that haven't improved with the initial approach. If you think you need to see a specialty provider, tell your current provider or contact one of the organizations listed in your provider network.

10. How will my health care provider know if I have depression?

Your health care provider will perform a thorough assessment of your physical and mental condition in order to diagnose depression. The following activities are commonly performed by health care providers in order to assist in their evaluation and diagnosis of your condition:

- Discussion of your symptoms
- Evaluation of your general health status
- Inquire about your family history of medical and mental disorders
- Perform a physical examination
- Perform some basic laboratory tests.

11. Are there different forms or types of depression?

You may hear depression described in terms of its impact upon your activities of daily living. It is often referred to as severe, moderate or mild in nature. Effective treatments exist for each type of depression and your provider will decide which is best for you.

- Severe depression refers to a condition which includes all or most of the symptoms that could occur and one that keeps the person from performing their usual daily living activities.
- Moderate depression refers to a condition in which many depression symptoms are present and they often keep the person from performing their usual daily activities.
- Mild depression refers to a condition in which only some of the symptoms of depression are present and they cause a person to exert extra effort to perform their usual daily activities.

12. How is depression usually treated?

The common types of treatment for depression include the following:

- Antidepressant medicine
- Psychotherapy
- A combination of psychotherapy and medication
- Other treatments including electro-convulsive therapy (ECT) and light therapy.

Your provider will discuss treatment options with you and you may want to explore risks and benefits of each. A treatment plan will be recommended by your provider based upon your specific needs and condition. It is often helpful to ask about the possible side-effects, the risks, and the improvement chances expected with each type of treatment. Often results are seen within three to four weeks, using medication. When using psychotherapy alone it may require longer, but some people see results after the first treatment.

13. How long will I take medication?

You may start to feel better in the first few weeks after beginning antidepressant medication. It is important to identify and promptly report any side-effects and to keep all follow-up appointments with your provider. Some common side-effects include the following:

- Dry mouth
- Dizziness
- Sleepiness or difficulty sleeping
- Weight gain/loss
- Skin rash
- Constipation
- Restlessness.

Depending upon your symptoms you may continue to take medication after the initial episode of depression has subsided. For some people continuation of medication on a long-term basis has proven very successful in prevention of new episodes. This will be a decision you will make with your provider.

(AHCPR, Patient's Guide,1993)

PATIENT REFERENCES –

ORGANIZATIONS

National Alliance for the Mentally Ill (NAMI)
2101 Wilson Blvd., Suite 302
Arlington, VA 22201
Toll free: 800-950-6264

National Depressive and Manic Depressive Association (NDMDA)
730 N. Franklin St., Suite 501
Chicago, IL 60610
Toll free: 800-82-NDMDA

National Foundation for Depressive Illness, Inc. (NFDI)
P.O. Box 2257
New York, NY 10116-2257
Toll free: 800-248-4344

National Mental Health Association (NMHA)
National Mental Health Information Center
1021 Prince Street
Alexandria, VA 23314-2971
Toll free: 800-969-6642

PAMPHLETS, BOOKS AND VIDEO EDUCATION

Channing L. Bete Co., Inc.
200 State Road
South Deerfield, MA 01373-0200

CD-ROM "Taking Control of Depression"
Contact Raymond Spry, MBA, MSOD
Program Manager
Employee Education System
Salt Lake City
415 S. East Oaks Drive
Fruit Height, UT 84037

Management of Major Depressive Disorder in Adults
Appendix 8. Electro-convulsive Therapy

Electroconvulsive therapy (ECT), perhaps one of the more time-tested therapeutic modalities, has advanced in terms of its importance in treating MDD, especially in its psychotic and treatment-resistant forms. Refinements in anesthetic, physiologic monitoring, stimulus control and neuromuscular blockade techniques are largely responsible for his, and have contributed to ECT's increasingly advantageous safety profile.

In order to refine clinical decision making at the earliest possible stage of treatment planning, specific areas of caution with respect to ECT administration are offered, along with a list of potential co-morbid diagnoses or differential conditions which may be resistant to ECT alone.

Primary ECT –ECT is presumed justified as primary therapy if there is a major depressive disorder with any of the following criteria:

1. Psychotic features
2. Catatonic stupor
3. Severe suicidality
4. Food refusal leading to nutritional compromise
5. A history of prior good response.

Use of ECT as a first line therapy indications follow:

1. Need for rapid, definitive treatment response on either medical or psychiatric grounds
2. Risks of other treatments outweigh the risks of ECT
3. A history of poor drug response
4. Patient preference.

Secondary ECT – Secondary ECT is presumed justified if the medical record documents any of the following:

1. Major Depression:

    a) Documentation of antidepressant treatment failure including dosage and time frame
    b) Intolerable side effects of antidepressant medications (e.g., seizures, blood dyscrasia, second- and third-degree heart block, severe hypotension, severe anxiety).

2. Mania:

    a) Documented failure to respond to mood stabilizers (lithium, carbamazepine, valproic acid)
    b) Intolerable side effects of mood stabilizers (e.g., blood dyscrasia, dermatitis)
        - Psychosis with acute neuroleptic malignant syndrome
        - Schizophrenia and other functional psychoses
        - History of favorable response to ECT.

3. Secondary Use Indications Include:

    a) Treatment failure
    b) Adverse effects that are unavoidable
    c) Deterioration of patient's condition such that first criterion is met.
    d) Informed Consent is Required In All Cases.

Contraindications Or Conditions Associates With Increased Risk In ECT

- Contraindication - Space occupying cerebral lesion or other condition resulting in elevated intracranial pressure –confers added risk of brainstem herniation

- Caution - Significant cardiovascular problems such as recent myocardial infarction, severe cardiac ischemic disease or profound hypertensive illness (whatever the cause). Simultaneous stimulation of both the sympathetic and parasympathetic systems result in changes in cardiac output and heart rate in the ictal and immediate post –ECT period, causing added risk of transient arrhythmias, cardiac ischemia and profound hypertension, conferring greater health risk in susceptible individuals.
- Caution - Recent intracerebral hemorrhage , or patients with bleeding or unstable vascular aneurysms or malformations.
- Caution - Degenerative diseases of the axial or appendicular skeleton – use of anesthetic and muscle relaxant techniques have added to the safety profile of ECT in these individuals.
- Patient currently taking monoamine oxidase inhibitor medication (MAOi). Ideally, MAOi's should be discontinued two weeks prior to initiating ECT in order to prevent threatening hypertensive changes during treatment as described above.
- Caution – Patient currently taking lithium. May result in neurotoxic syndrome marked by increased mental confusion, disorientation and unresponsiveness.
- High Anesthesia risk – American Society of Anesthesiologists level 4 or 5.

The basic pre-ECT workup may be varied, but should generally reflect those concerns presented above. The basic components of the pre-ECT evaluation involve:

1. Complete diagnostic history, mental status examination, and physical examination
2. Review of the patients past and current medical illnesses and treatments rendered
3. Formulation of a patient-specific risk-benefit inventory with comparison of ECT to other forms of treatment
4. Determination of the setting of ECT administration (inpatient versus outpatient)
5. If ECT is indicated, obtaining written consent from the patient after reviewing the benefits and risks or ECT, along with an explanation detailing other available therapeutic options
6. Initiating a medical workup as necessary in order to further assess and minimize risk to the patient
7. Anesthesia evaluation.

As a general guideline, the following studies may be considered, time permitting:

- Complete blood count
- Serum electrolytes
- Electrocardiogram
- CNS imaging - consider especially if there is suggestion of presence of aforementioned CNS pathology. May appear in the form of CT or MRI, usually within the past year.
- Baseline clinical assessment of cognitive functioning
- Spinal x-ray - Not generally recommended, but consider especially in cases where there is a history of musculoskeletal symptoms or disease
- Urinalysis
- Blood urea nitrogen and creatinine
- Chest x-ray (PA and lateral)
- Other testing where necessary.

ECT has not been proven beneficial for the following illnesses which may be considered in the differential diagnosis of prolonged dysphoria, or conditions which may occur concomitantly with MDD:

- Personality disorders
- Dysthymia

- Substance abuse and dependence
- Somatoform disorders
- Anxiety disorders
- Eating disorders.

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VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER** IN ADULTS

GLOSSARY

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN ADULTS
Glossary

ADA	American Diabetes Association
AHCPR	Agency for Health Care Policy and Research
AUDIT	Alcohol Use Disorders Identification Test
BDI	Beck Depression Inventory – Click Here
BP	blood pressure
CAGE	screening pneumonic for determining drunkenness (*Cutting* down drinking; *Annoyance* at others for receiving criticism about drinking; feeling *Guilty* or bad about drinking; using alcohol as an *Eye-opener* in the morning
CBC	complete blood count
CBT	cognitive behavioral therapy
CESD	Center for Epidemiological Studies – Depression Scale
CHF	congestive heart failure
CNS	central nervous system
CO_2	carbon monoxide
DAST	Drub Abuse/dependence Screening Test
DM	diabetes mellitus
DSM-IV	Diagnostic and Statistical Manual of Mental Health Disorders
DTR	deep tendon reflex
ECG	electrocardiogram
ECDT	elevated carbohydrate deficient transferrin
ECT	electro-convulsive therapy
ESR	erythrocyte sedimentation rate
ESRD	end stage renal disease
ESTs	empirically supported psychotherapies
ETOH	ethanol
g	gram
GAF	Global Assessment of Function
GAS	Health-Sickness Rating Scale called the Global Assessment Scale: A Procedure for Measuring Overall Severity of Psychiatric Disturbance
GGTT	Gamma glutamic transferase
Ham-D	Hamilton Depression Scale
LBP	low back pain
LFT	liver function tests
MAST	Michigan Alcoholism Screening Test
MCV	mean corpuscular volume
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MH	mental health
MMSE	Mini-Mental Status Examination-Folstein
mg/dL	milligrams per deciliter
mmols/dL	millimoles per deciliter
MSE	Mental Status Examination
MOS	Medical Outcomes Study
PBMMAP	Pharmacy Benefits Manual Medical Advisory Panel
PCM	primary care manager
PRIME MD	Primary Care Evaluation of Mental Disorders
PTSD	Post Traumatic Stress Disorder
OTC	over the counter
QE =	quality of evidence

RCT	randomized control trial
SAMe	s-adenosylmethionine
SDDS-PC	Symptom Driven Diagnostic System for Primary Care
SF-36	Standard Form-36, Quality of Life
SIRS	Systemic Inflammatory Response Syndrome
SLE	Systemic Lupus Erythematosis
SMAST	Short Michigan Alcoholism Screening Test
SMBG	self-monitoring blood glucose
SR=	strength of recommendation
SSRIs	Selective Serotonin Reuptake Inhibitors
SUD	substance use disorder
TCAs	Tricyclic antidepressants
TSH	Thyroid Stimulating Hormone
VHA	Veterans Health Administration

VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER** IN ADULTS

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VHA/DOD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MAJOR DEPRESSIVE DISORDER** IN ADULTS

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