FROM ANGST TO ILLNESS: DIAGNOSIS AND MANAGEMENT OF DEPRESSION IN PRIMARY CARE

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Experts predict depression, alcohol will top cancer as burden on system

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INTRODUCTION

Depressive disorders are a serious problem both at the personal and public health levels. The *point prevalence* of major depressive disorder (MDD) in the *community* is 4.9% (4.5% to 9% for women and 2% to 3% for men). The *lifetime risk* varies from 20%-25% for women and 7%-12% for men. The point prevalence in primary care populations is higher than the point prevalence in the community (6%-8%), because these disorders often present with somatic complaints and patients with several chronic medical conditions are at increased risk for developing MDD. For this reason, a vast majority of patients with MDD are treated exclusively in the primary care setting (Regier et al 1978) and only a fraction of these patients are recognized to be depressed. The yearly economic burden of depression was calculated to be $43.7 billion in 1990 dollars. It is a highly treatable disorder and therefore it is important for the primary care practitioners to recognize and treat it.

CLINICAL FEATURES OF MAJOR DEPRESSIVE DISORDER

Signs and Symptoms of Major Depressive Disorder

There are nine cardinal signs and symptoms of major depression as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) that are summarized in Table I.

Table I. Signs and Symptoms of Depression

Essential Symptoms
1. Depressed mood
2. Loss of interest or pleasure (anhedonia)

Physical symptoms
3. Change in appetite or weight
4. Changes in sleep
5. Fatigue
6. Change in psychomotor activity

Psychological symptoms
7. Feeling of guilt or worthlessness
8. Difficulty in thinking, concentrating or making decisions
9. Recurrent thoughts of death and/or suicidal plans or attempts

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)

The diagnosis of major depression requires the patient to have ≥ 5 out of these 9 symptoms. One of the 9 must be either a depressed mood or pervasive loss of interest or pleasure. For a symptom to be counted, it must be present most of the day, nearly everyday, for a 2-week period of time. These symptoms cannot be attributed to some underlying medical condition and represent a change from the patient's usual state. It is useful to group these symptoms into three subgroups.

Essential Symptoms: There are two essential symptoms of MDD, depressed mood and anhedonia.

The patient with depressed mood describes *"mood to be depressed, sad, hopeless, discouraged, blue" or "down in the dumps."* It is the most common and relatively straightforward symptom of depression. While sadness is a common human experience, the dysphoric mood of major depression must be present nearly everyday, for most of the day, and for at least 2 weeks. In some patients the mood may be more irritable than sad. Anhedonia refers to *"loss of interest or pleasure in living"*. This is the second hallmark of depression. Elicitation of this symptom may be easier than elicitation of sad mood, because patients often deny presence of sad mood for various reasons such as using the "good reasons" argument to explain away a sad mood because there may be some concurrent life stress or physical problem. The patients may also deny the sad mood because of the social stigma attached to mental disorders. Patients who deny depressed mood often acknowledge profound anhedonia. Activities that were pleasurable elicit no interest or decreased interest (e.g. an avid television watcher no longer watches television). Patient may also report a significant reduction in levels of sexual interest or desire.

Physical Symptoms. There are four cardinal physical symptoms of depression: sleep disorder, lack of energy, appetite or weight changes, and psychomotor retardation or agitation.

Sleep disturbance usually results in insomnia. Patients typically have middle insomnia (i.e. waking up during the night and having trouble going back to sleep) or terminal insomnia (i.e. waking up too early in the morning and being unable to return to sleep. Initial insomnia (i.e. inability to fall asleep) may also occur. Fatigue, decreased energy and tiredness are common. Patients report sustained fatigue without exertion. Simply getting washed and dressed in the morning may exhaust the person. Even small tasks seem to require substantial effort. The efficiency with which tasks are accomplished may be reduced. Appetite is usually poor resulting in substantial weight loss. Psychomotor retardation may result in slowed speech, thinking, and body movements; there may be prolonged pauses before the patient answers questions; speech may be decreased in volume, inflection, amount or variety of content. Some patients may have psychomotor agitation rather than retardation. These patients may be unable to sit still. There may be pacing, hand wringing, or pulling or rubbing of the skin, clothing or other objects. The speech may be rapid. The affect of these patients may be anxious rather than sad. These physical symptoms are also called the neurovegetative symptoms and their presence indicates increased likelihood of response to therapy.

Psychological Symptoms. There are three psychological symptoms of major depression: inability to concentrate or indecisiveness, low self-esteem (feelings of guilt and worthlessness) and recurrent thoughts of death or suicidal ideation.

Many patients report impaired ability to think, concentrate or make decisions and complain of memory difficulties. In elderly individuals with major depression disorder (MDD), memory problems may be the chief complaint and may be mistaken for early signs of dementia (pseudodementia). However, when the MDD is successfully treated the memory problems fully resolve. The sense of guilt or worthlessness may be profound and may include unrealistic negative evaluations of one's worth. There is a preoccupation with minor past failings. Patients may also have an exaggerated sense of responsibility for untoward events which may sometimes reach delusional proportions, for example the patient may hold himself/herself responsible for world hunger. Frequently there are suicidal thoughts which can range from a belief that others

would be better off if the person were dead, to transient but recurring thoughts of committing suicide, to actually having specific plans of how to carry it out. The risk for subsequent suicide for an individual hospitalized for an episode of severe MDD is estimated to be 15% (Coryell et al 1982). Conversely 60% of all suicides are thought to be secondary to major depression (Barraclough et al 1974).

Course of Depression

Major Depression Disorder may present at any age although it usually presents in the mid 20s – 30s. Symptoms may develop over days to weeks. Some people have only one episode but more than 50% will eventually develop a second episode. The risk of recurrence is higher in patients with first-degree relatives who also have MDD. Studies of MDD have found that most untreated episodes last 6 to 24 months. Approximately two thirds of patients have a complete remission. In about 5%-10% the full episode may persist for 2 years and 20%-25% develop a partial recovery. The patients with partial recovery have a higher risk of developing another episode of MDD. Studies also indicate that treatment for MDD is more effective earlier in the episode, before it becomes chronic (Depression Guideline Panel 1993).

Subgroups of major Depression

Studies of major depression disorder reveal heterogeneity with regard to biology, family history, course of illness and pharmacologic response. Consideration of these groups is important as it has treatment implications. There are 4 subgroups that need to be considered.

MDD with Psychotic features: The diagnosis of MDD with psychotic features is made when both a mood disorder and psychotic features coexist. These patients need to be treated either with a combination of tricyclic antidepressants (TCAs) and neuraleptics or electroconvulsive therapy (ECT)

MDD with Melancholic Features: Melancholic features are commonly present in the older depressed patients. They include psychomotor retardation or agitation; anhedonia; lack of reactivity to usually pleasant stimuli; worse depression in the morning; early morning awakening; significant anorexia or weight loss; and excessive or in appropriate guilt. These features indicate a greater likelihood of response to antidepressants and ECT.

MDD with Atypical Features: Some patients with MDD present with atypical features which include: overeating; oversleeping; weight gain; a reactive mood (i.e. a mood still responds to events); patients with atypical depression respond better to monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs) than TCAs (Depression Guideline Panel 1993, Vol. 1).

MDD with Seasonal Pattern: MDD with seasonal pattern is by definition recurrent. Patients must have 2-3 episodes that are seasonal. Most patients develop the depressive episode in fall and get better in spring. Light therapy has been found to be effective in these patients.

EPIDEMIOLOGY

Prevalence

The reported prevalence of depression varies depending on the types of subjects studied, (e.g. community residents, primary care patients, inpatients) and the time period for which the prevalence is estimated.

Lifetime Risk and Lifetime Prevalence: Lifetime risk refers to the proportion of individuals being studied who would develop the disorder if all lived to a designated age. Estimates of lifetime risk for MDD in community samples vary from 20% - 25% for women and 7% to 12% for men (Depression Guideline Panel 1993, Vol. 1). Lifetime prevalence refers to those individuals who up to the time of assessment, have had an episode of major depression at some point in their lives. The National Comorbidity Study (NCS) (Kessler et al 1994b) estimated the overall lifetime prevalence of major depression to be 17.1%. The lifetime prevalence for men and women was 12.7% and 21.3% respectively. Patients older than 54 were not included in this study.

Point Prevalence in the Community: Point or current prevalence refers to the proportion of individuals who have the disorder at a designated time. The specific point prevalence of MDD in *community samples* has ranged from 4.5% to 9% for women and 2% to 3% in men. (Depression Guideline Panel 1993, Vol. 1). The current overall prevalence estimated in the National Comorbidity Study is 4.9%.

Prevalence in Primary Care Settings: The prevalence of MDD in primary care patient populations is higher than in community samples. Two principle methods have been used to estimate the point prevalence of depressive disorder in primary care population: 1) Use of self administered case-finding instruments only. A number of case-finding instruments are available for detection of depressive disorders. A description of these can be found in the appendix. 2) The second approach has been to screen a large number of patients with one of the case-finding instruments. A subset of the screen positive (subjects who score higher than a certain cut-off point on the instrument) and screen negative subjects are then interviewed with a more structured diagnostic interview that results in uniformly accepted psychiatric diagnoses. Different diagnostic criteria (e.g. DSM III, DSM III-R, Research Diagnostic Criteria, Feigner Criteria) have been used, depending on the acceptable criteria at the time the study was done.

Table II. Prevalence of Depressive Disorders Diagnosed by Case Finding Instruments

Study	Number of Subjects and Setting	Case-Finding Instruments Used	Cut-off Point Used	Prevalence of Depression
Moore et al 1978	University affiliated family medical center n= 212	SDS	≥ 50 ≥ 60	45% 19%
Linn and Yager 1980	University affiliated ambulatory care center n= 100	SDS	≥ 50 ≥ 60	42% 21%
Nielsen and Williams 1980	Prepaid health plan n=526	BDI	≥ 13 ≥ 17	12.2% 5.5%
Zung et al 1983	University affiliated family medical center n=1086	SDS	≥ 55	13.2%
Rosenthal et al 1987	Family practice center n=123	BDI SDS	≥ 13 ≥ 55	28% 21%

n=number of subjects SDS = Zung self Assessment Depression Scale
BDI = Beck Depression Inventory

The prevalence of depression in studies using case finding instruments only (Table II) ranges from 5.5%-45%. Some of this variation results from using different cut-points for the instruments e.g. in the studies by Moore et al and Linn and Yager, when patients scoring 50 or more points on the SDS scale are said to suffer from depression, the prevalence is 45% and 42% respectively. When the cut-off point is raised to 60 or higher, the prevalence drops to 19% and 21% respectively. Another reason for this variability probably resides in the different patient populations studied. For example, in the study of Nielsen and Williams, one third of the patients (176 of 526) had come in for a routine physical examination. It is likely that patients who make an office visit for routine physical examination have a lower prevalence of depression. In general, the sensitivity of the case finding instruments is very high (77%-100%) but the specificity is much lower, ranging from 58%-84% (Mulrow et al 1995, Whooley et al 1997). Because of this poor specificity the prevalence of depression estimated by this approach is falsely high.

Results from 15 studies using the combined case-finding instrument use and diagnostic interviews are given in table III. The point prevalence of MDD in primary care populations using this approach ranges from 3.3%-12%. Several factors contribute to this wide variability: 1) Some studies specifically excluded patients with known psychiatric disorders while others did not; 2) The studies have been done in different settings such as university affiliated family medicine, internal medicine and ambulatory care centers, county hospitals, prepaid health plans, HMOs, fee for service practices, rural primary care clinics and an army medical center. It is likely that prevalence in these settings is dissimilar; 3) In some studies the diagnostic interviews were carried out by lay interviewers while in others they were carried out by psychiatrists, psychologists or even PCPs. 4) Use of different diagnostic criteria that were the accepted criteria at the time the study was done. 5) In most investigations only a fraction of eligible patients completed the study and hence suffered from selection bias. Despite these problems, it appears that MDD is a fairly common disorder in primary care patients and the true point prevalence is probably in the vicinity of about 6%-8%.

Table III. Prevalence of Depressive Disorder in Primary Care Setting (Combined Approach)

Study	Setting	Case Finding Instruments Diagnostic interview and criteria used	Number of Subjects	Major Depression	Other Mood Disorders
Hoeper et al 1979	Primary Care	GHQ SADS-L RDC	1072 screened 247 interviewed	5.8%	5.0% intermittent depression; 3.4% minor depression
Schulberg et al 1985	Primary Medical Care Center	CES-D DIS and DSM III	1554 screened 294 interviewed	6.2%	30% dysthymic and adjustment disorder
Von Korff et al 1987	University affiliated primary care clinic	GHQ DIS DSM III	1242 screened 736 interviewed	5.0%	3.7% Dysthymia
Kessler et al 1987	ECA users of health care 5 sites	DIS DSM III	18,572	F 6.9-9.3% M 3.3-6.5%	Not reported
Barrett et al 1988	Fee-for-service rural general medical practice	SCL-S SADS RDC	1055 screened 260 interviewed	2.2% (6.4% masked major depression)	3.6% episodic minor depression; 2.1% chronic depression
Blacker and Clare 1988	General Practice U.K.	GHQ SADS & PSE RDC	2308 screened 1019 interviewed	4.3%	5.7% minor depression
Zich et al 1990	University affiliated Ambulatory care clinic	CES-D, BDI DIS DSM III	471 screened 65 interviewed	7.7%	Not reported
Ormel et al 1990	25 family practices Groningen Netherlands	GHQ PSE and GSDS Bedford College criteria	1994 screened 296 interviewed	5.6%	4.7% border-line depression similar to minor depression
Coulehan 1990	University affiliated Clinic	CES-D DIS DSM III	618 screened 98 interviewed	6.6%	9.5% current or past MDD
Spitzer et al 1994	4 Primary care sites	Prime MD CEG DSM-III R	1000 screened 1000 interviewed with CEG 431 interviewed with SCID	12%	8% Dysthymia 6% partial remission or recurrence of MDD 6% minor depression
Williams et al 1995	University affiliated Veterans Affairs Clinic; County supported medical clinic; Community based family medicine clinic	SDS SCID DSM-III	221 screened 99 interviewed	4.0%	16% subsyndromal depression
Simon and Von Korff 1995	HMO	GHQ-12 CIDI DSM IV	1952 screened 373 interviewed	6.6%	8.8% subthreshhold depression
Tiemens et al 1996	6 Primary Care Practices Netherlands	GHQ-12 CIDI ICD-10 definitions	1271 screened 340 interviewed		14.7 current depression or dysthymia. Of current depression ;4.2% mild 5.3% moderate; 4.0% severe
Philbrick et al 1996	Primary care in rural Virginia	Prime MD CEG DSM-III-R	350 screened 302 interviewed	8.0%	4.6 % Dysthymia 6.0% partial remission or recurrence of MDD 8.9% minor depression
Kroenke et al 1997	Urgent Care Walter Reed Army Medical Center	Prime MD CEG DSM IV	500 screened screen positive interviewed	8.4%	2.8% partial remission or recurrence MDD 1.4% Dysthymia 10.4 % minor depression

Legend for Table III

CES-D = Center for Epidemiolgic Studies Depression Screen; DIS = The Lay Diagnostic Interview Schedule; DSM III= Diagnostic and Statistical Manual of Mental Disorders, third edition; GHQ = General Health Questionnaire; SADS-L = Schedule for Affective Disorder and Schizophrenia-Lifetime Version; RDC = Research Diagnostic Criteria; SCL-S = 20 item depression scale used in this study; PSE = Present State Examination; BDI = Beck Depression Inventory; GSDS = Groningen Social Disability Schedule; PRIME MD = Primary Care Evaluation of Mental Disorders; CEG = Clinical Evaluation Guide; SDS = Zung Self Assessment Depression Scale; SCID = Structured Clinical Interview for DSM-III-R; GHQ-12 = General Health Questionnaire 12 Question Version; CIDI = Composite International Diagnostic Interview; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, third edition, revised; ICD-10 = World Health Organization International Classification of Directors, tenth edition.

Risk Factors for Major Depression

Several risk factors that predispose to the occurrence of MDD have been identified. They are:

Gender: In prepubescent children the gender ratio for MDD is about 1:1 (Angold et al 1993). However by young adulthood women are roughly twice as likely as men to develop MDD (Weissman et al 1977). The sex related differences appears by age of 12 years; by the age of 15 years, female preponderance is established (Angold et al 1993) and it persists until age 55 (Burke et al 1990). The lifetime risk, the point prevalence (Depression Guideline Panel 1993, Vol. 1) and the lifetime prevalence (Kessler et al 1994b) are all approximately twice as high in women as in men.

History of MDD: Patients who develop a major depressive episode have a 50% chance of developing a second episode. Patients with history of 2 episodes of MDD have a 70% chance of recurrence and those with 3 or more episodes of MDD have a 90% chance of recurrence. (Depression Guideline Panel 1993: Vol. 1, p.73).

Family History of Mood Disorder: First degree relatives of patients with bipolar disorder are at a substantially higher risk for developing either a recurrent MDD (about 12%) or bipolar disorder (about 12%)(Depression Guideline Panel 1993: Vol. 1, p.73)

Postpartum Period: Women are at an especially high risk to develop depression in the postpartum period. The depression may occur anywhere from 2 weeks to 12 months postpartum but typically occurs within 6 months. The prevalence is 10%-15% within the first 3-6 months after delivery.

Age Effect: Analysis of the ECA study has shown that a higher prevalence of depressive disorders was seen in young adults whereas the rates were lower for the elderly. (Myers et al 1984). Part of the increased prevalence of depression in the young may be due to the birth cohort effect.

Birth Cohort Effect: A marked birth cohort effect has been seen by analysis of the data from the NIMH Collaborative Program on the Psychobiology of Depression and the ECA study (Klerman 1988), the National Comorbidity study (Kessler et al 1994a), and from multiple epidemiologic studies carried out in 9 countries and 3 family studies. (Cross

National Collaborative Group 1992). These analyses show that for each successive birth cohort in the 20th century the cumulative rates of depressive illness are increasing and the illness is occurring at an earlier age. Not everyone agrees with this interpretation as methodological problems can cause "birth cohort" like effect (Burvill 1995).

Socioeconomic Status: Lower socioeconomic status may also be a risk factor for MDD. Patients in lower socioeconomic groups were 1.5 to 2 times more likely to have MDD than those who were economically well off (Regier et al 1993, Kessler et al 1994b).

Lack of Social Support and **Stressful Life Events** were two other risk factors identified by the Depression Guideline Panel 1993.

Physical Illness: Whereas the prevalence of MDD is 3.3% - 12% in unselected primary care populations, the Depression Guideline Panel found an especially high prevalence in association with the following medical conditions: 1) **Stroke:** A prevalence of MDD between 10% - 27% within 2 months of the stroke has been documented with an average duration of depression of approximately 1 year. 2) **Parkinson's Disease:** Approximately 50% of Parkinson's patients with dementing symptoms have MDD. The cognitive symptoms appear to improve with improvement of mood. Therefore, treatment of the depression may be especially helpful for these patients. 3) **Diabetes:** MDD is approximately three times more common in patients with diabetes than in the general population and is associated with poor glucose regulation, probably because of poor adherence. Thus diagnosis and treatment of MDD may result in improved control of diabetes and fewer complications from it. 4) **Coronary Artery Disease:** The prevalence of ***various*** forms of depression in patients who have had a myocardial infarction is estimated to be at 40%-65%. The point prevalence of MDD is 18%-25% for those with recent myocardial infarction and 18%-20% in those with known CAD without an MI. Further, depressed patients are slower to return to work and show poor adherence to their treatment regimens. 5) **Cancer:** It is estimated that 20 – 25% of cancer patients suffer from MDD at some point during their illness. These rates are not higher than for patients with other general medical conditions. In these patients MDD is associated with increased distress, significantly impaired functioning and decreased capacity to follow treatment recommendations. Treatment of MDD in these patients may improve their quality of life. 6) **Chronic Fatigue Syndrome (CFS):** Lifetime rates of MDD range from 46-75% in patients with CFS. According to CDC criteria the presence of a psychiatric disorder excludes the presence of CFS. Thus patients who fulfill the criteria both for CFS and MDD should be diagnosed and treated for MDD. The etiological relationship between CFS and MDD is unclear. 7) **Fibromyalgia:** Patients with fibromyalgia also have high lifetime rates of mood disorders. Hudson et al (1989) reported 26% of their patients to be currently depressed whereas the lifetime rate of MDD was 71%. 8) **Patients with chronic pain, acquired immunodeficiency syndrome** and **Alzheimer-type dementia** are also at an increased risk of developing MDD (Burvill 1995).

Comorbid Psychiatric Disorders: Patients with certain non-mood psychiatric disorders are also at an increased risk of developing MDD. Some of these disorders are: **Alcohol**

and Drug Dependence: It is common for patients with alcohol dependence to develop MDD but alcoholism is not thought to be a common consequence of mood disorders. Between 10%-30% of patients with alcoholism manifest depression. Analysis of the ECA data showed that alcoholics were 1.7 times more likely than nonalcoholics to develop MDD. (Helzer et al 1988). Conversely, alcoholism is thought to occur in less than 5% of patients with MDD (Depression Guideline Panel 1993, Vol 1), a rate that is no different than from that in the general population. However, some gender differences are present. Women with MDD are more likely to become dependent on alcohol than men. Alcohol dependent patients who stop drinking have a spontaneous remission of the depressive symptoms in the first 2-4 weeks of sobriety. Association of depressive symptoms and drug abuse is common also. Intake of CNS depressants and withdrawal from CNS stimulants such as cocaine and amphetamines is known to cause dysphoric mood and other symptoms of depression. **Anxiety Disorder:** Most longitudinal studies of patients with anxiety disorders have found an increased incidence of depressive disorders over time. The combination of panic disorder and MDD results in a more severe disorder with greater impairment than does either disorder alone. These patients have a more severe depressive illness and are less likely to recover during a 2-year follow-up than patients with MDD alone. **Eating Disorders:** Approximately one-third to one-half of patients with eating disorders (anorexia or bulimia) suffer concurrently from a MDD, and 50% to 75% of patients with eating disorders develop MDD at sometime during their life. **Obsessive Compulsive Disorder (OCD):** Patients with OCD very commonly have depressive **symptoms** (lifetime risk 80%-100%). The point prevalence of MDD ranges from 10%-30%. The onset of MDD typically follows the manifestations of OCD. **Grief and Bereavement:** Depressive symptoms associated with normal grieving usually begin within 2 to 3 weeks of the loss and resolve spontaneously in 6-8 weeks. If signs of MDD persist for more than 2 months beyond the death of a loved one, an episode of MDD can be diagnosed and should be treated as such. High rates of MDD have been found in individuals who have lost a loved one. It has been reported that 25% of widowed men and women met criteria for MDD at 7 months and 17% met the criteria for MDD at 13months. Overall 46% were depressed at some time during the first year following the loss of spouse (Depression Guideline Panel 1993, Vol. 1).

ECONOMIC BURDEN OF DEPRESSION

Depression represents a substantial economic burden to the society. There are direct costs associated with diagnosis and drug therapy, as well as indirect costs related to increased mortality, morbidity, lost productivity and intangibles such as poor quality of life and increased likelihood of marital breakdown.

Direct Costs: In an analysis of the economic burden of depression in 1990, Greenberg et al (1993) calculated that the inpatient and outpatient care and pharmaceutical cost for treatment of patients with MDD was $12.41 billion. In addition, patients with MDD utilize the nonpsychiatric health care sector in excess of the non-depressed individuals. They make more telephone call to their physicians, have more office visits and incur more diagnostic tests (Katon et al 1986). When hospitalized for non-psychiatric ailments, their hospital stays are longer (Saravay et al 1991). These costs are not included in Greenberg's estimate of direct costs of health care utilization by depressed individuals.

Indirect Costs: from depression can be due to **increased mortality** and **increased morbidity** which can result in decreased productivity and reduced lifetime earnings. The increase in mortality results both from higher suicide rates in depressed individuals as well as from non-suicide related causes. Psychological studies show that more than 60% of suicides are related to depression (Barraclough et al 1974). Greenberg (1993) estimated an approximate cost of $7.5 billion due to lost lifetime earnings secondary to suicide. In addition, patients with depressive disorders are 1.5 to 4 times more likely to die than nondepressed individuals from usual nonsuicide related causes (Coryell and Clancy 1982, Bruce and Leaf 1989, Rovner et al 1991). Greenberg's estimate does not take this excess mortality into account. MDD is associated with increased morbidity also. Several studies have shown that patients suffering from depression have impaired occupational functioning (Ormel et al 1993, Spitzer et al 1995), incur four and a half times the number of disability days as compared with psychiatrically well patients (Broadhead et al 1990, Ormel et al 1994) and are twice as likely to lose time from work (Olfson et al 1997). Greenberg et al estimated that approximately $11.7 billion was lost in 1990 due to excess absenteeism from work and another $13.1 billion was lost secondary to decreased productivity during episodes of MDD.

Intangible Losses: Patients with MDD also have impairment in their social and family life, perceive their general health to be poorer and suffer from more bodily pain as compared with nondepressed patients (Ormel et al 1993, Spitzer et al 1995). In fact they are significantly worse in several domains of their functioning (physical, social, role, number days in bed, current health perception and freedom from pain) when compared with common medical conditions such as hypertension, diabetes, arthritis, gastrointestinal disorders, lung diseases and back problems (Wells et al 1989b). Depressed patients are also 7.5 times more likely to suffer from marital distress (Olfson et al 1997). The cost of these intangibles is hard to judge.

The economic costs associated with depressive disorder as estimated by Greenberg et al in 1990 can be summarized as follows:

Direct costs	$12.4 billion
Mortality costs (suicide)	$ 7.5 billion
Costs of lost productivity due to absenteeism	$11.7 billion
Cost of decreased productivity	$12.1 billion
Total	**$43.7 billion**

This impressive number of $43.7 billion, represents economic burden of MDD in 1990 dollars and does not include the increased costs incurred from excessive health care utilization in the non-psychiatric sector, the costs of excess mortality unrelated to suicide or the intangible losses discussed above.

UNDERRECOGNITION OF DEPRESSIVE DISORDERS BY PRIMARY CARE PRACTITIONERS

Several investigators have also looked at the proportions of patients with depression who were recognized by their primary care practitioners (PCPs). As can be seen from table IV, the rate of recognition varies from 29% - 75%. The rates of recognition were higher (60%-75%) in studies that specifically required the PCP to report the presence of psychological disorders in the patient (Gerber et al 1989, Ormel et al 1990, Simon et al 1995, Tiemens et al 1996, and Von Korff 1987). In studies not requiring such a report the recognition rates were much lower ranging from 29% - 50%, despite the fact that in most studies, the PCPs were aware that a study on depression was being conducted in their patients. In general, patients with more severe depression were recognized more frequently.

Table IV. Recognition of Depressive Disorder in Primary Care Physicians

Study	Setting	Screening Questionnaire Diagnostic interview and criteria used	Prevalence of Major Depression	Percent depressed Patients recognized
Schulberg et al 1985	Primary Care	CES-D DIS and DSM III	6.2%	44.4
Von Korff et al 1987	University affiliated primary care clinic (PCC)	GHQ DIS, DSM III	5.0%	75%*
Jones 1987	University affiliated PCC	GHQ 28 DIS	NR	29%
Gerber et al 1989	Primary care Rural NH	HSCL SADS RDC	NR	57%*
Wells et al 1989a	Primary care sites, small group practice large multiple specialty groups	DIS –DSM III	NR	46-50%
Perez-Stable et al 1990	University affiliated medical clinics	CES-D, BDI, DIS, DSMIII	NR	36%
Ormel et al 1990	25 family practices Groningen Netherlands	GHQ PSE Bedford College criteria	5.6%	68%*
Coulehan et al 1990	University affiliated clinic	CESD DIS DSM III	6.6%	44%
Spitzer et al 1994	4 Primary care sites	Prime MD CEG DSM-III-R	12%	33%
Simon et al 1995	HMO	GHQ-12 CIDI, ICD-10	6.6%	64%*
Tiemens et al 1996	6 Primary Care Practices Netherlands	GHQ-12 CIDI ICD-10	NR	60%*

LEGEND FOR TABLE IV

*PCPs questioned about patients' psychological status; NR = Not reported; CES-D = Center for Epidemiologic Studies Depression Screen; DIS = The Lay Diagnostic Interview Schedule; DSM III = Diagnostic and Statistical Manual of Mental Disorders, third edition; GHQ = General Health Questionnaire; GHQ28 = General Health Questionnaire 28 question version; BDI = Beck Depression Inventory; PSE = Present State Examination; PRIME MD = Primary Care Evaluation of Mental Disorders; CEG = Clinical Evaluation Guide; GHQ-12 = General Health Questionnaire 12 Question version; CIDI = Composite International Diagnostic Interview; SADS-L = Schedule for Affective Disorder and Schizophrenia-Lifetime version; RDC = Research Diagnostic Criteria; SCL-S = 20 item depression scale used in this study; GSDS = Groningen Social Disability Schedule; SDS = Zung Self Assessment Depression Scale; SCID = Structured Clinical Interview for DSM-III-R; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, third edition, revised; ICD-10 = World Health Organization International Classification of Diseases, 10th edition.

Barriers to Recognition of Depression in Primary Care

There are several factors that lead to under recognition of depressive disorders in the Primary Care setting. According to Cole and Raju (1996b) they are as follows:

Culture of Medicine: Most PCPs are taught and practice medicine based on "biomedical model of illness" i.e. medical problems are viewed as physical and molecular in nature. Patients with somatic symptoms resulting from mental disorders are often derisively referred to as "crocks and trolls".

Social Stigma: The social stigma attached to mental illness follows from the biomedical model of illness. Mental disorders in many cultures are viewed as indicators of character weakness and therefore are associated with denial, shame, and anger. To remove this stigma one must accept a biopsychosocial model of illness in which psychological and social problems are accepted as contributing to illness.

The fallacy of good reasons: Physicians and patients often "explain away" the emotional disorders with an assertion like "There is a **good reason** to be depressed". This stems from the fact that depression is often precipitated by some form of psychosocial stress such as death of a loved one, divorce, loss of job or diagnosis of a devastating illness. In these situations, depression should be aggressively looked for and treated.

Lack of time: Most patients seen in general medicine practices have multiple medical problems and are on multiple medicines. Addressing these issues and issues of health maintenance is very time consuming. The paperwork associated with patient encounters is ever increasing and time being allotted to PCPs for each patient with advent of managed care is decreasing. This leaves the PCP very little time to explore the "feelings" of their patients.

Knowledge Deficits: Lack of knowledge of mental disorders and appropriate interviewing skills may also be a barrier to recognition of depression by PCPs. Physicians must be taught to improve their interviewing skills so that more can be accomplished in lesser time. PCPs who learn good communication skills are actually able to improve the accuracy with which they detect mental disorders, achieve improved clinical outcomes in their patients and keep their total interviewing times unchanged (Roter et al 1995).

Discrimination: Both patients and physicians may also avoid the diagnosis of mental disorders, because of widespread discrimination in employment opportunities and determination of insurability.

Financial disincentives related to inadequate reimbursement by insurance companies for treatment of mental disorders may also play a role in under recognition of depression.

Diagnosis of depression is clinical. There are no laboratory tests to confirm the clinical impression. Physicians in general are uncomfortable making diagnoses that cannot be confirmed with a laboratory test.

Somatization: The most important reason for under recognition of depression in primary care setting is that only a minority of patients with depression present with complaint of "sad mood" or "loss of pleasure." A vast majority of patients with depression present to their PCP with somatic complaints. Both PCPs and the patients are primarily concerned about missing a serious physical illness. Furthermore, since patients truly experience the physical symptoms, they are reluctant to accept the diagnosis of a mental disorder as an explanation for their problems.

Clinical Clues to Recognition of Patients with MDD in Primary Care

The primary care physicians are fairly proficient at diagnosing psychiatric illness if patients present with psychological complaints (Bridges and Goldberg 1985). However, depression is underdiagnosed in this clinical setting because only a minority of patients (16% - 23%) present with the chief complaint of sadness (Widmer and Cadoret 1978, Wilson et al 1983). This is true even if the patients have a depressed mood. Widmer and Cadoret (1978) reported that only 23% of their depressed patients presented with the chief complaint of low mood. However, on questioning a depressed mood was elicited in 76% of patients. A vast majority of patients with MDD present with somatic complaints, the two most common being **sleep disturbance** and **fatigue**. Widmer and Cadoret (1978) reported that 33% of their depressed patients had a chief complaint of sleep problems and 31% of fatigue.

There is also a very strong association of **pain** with depression. Lindsay and Wyckoff (1981) reported that 87% of 300 consecutive patients referred to pain clinic were depressed and conversely of 196 patients with depression referred to an internist-psychiatrist, 59% had some significant complaint of chronic pain. The common locations of pain were the head (60%), abdomen (29%), back (28%), chest (20%) and neck (11%). Further, 83% of patients obtained significant pain relief with antidepressant medication treatment.

Other complaints seen commonly in depressed patients include weakness, palpitations, dizziness, weight problems, shortness of breath, appetite changes, anxiety and nonspecific GI complaints such as change of bowel habit, nausea, vomiting, flatulence, bloating and gas pain (Gerber et al 1992, Katon et al 1986, Mathew et al 1981, Widmer and Cadoret 1978, Wilson et al 1983). Patients who present with **multiple somatic complaints, vaguely stated problems** or **amplified complaints** have a high likelihood of suffering from depression also (Gerber et al 1992, Kroenke et al 1994 and Waxman et al 1985). In fact Kroenke et al reported that the prevalence of depression increased with increasing number of somatic complaints. The prevalence of depression with 1-2, 3-5 and $\geq$ 6 somatoform symptoms was 42%, 46% and 69% respectively.

Another clue to the presence of depression is the perception that the patient is "**difficult**". Hahn et al (1996) reported that patients judged to be "difficult" by the Difficult Doctor-Patient Relationship Questionnaire had a high likelihood of having psychiatric disorders

including major depression. The "difficult" patients were 3 times as likely to have MDD and 4 times as likely to have dysthymia as compared to "non-difficult" patients.

In summary, depression should be suspected and ruled out in patients who present with somatic complaints such as sleep disturbances, fatigue, chronic pain syndromes, nonspecific musculoskeletal pain, back pain, appetite or weight changes, nonspecific gastrointestinal problems, dizziness and anxiety. Depression should also be suspected in patients whose complaints are multiple, vaguely stated or amplified. Psychiatric pathology including depression should be considered in patients perceived to be difficult.

How to Make the Diagnosis

Diagnosis is made with a 5-10 minute interview evaluating the 9 criteria defined by DSM-IV. A simple mnemonic can be used to remember these criteria: SAD-A-FACES

S Sleep – Insomnia/Hypersonmia
A Appetite or Weight Change
D Dysphoria – "Bad Mood" – Irritable, Sad, Blue, Down in the Dumps

A Anhedonia – Lack of Interest or Pleasure
Lack of Sex Drive
F Fatigue
A Agitation/Retardation
C Concentration problems
E Esteem (Low) Guilt
S Suicide/Thoughts of Death

Some useful screening questions include:

Dysphoria: "Have you been feeling sad, blue, down, in the dumps?"
Anhedonia "What do you do for fun?"
"Has your interest in(the fun activity) changed any?"
Low self-esteem: "Have you been down on yourself lately?"
Thoughts of death/
Suicidal ideation: "How does the future look to you?"
"Do you sometimes feel life is not worth living?"
"Many patients with your symptoms find living intolerable. Do you ever wish you were dead?"
"Do you ever have thoughts about hurting yourself?"

DIFFERENTIAL DIAGNOSIS OF DEPRESSION

Secondary causes of MDD must be ruled out with a clinical history, physical examination and appropriate laboratory tests. Specifically one must rule out medical causes of depression; depression secondary to medications; and certain psychiatric disorders that can masquerade as depression (such as substance abuse, grief reaction, dysthymia and

minor depression). The common medical disorders and medications associated with depression are listed in Tables V and VI (Rauch and Hyman 1995, Cole and Raju 1996a)

Table V. Medical Illnesses Associated with Depression

Neurologic diseases: stroke, subdural hematoma, multiple sclerosis, brain tumor, Parkinson's disease, Huntington's disease, epilepsy, dementias.

Infectious Disorder: viral infections (especially mononucleosis and influenza), HIV with or without AIDS, syphilis.

Nutritional Disorders: Vitamin B_{12}, folate, thiamine, B_6 or niacin deficiency.

Endocrinopathies: hypothyroidism or hyperthyroidism (especially in the elderly) Cushing's Disease, hyperparathyroidism, and diabetes mellitus.

Other: carcinomas (especially pancreatic and other gastrointestinal cancers), carcinoid, collagen vascular disease, lymphomas.

The importance of recognizing the general medical disorder lies in the fact that the depressive symptoms may resolve with the treatment of the general medical disorder. If the symptoms of depression persist then they must be specifically treated. (Depression Guideline Panel 1993, Vol. 1).

Table VI. Medications Associated with Depression

Cardiovascular drugs: Alpha-methyldopa (±) antiarrhythmics, digoxin, clonidine, thiazide diuretics, guanethidine, reserpine (++) and propranolol ((±)

Hormones: oral contraceptives(±) corticotrophin and glucocorticoids (++) and anabolic steroids (+)

Psychotropics: benzodiazepines and neuraleptics

Anti inflammatory agents: NSAIDS, bacolfen

Others: cycloserine, ethambutol, disulfiram, sulfonamides, metoclopramide, levodopa (±), cimetidine, ranitidine, and withdrawal from cocaine and amphetamines (++)

The degree of certainty of a causal relationship is shown in parentheses for selected drugs.

Most of the evidence for the above medications being associated with depression rests on case reports. Therefore, if a patient develops depression after being started on one of these medications good clinical judgement mandates that the medication should be discontinued and the patient's course followed. In addition one must remember that idiosyncratic reactions to medications do occur. Therefore, if depression develops after beginning the use of **any** drug, the medication should be stopped and alternative therapy tried (Depression Guideline Panel 1993, Vol. 1).

Laboratory Tests: No routine laboratory tests are indicated in patients with depression. Laboratory tests should be tailored for each patient. However, in women over the age of 50 with depressive symptoms, thyroid functions should be done to detect thyroid disease

(Depression Guideline Panel 1993, Vol. 1, p. 81). When appropriate neuropsychological testing should be considered to differentiate depression from dementia.

TREATMENT OF DEPRESSION

Objectives

The treatment of MDD proceeds in three phases: acute, continuation and maintenance. The aim of the acute phase treatment is to return the patient to a fully asymptomatic state. The aim of the continuation and maintenance phases of treatment is to prevent a relapse and recurrence, respectively. A relapse in defined as return of the MDD within 6 months following a remission . A recurrence is said to occur if symptoms of MDD return after 6 months following a remission.

Clinical Management of the Patient

There are several modalities available for treatment of MDD. In addition to selecting the appropriate treatment, the PCP must develop an understanding, supportive and empathetic relationship with the patient and provide advice, reassurance and hope (Fawcett et al 1987). It is also very important for the PCP to educate the patients (and their families) about the nature course and prognosis of depression and available treatment modalities.

Education of the patient: All depressed patients and their families should be educated about the following important points: first, that depression is quite common and it is real; that depression is caused by a chemical imbalance in the brain and does not represent "weakness" of character; that with proper treatment, there is a high likelihood of remission; and finally, that treatment needs to be carried out for prolonged periods (several months or years) to prevent relapse and recurrence. Patients should be invited to actively participate in selecting a therapy. If antidepressant medication is selected as the therapy of choice, the patients need to be told that the improvement is likely to be gradual and progressive (may take 2-6 weeks) and that dosage adjustments may be necessary. Patients should also be told that treatment is specific for the disorder and is not a nonspecific sedative or tranquilizer. Some education about the expected side effects and how to handle them should also be provided. Patient education has been shown to be helpful with treatment compliance in patients with depression (Altamura et al 1985, Myers and Calvert 1984).

Management of Mild Depression

For patients who have mild depression (i.e. who are not in any imminent danger, have minimal functional impairment, depression is not chronic or recurrent, are nonpsychotic), or for patients whose diagnosis is unclear (i.e. major depression versus adjustment reaction with depressed mood) the PCP may want to schedule one to two additional weekly evaluation visits to determine whether symptoms will resolve without formal treatment. There is evidence that with education and support approximately 20%-30% of patients achieve remission (Elkin et al 1989). However, these patients should be followed carefully over the next 6-12 months (2-3 visits) because a large fraction may suffer a recurrence (Shea et al 1992).

Management of Moderate, Severe, Chronic and Recurrent Depression

For patients who do not achieve remission with education and support, are more severely depressed, or those who have recurrent or chronic depression, one of the following treatment modalities may be used:

1) Antidepressant medications
2) Psychotherapy
3) Combination of medication and psychotherapy
4) Electroconvulsive therapy
5) Light therapy

Out of these, the only treatment modality available to the PCP is medications and therefore it will be discussed in greater detail. However a short description of the indications of other modes of therapy follows:

Psychotherapy alone: Psychotherapy alone to treat MDD may be considered first-line in patients with mild to moderate depression who either prefer psychotherapy, have a contraindication to antidepressant medications or have severe psychosocial problems. Psychotherapy, obviously can only be offered if a competent psychotherapist is available. If psychotherapy is completely ineffective by 6 weeks or if it does not result in a nearly full symptomatic remission within 12 weeks, a switch to medication is appropriate (Depression Guideline Panel 1993 Vol. 2).

Combination of Medication and Psychotherapy: A combination of medication and psychotherapy may be a reasonable consideration in patients in whom the depression is chronic or characterized by poor interepisode recovery and in those with only partial response to either treatment alone. It may also benefit patients with chronic psychosocial problems or those who have problems with compliance (Depression Guideline Panel 1993, Vol. 2).

Electroconvulsive Therapy (ECT): Elderly patients who are psychotically depressed, severely incapacitated, refractory or unable to take drug therapy should be referred for consideration of electroconvulsive therapy. ECT is also useful in aborting acute suicidal drive for patients who require rapid resolution of symptoms (Depression Guideline Panel 1993, Vol. 2).

Treatment with Medications: Antidepressant medications have been shown to be effective in all forms of MDD. Unless contraindications are present, antidepressant medications are the first line treatment for MDD in patients with moderate to severe depression. Medications are also indicated in patients with mild to moderate depression if no competent psychotherapist is available or patient prefers medications, especially if the patient has shown a good response to pharmacotherapy in the past. Antidepressants are also indicated for maintenance therapy because maintenance psychotherapy is not effective (Frank et al 1990).

Efficacy of Antidepressant Medications: Intention to treat meta-analyses of all randomized controlled trials of antidepressants published since 1975 in the English language by the Depression Guideline Panel indicated that, in general, most antidepressant medications have comparable efficacy in patients seen in outpatient mental health and primary care sectors. The efficacy in geriatric patients was similar to that seen in younger adults. Antidepressant medications are effective in approximately 50%-70% of patients (Table VII).

Table VII. Efficacy of Antidepressants

Drug Type	Psychiatric Outpatient Adult	Psychiatric Outpatient Geriatric	Primary Care
Tricyclics	45% - 63%	32% - 50%	45% - 66%
Heterocyclics	59% - 67%	37% - 58%	50% - 91%
SSRIs	47% - 59%	49% - 65%	51%
MAOIs	53% - 60%	57.7%	NA

Adapted from Depression Guideline Panel 1993, Vol 2 pages 48-54.

ANTIDEPRESSANT MEDICATIONS

Currently there are close to two dozen-antidepressant medications available. A brief overview of some of these agents follows:

Mechanism of action: The actual basis for the therapeutic action of antidepressant drugs in unknown. All antidepressants potentiate the action of the biogenic amines, norepinephrine, serotonin and dopamine in the CNS by blocking their major means of physiologic inactivation i.e. reuptake at nerve terminals. However inhibition of the uptake of biogenic amines by itself is not a sufficient explanation for the antidepressant action of these drugs, because even though the blockade of the amine uptake is established promptly, the appearance of antidepressant effects usually requires administration of the drugs for several weeks. It is believed that the initial effects on monoamine transmission result in adaptive changes at receptors that ultimately mediate the therapeutic response. The various antidepressants differ considerably in selectivity, potency, and the mechanisms, by which they achieve these effects (Baldessarini 1996, Sussman and Stahl 1996).

Classification: The antidepressants in current use can be classified into several groups (Sussman and Stahl 1996, Gruenberg and Goldstein 1997) as shown in Table VIII.

Table VIII. Antidepressants

Selective serotonin reuptake inhibitors (SSRIs)
Fluoxetine, Paroxetine, Sertraline

Catecholamine reuptake inhibitors
Bupropion*

Tricyclic antidepressants (TCAs)
Tertiary amines: Amitriptyline, Doxepin, Trimipramine, Imipramine, Clomipramine.
Secondary amines: Nortriptyline, Desipramine, Protriptyline
Others: Amoxapine*, Maprotiline*

Sertonin 2A antogonist/serotonin reuptake inhibitors
Trazodone*

Serotonin 2A antagonist/serotonin reuptake and norepinephriane reuptake inhibitors
Nefazodone

Serotonin/norepinephrine reuptake inhibitors
Venlafaxine

Monoamine oxidase inhibitors (MAOIs)
Phenelzine, Tranylcypromine, Isocarboxazid

* Can also be classified as heterocyclics

Selective Serotonin Reuptake Inhibitors (SSRIs)

The three SSRI antidepressants **fluoxetine, sertraline, and paroxetine** are structurally unrelated but are all able to selectively and potently inhibit reuptake of serotonin. Because of this selectivity, the SSRIs lack many of the side effects associated with the TCAs and other antidepressants. All the SSRIs are effective in MDD, dysthmia and atypical depression. They are well tolerated even in patients with comorbid major medical disorders and overdoses with SSRIs have been relatively benign. For these reasons SSRIs have become the most commonly prescribed antidepressants (Depression Guideline Panel 1993, Hollister and Claghorn 1993, Sussman and Stahl 1996).

In addition, it is important to remember that not all patients respond to the same agent. Some retrospective data and open clinical trials indicate that 42%-71% of patients who are given a second SSRI after an initial failure respond to the new SSRI (Brown et al 1995, Joffe et al 1996, Sacchetti et al, 1994). All of the SSRIs are effective in obsessive compulsive disorder (OCD) and paroxitene is effective in panic disorder as well. So these agents are a good choice in patients with depression who are suffering concomitantly from OCD or panic disorder.

Pharmakokinetics of SSRIs: The SSRIs are extensively metabolized by the hepatic microsomal enzymes. All of the SSRIs have the potential to inhibit cytochrome P4502D6, which can lead to increased concentrations of other drugs that are predominantly metabolized by this enzyme. Of most concern is concomitant therapy with drugs that have a narrow therapeutic index (e.g. type 1C antiarrhythmics flecainide

and propafenone, vinblastine, tegretol and TCAs). In addition, sertraline also inhibits cytochrome P4503A4 and thus may lead to increased levels of concomitantly administered astemizole and cisapride, causing prolongation of the QT interval and predisposing patients to torsades de pointes type of ventricular tachycardia. All three drugs are highly protein bound and thus have the potential of altering levels (by displacement) of other highly protein bound drugs such as dilantin and warfarin.

Side effects: There are a number of side effects associated with the SSRIs. The most common are gastrointestinal effects (e.g. nausea, vomiting, diarrhea/loose stools) or effects related to CNS stimulation (e.g. insomnia, tremor, agitation, anorexia). Less common side effects that appear to be dose related and that may be ameliorated by reducing the SSRI dose are headache, sweating, lethargy and sexual dysfunction. Sexual problems include lack of interest, impotence, delayed ejaculation, and anorgasmia or delayed orgasm. Of the three drugs, sertraline causes the least anorexia and fluoxetine causes the least sexual dysfunction (sexual dysfunction is reported in 10%-15% of patients with sertraline and paroxetine but in only 1%-2% with fluoxetine). Benzodiazopines or trazdone can be used to manage the insomnia and cisapride is useful for the gastrointestinal side effects (Hollister and Claghorn 1993, Physicians' Desk Reference 1997, Sussman and Stahl 1996).

Drug interactions: All SSRIs can cause a life-threatening "serotonin syndrome" if taken concurrently with an MAOI. The manifestations of this syndrome include hyperthermia, rigidity, myoclonus, diaphoresis, autonomic instability, extreme agitation, delirium, coma and death. Since the half-lives of fluoxetine and its active metabolite norfluoxetine are very prolonged (4-6 days and 4-16 days respectively), special precautions must be taken when switching from one drug to the other. It is recommended that fluoxetine should be discontinued for 5 weeks and sertraline and paroxetine for 2 weeks before starting an MAOI. SSRIs should be started 14 days after discontinuing an MAOI (Hollister and Claghorn 1993).

One must remember that L-deprenyl used in treatment of Parkinson's disease is an MAOI and that serious toxicity can occur with concurrent use of SSRIs. Although toxicity is more likely to occur at L-deprenyl doses of 20-40 mg, it can occur with doses of 10 mg/day (the usual dose for Parkinson's disease) as well (Sussman and Stahl 1996). Sexual dysfunction caused by the SSRIs has been successfully treated with coadministration of yohimbine, cyproheptadine or amantadine or by switching patients to bupropion (Montano 1994, Sussman and Stahl 1996).

Dosage and Administration: SSRIs are given once daily usually in the morning to minimize the risk of insomnia. In general the SSRIs have a flat dose-response profile. Some patients with an initial partial response may benefit from a dose increase. The necessity of dose escalation is more common with sertraline than with other SSRIs (see Table IX). Lower doses are recommended for the elderly and patients with renal or hepatic insufficiency. Doses for these patients are also adjusted after longer intervals.

Table IX. SSRI Dosage Recommendation						
SSRI	**Starting Dose**	**Usual Effective Dose**	**Minimum Time Before Dose should be Increased**	**Recommended Increase**	**Maximum Dose per day**	**Range in the Elderly**
Fluoxetine	20 mg/d	20 mg/d	3-4 wks	20 mg monthly	80 mg	5-60 mg
Sertraline	50 mg /d	100-150 mg/d	3-4 wks	50 mg at 1-2 wk intervals	200 mg	50-200 mg
Paroxetine	20 mg/d	20 mg/d	3-4 wks	10 mg at 1-2 wk intervals	50 mg	10-40 mg

Adapted from J. Clin. Psychiatry 55:12 (Suppl), December 1994

Special considerations: The much shorter elimination half-lives of paroxetine (21 hours) and sertraline (26 hours) compared with fluoxetine and their lack of clinically active metabolites render them safer for medically frail elderly patients in whom antidepressant may have to be withdrawn quickly because of side effects or drug interactions (Montano 1994).

Catecholamine Reuptake Inhibitors

Bupropion represents this class. Its precise mechanism of action is not known but it is known to inhibit norepinephrine and dopamine reuptake. Its efficacy as an antidepressant is similar to TCAs and SSRIs. However, it has a very beneficial side effect profile. Specifically it causes no orthostasis, anticholinergic effect, sexual dysfunction or cardiovascular toxicity and little sedation and cognitive impairment. It suppresses appetite and causes weight loss and may achieve better compliance in patients who gain weight with other antidepressants. It is not lethal in overdose situations. It is a CNS stimulant like the SSRIs, so common side effects include agitation, anxiety and insomnia. The effects are dose related and may respond to dose reduction. Other side effects include: dizziness, constipation, dry mouth, sweating and tremor. Occasionally it can cause psychosis. The most serious adverse effect is its propensity to produce seizures in 0.4% of patients. It is therefore relatively contraindicated in patients with seizure disorder. Its other drawback is its short half-life necessitating BID to TID dosing. Recommended dose is 75 mg bid which can be gradually increased (every 3-4 days) to 100 mg TID. An increase in dosage to 450 mg/day given in divided doses of not more than 150 mg each may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day. There must be at least 4-6 hours in between doses to reduce the likelihood of seizures. Bupropion's stimulating effects and beneficial side-effect profile make it particularly useful in the depressed elderly, especially those exhibiting lethargy and psychomotor retardation. It is also a useful substitute in patients who experience sexual dysfunction with SSRIs (Montano 1994, Nemeroff 1994, Physicians' Desk Reference 1997, Rauch and Hyman 1995, Sussman and Stahl 1996).

Tricyclic Antidepressants (TCAs)

All the TCAs share a common three-ring molecular core and because of their structure the trivial name tricyclic antidepressants is used for this group. In addition to blocking the reuptake of the biogenic amines, all the TCAs to varying degrees also block muscarinic, cholinergic, α_1 adrenergic, H_1 histamine, gamma-aminobutyric acid (GABA), and dopamine receptors. These actions are not thought to contribute to the efficacy of these agents but do result in side effects and toxicities that have limited the use of these drugs. The main side effects of TCAs include anticholinergic effects such as blurred vision, dry mouth, constipation and urinary retention and weight gain. The TCAs also have significant cardiovascular effects which include postural hypotension, mild sinus tachycardia, prolonged conduction times at all levels of intracardiac conduction system, and myocardial depression. Thus they must be used with great caution in patients with cardiac disease. All TCAs are equally effective and require 2-4 weeks of continuous use before clinical improvement is manifest. The major differences amongst the various TCAs are in the degree of their side effects (see Table X). Because of these side-effects they are probably best used as second-line agents.

Selecting Among Tricyclics: Choice of a TCA for a given patient is determined by the side effects of the available agents. As can be seen from Table X, amitriptyline has the worst side effects in terms of anticholinergic effects, drowsiness, orthostasis, potential for cardiac arrhythmias and weight gain. For this reason it is probably not an optimal first-choice agent in any patients unless low doses suffice. The general strategy is to have the adverse effects work for the patient, e.g. patients with severe insomnia may do best with a strongly sedating drug such as doxepin given at bed time. Desipramine and nortriptyline have relatively mild anticholinergic, orthostatic and sedating effects and so may be considered for elderly patients and for those with prostatic hypertrophy. Patients with great anergy and psychomotor retardation are best treated with a nonsedating, slightly activating TCA like desipramine or an SSRI.

Dosage: Metabolism of TCAs varies widely so doses must be carefully tailored. Patients are usually started at 25 mg daily, with increases of 25 mg every 3-4 days until therapeutic dose-range without intolerable side effects is achieved (for dose ranges see Table XI). Dosages are reduced by 50 percent in the elderly. The daily dose is best taken at bedtime to minimize side effects and facilitate compliance. Since tricyclics can have lethal cardiovascular toxicity when taken in an overdose, no more than one gram of TCAs should be prescribed to a potentially suicidal patient (Depression Guideline Panel 1993, Vol. 2, Gruenberg and Goldstein 1997).

Table X. Side Effect Profiles of Antidepressant Medications.

Drug	Side Effect[1]								
		Central Nervous System		Cardiovascular		Other			Relative Cost
	Anti-Cholinergic	Drowsiness	Insomnia/ Agitation	Orthostatic Hypotension	Cardiac Arrhythmia	GI Distress	Weight Gain (over 6 kg)	Seizures	
Amitriptyline	4+	4+	0	4+	3+	0	4+	2+	1.0
Clomipramine	3+	2+	2+	2+	3+	3+	1+	3+	-
Desipramine	1+	1+	1+	2+	2+	0	1+	1+	9.4
Doxepin	3+	4+	0	2+	2+	0	3+	2+	5.0
Imipramine	3+	3+	1+	4+	3+	1+	3+	2+	1.3
Nortriptyline	1+	1+	0	2+	2+	0	1+	2+	15.5
Protriptyline	2+	1+	1+	2+	2+	0	0	3+	-
Trimipramine	1+	4+	0	2+	2+	0	3+	2+	-
Amoxapine	2+	2+	2+	2+	3+	0	1+	2+	-
Maprotiline	2+	4+	0	0	1+	0	2+	3+	-
Trazodone	0	4+	0	1+	1+	1+	1+	0	7.0
Nefazodone	0	3+	0	1+	0/+	1+	0/+	0	-
Bupropion	0	0	2+	0	1+	1+	0	4+	12.5
Fluoxetine	0	0	2+	0	0	3+	0	0/+	12.0
Paroxetine	0	0	2+	0	0	3+	0	0	10.0
Sertraline	0	0	2+	0	0	3+	0	0	10.5
Venlafaxine	0	0	2+	Hypertension	0/+	2+	0	?	-
Monoamine Oxidase Inhibitors (MAOIs)	1+	1+	2+	2+	0	1+	2+	0	-

[1]0 = absent or rare
1+
2+ = in between
3+
4+ = relatively common

[2]Dry mouth, blurred vision, urinary hesitancy, constipation

(Adapted from Depression Guideline Panel 1993, Vol 2: p 56 and Rauch and Hyman 1996)

Table XI. Pharmacology of Antidepressant Medications			
Drug	**Therapeutic Dosage Range (mg/day)**	**Average (Range) of Elimination Half-lives (Hours)[1]**	**Potentially Fatal Drug Interactions**
Tricyclics			
Amitriptyline (Elavil, Endep)	75-300	24 (16-46)	Antiarrhythmics, MAOIs
Clomipramine (Anafranil)	75-300	24 (20-40)	Antiarrhythmics, MAOIs
Desipramine (Norpramin, Pertofrane)	75-300	18 (12-50)	Antiarrhythmics, MAOIs
Doxepin (Adapin, Sinequan)	75-300	17 (10-47)	Antiarrhythmics, MAOIs
Imipramine (Janimine, Tofranil)	75-300	22 (12-34)	Antiarrhythmics, MAOIs
Nortriptyline (Aventyl, Pamelor)	40-200	26 (18-88)	Antiarrhythmics, MAOIs
Protriptyline (Vivactil)	20-60	76 (54-124)	Antiarrhythmics, MAOIs
Trimipramine (Surmontil)	75-300	12 (8-30)	Antiarrhythmics, MAOIs
Heterocyclics			
Amoxapine (Asendin)	100-600	10 (8-14)	MAOIs
Bupropion (Wellbutrin)	225-450	14 (8-24)	MAOIs (possibly)
Maprotiline (Ludiomil)	100-225	43 (27-58)	MAOIs
Trazodone (Desyrel)	150-600	8 (4-14)	--

[1]Half-lives are affected by age, sex, race, concurrent medications, and length of drug exposure.
Source: Depression Guideline Panel 1993: Vol. 2.

Serotonin-2A Antagonist-Serotonin Reuptake Inhibitors

Trazodone is the only agent in this class. It is a 5-HT2A receptor antagonist and blocks reuptake of serotonin. The incidence of anticholinergic side-effects is low and it is not lethal in overdose situations. Common side-effects include: sedation, postural hypotension, indigestion, nausea, headaches and priapism. In patients with pre-existing cardiac disease, it can cause arrhythmias. It should be given at an initial dose of 150 mg/day which can be titrated up to 600 mg/day. Most patients respond to approximately 300 mg/day. It has a short half-life of 3-9 hours so has to be dosed on BID to TID schedule. Because of sedation a major portion is given at bedtime. To reduce the likelihood of orthostasis it should be taken with food. Currently, because of its side-effects, it is mainly used to manage insomnia caused by other antidepressants in doses of 25-100 mg given at bedtime. Priapism is not dose related and so all patients must be warned of its possibility and potential seriousness (Nemeroff 1994, Rauch and Hyman 1995, Sussman and Stahl 1996).

Serotonin-2A Antagonist and-Serotonin-Norepinephrine Reuptake Inhibitors

Nefazodone is an analogue of trazodone. It blocks the 5-HT 2A receptors and also inhibits uptake of serotonin. It has a modest inhibiting effect on norepinephrine uptake. It is effective in severely depressed patients including patients with major depression with melancholic features. The efficiacy of nefazodone is dose related; thus dose titration is necessary. It has no anticholinergic activity and little associated cardiotoxicity. Postural hypotension is seen in <3% of patients. No sexual dysfunction is reported. It is not lethal in overdose situations. Common side effects are somnolence, dry mouth, nausea, dizziness, light headedness, headache, constipation, asthenia, confusion, blurred vision

and other visual symptoms such as scotomas and image trailing. Most of these diminish with ongoing treatment. Symptoms of overdose include nausea, vomiting and somnolence. No life-threatening or residual complications have been reported. Nefazodone inhibits P4503A4 isoenzyme leading to excessive accumulation of coadministered astemizole and cisapride, which can cause serious cardiac arrhythmias. Doses should start at 50 mg to 100 mg twice a day and should be gradually increased to 300-600 mg/day. The optimal dose range for the elderly is 200-400 mg/day. It should be considered for patients who are depressed and highly anxious or agitated, sleep-disturbed or those who have developed sexual dysfunction with SSRIs (Nemeroff 1994, Physicians' Desk Reference 1997, Sussman and Stahl 1996).

Serotonin-Noreprinephrine Reuptake Inhibitors

Venlafaxine is a structurally unique compound that inhibits neuronal reuptake of both serotonin and norepinephrine. It is considered to be a second-line agent because of its problematic side effect profile and need for BID or TID dosing. It can cause nausea in substantial number of patients which limits its tolerability. Other side-effects include headache, somnolence, dry mouth, dizziness, insomnia, constipation, nervousness, sweating, anorexia, sexual dysfunction and sustained increases in blood pressure, heart rate and cholesterol levels. It is effective for treatment-resistant depression and it has been noted clinically that patients unresponsive to other treatments often respond to it (Nemeroff 1994, Montano 1994). The recommended dose range is 75-375 mg/day in divided doses. Starting doses of 25 mg/day are recommended to reduce side effects. Cisapride is effective in management of nausea (Sussman and Stahl 1996).

Monoamine Oxidase Inhibitors

These drugs act primarily by irreversible inhibition of both the A and B forms of monoamine oxidase the enzyme responsible for the metabolism of the neurotransmitters dopamine, serotonin and norepinephine. MAOIs are very effective in treatment of patients with atypical or melancholic depression and in patients resistant to other antidepressants. MAOIs can cause orthostatic hypotension, sedation, dizziness, insomnia, sexual dysfunction, tachycardia, constipation, agitation and edema (Rudorfer 1992). Administration of meperidine is contraindicated in patients receiving MAOIs as it can lead to serious and even fatal reaction. However, the main problem with MAOIs is the possibility of hypertensive crisis due to unpredictable interactions with many drugs and foods. Serious interactions can occur with precursors of biogenic amines such as levodopa, aldomet, dopamine other sympathomimetic medications including those found in combination cold tablets, nasal decongestants and appetite suppressants. Serious reactions also occur with the tyramine which is found in a variety of foods such as cheese, beer, wine, pickled herring, snails, chicken liver, yeast, large quantities of coffee, citrus fruits, canned figs, broad beans and chocolates and cream or their products. Tyramine acts peripherally, primarily, by releasing the stores of catecholamines in the nerve endings, the concentrations of which are elevated due to the action of MAOIs. For this reason the MAOIs are reserved for patients who fail to respond to vigorous trials of at least one of the newer agents and a standard tricyclic antidepressants and are best managed by the psychiatrists (Baldessarini 1996, Potter et al 1991).

Relative Advantages and Drawbacks of Newer Antidepressants	
Advantages	Potential Drawbacks
SSRIs Low sedative, anticholinergic, hypotensive side effects; no weight gain (perhaps loss); low potential for cardiotoxicity; overdoses nonlethal; dosing QD.	Inhibition of P4502D6 and potential for interactions; GI symptoms; anxiety; insomnia; sexual dysfunction. Sertraline inhibits P4503A4
Bupropion Low incidence of sedation, hypotensive, and anticholinergic side effects; no weight gain (perhaps loss) no electrocardiographic changes. Overdose rarely lethal.	Constipation, dry mouth, agitation, excessive sweating, dizziness, nausea, vomiting, blurred vision, insomnia, seizures (0.4%). Dosing TID.
Nefazodone Rare cardiotoxicity; no anticholinergic activity; no clinically significant EKG changes; overdose nonlethal.	Somnolence, dry mouth, nausea, dizziness, constipation, asthenia, light headedness, blurred vision, confusion and abnormal vision (scotomas, visual trails). BID dosing; inhibits P4503A4 coadministration of astemizole, cisapride contraindicated. Dosing BID.
Venlafaxine Low sedative, anticholinergic, hypotensive side effects; weight loss; no conduction abnormalities on EKG; low cardiac toxicity. Overdose (with no other substances) nonlethal.	Nausea, somnolence, dizziness, abnormal ejaculation, dry mouth, sweating, constipation, anorexia, insomnia and nervousness. Sustained hypertension (3%-13% depending on dose), seizure (0.26%) Dosing BID to TID.

Antidepressant Medication Selection

All antidepressants have equivalent efficacy and no agent provides remission for all patients. Therefore selection of an antidepressant for a specific patient is made by considering the side-effect profile of the agent, comorbid illnesses of the patient and duration of treatment necessary. Because of the relative lack of side-effects and safety in patients with comorbid illnesses SSRIs are a good first choice. All of the SSRIs are equally effective. In view of their short half-lives, sertraline and paroxetine are preferred in elderly patients. Fluoxetine and paroxetine cause more anorexia than sertraline, so the latter may be preferred in patients with profound anorexia. Other good first choices are bupropion and nefazodone. All these do not cause significant weight gain and have minimal anticholinergic effects and so may be more appropriate for long-term use. Bupropion and nefazodone are good alternative choices especially in patients who develop sexual dysfunction with SSRIs. In patients with cardiac disease, SSRIs, bupropion and nefazodone are preferable because they cause little or no orthostatic hypotension or conduction abnormalities.

Tricyclic antidepressants and venlafaxine are good second-line agents. Of the tricyclics, the secondary amines (e.g. desipramine, nortriptyline) have equal efficacy but fewer side effects than the parent tertiary amines (e.g. imipramine, amitriptyline) and are therefore preferable especially in elderly patients. Monoamine oxidase inhibitors are best handled by the psychiatrist who have more experience with it.

There are several other factors worthy of note in prescribing antidepressants: Patients who have responded to an antidepressant in the past are likely to respond to the same agent again. Conversely if a patient failed to respond to an agent or was unable to tolerate the side effects, that agent should be avoided. There is some evidence in the literature that response to different classes of medicines runs in the families. Therefore history of response to an agent in a first degree relative makes it more likely that the patient will respond to the same agent. Patients with atypical features respond better to MAOIs and SSRIs than to TCAs.

Followup of patients with depression

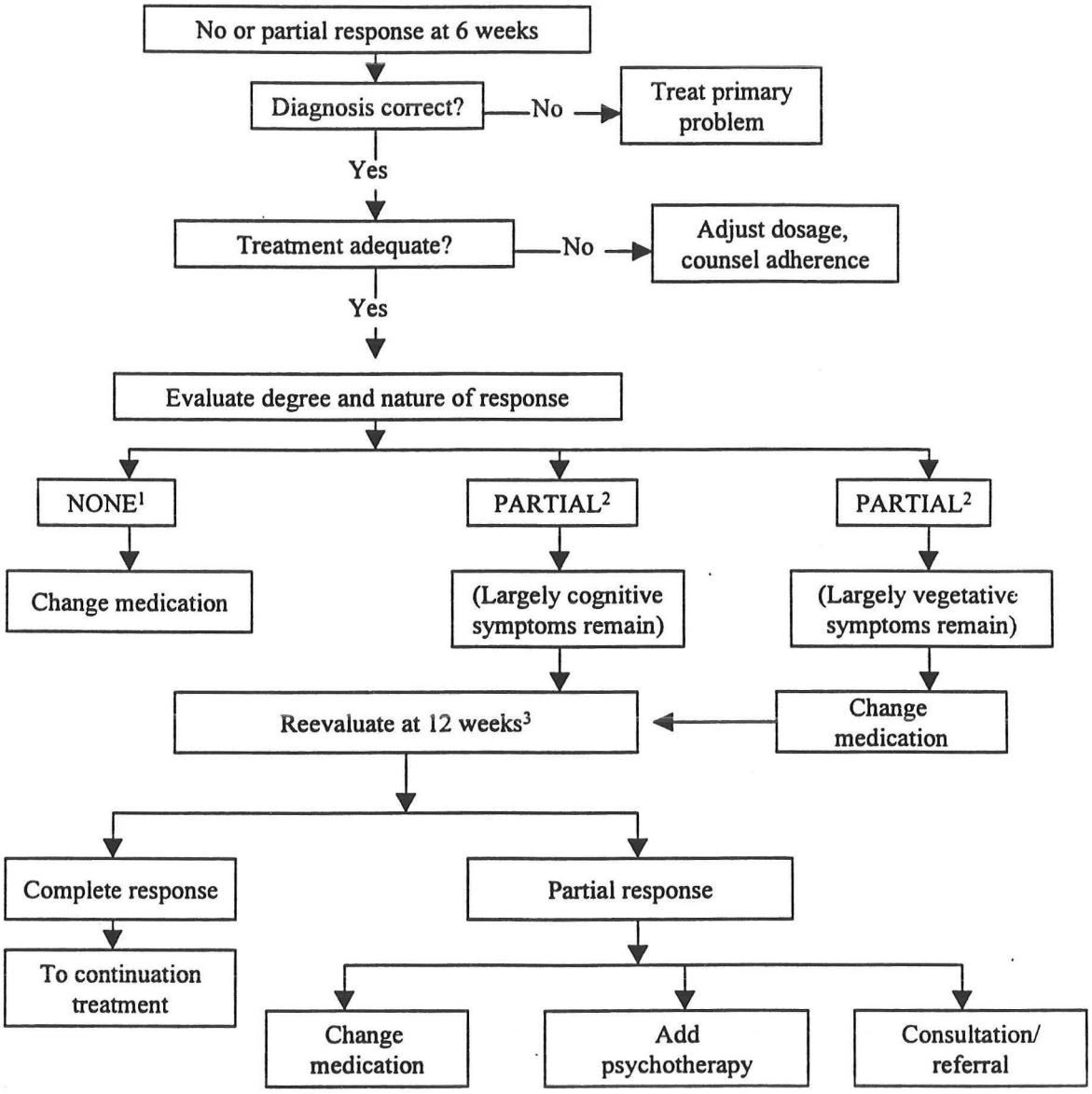
The Depression Guideline Panel recommends that patients with more severe depression should be seen weekly for the first 6-8 weeks of acute treatment. These weekly visits provide an opportunity to provide support to the patient, monitor side effects, adjust medication dosage and monitor patient's progress. Patients with less severe depression may be seen every 10-14 days for the first 6-8 weeks. Once the depression is resolved, patients may be seen every 4-6 weeks.

Evaluation and management at six weeks: The patients should be evaluated after six weeks of therapy. Further management depends on the response.

Responders: Patients may have complete response with normal psychosocial function. These patients should continue to receive the antidepressant for 4-9 months to prevent a relapse. Those who continue to have psychosocial dysfunction need psychotherapy added to their regimen.

Nonresponders: Those who show **no or partial response** at 6 weeks should be reevaluated for secondary causes of depression such as: ongoing but undisclosed alcohol or other substance abuse; presence of comorbid psychiatric disorder; or presence of an underlying medical condition; If these are ruled out then the PCP should evaluate dosage and compliance (drug levels may be helpful) and adjust medication dosage if necessary. If the patient has been receiving adequate medication dosages and there is no response or partial response with persistent physical symptoms then it is appropriate to change to a different drug (a different agent if the initial drug is an SSRI or a different class for other drugs). If the response is partial and only cognitive symptoms remain, then the same medication should be continued and the patient should be reevaluated at 12 weeks (Depression Guideline Panel 1993, Vol. 2).

Figure 1. Six-week evaluation: partial responders or nonresponders to medication



[1]No response – patient is nearly as symptomatic as at pretreatment.
[2]Partial response – patient is clearly better than at pretreatment, but still has significant sypmtoms. Consultation or referral may be valuable before proceeding further.
[3]Suggestions for management are based on some indirectly relevant studies, logic, and clinical experience.
Adapted from Depression Guideline Panel 1993, Vol. 2, p. 67.

Reevaluation at 12 weeks: Patients with a complete response need to continue their treatment for 4-9 months to prevent relapse. Those with a partial response can be managed either by changing medication, adding psychotherapy or referring to a psychiatrist (Depression Guideline Panel 1993, Vol. 2).

Duration of Treatment

Duration of treatment will depend on whether or not the patient is a candidate for maintenance treatment. All patients should receive continuation treatment.

Continuation Treatment: It is recommended that all patients who have responded to treatment in the acute phase (12 weeks) should be continued on the same medication and dosage for an additional 4-9 months. Early discontinuation is followed by an approximately 25% relapse rate within 2 months. If the patient is not a candidate for maintenance therapy, the medication can be tapered at the end of 9 months to prevent withdrawal reaction (Depression Guideline Panel 1993, Vol. 2).

Maintenance Treatment: Several studies have shown a lower recurrence rate of MDD with prolonged maintenance therapy in patients who are at high risk for recurrence. Patients with $\geq$3 episodes of MDD had a recurrence rate of 23% with maintenance therapy during a 3 year follow up, while those on placebo had an 80% recurrence rate (Frank et al 1990). Efficacy of maintenance treatment has also been shown in patients who have had 2 episodes of depression over a 5-year period (Montgomery et al 1988). In addition, the Depression Guideline Panel also strongly recommends maintenance treatment in patients with two episodes of MDD who also have (a) family history of bipolar disorder or (b) history of recurrence within 1 year after an effective medication was discontinued or (c) a family history of recurrent major depression (d) or had onset of first episode at age younger than 20 years (e) or both episodes were severe, sudden or life threatening in the past 3 years.

The patients should be seen every one to 3 months during the maintenance phase of therapy. If symptom breakthrough occurs during this period, drug levels may be checked to assess adequacy of therapy and medication should be adjusted as necessary. If these measures fail, psychiatry referral is indicated.

Blood Drug Levels

Patients differ widely in the blood levels achieved with a fixed oral dosage. Four antidepressants (nortriptyline, desipramine, imipramine, and amitriptyline) have more consistent evidence of minimal therapeutic blood levels. Most have established toxic ranges and one (nortriptyline) has an established upper therapeutic range. **Nortriptyline is as ineffective at levels >150 ng/ml as it is at levels <50 ng/ml.** Patients in whom blood level monitoring may be helpful include those who show partial or no response to therapeutic dosages of medication; those with suspected toxicity; elderly or pregnant patients (because of altered metabolism); those of African or Asian descent (because of slower metabolism); suspected noncompliance; those taking medications that may interact with antidepressants; and those with particular medical risks for side effects, such that minimal effective levels are highly desirable.

Well Established Therapeutic Ranges

Nortriptyline	-	50-150 ng/ml
Amitriptyline	-	80-250 ng/ml of amitriptyline plus nortriptyline
Desipramine	-	125-300 ng/ml
Imipramine	-	150-250 ng/ml of imipramine plus desipramine

Less Well Established Therapeutic Ranges

Doxepin	-	150-250 ng/ml of doxepin plus desmethyldoxepin
Fluoxitene	-	200-700 ng/ml of fluoxetine plus norfluoxetine
Trimipramine	-	150-250 ng/ml
Amoxapine	-	200-600 ng/ml of amoxapine plus 8 hydroxyamoxapine
Clomipramine	-	Up to 700 ng/ml of clomipramine plus desmethylclomipramine

Referral to Psychiatry

A consultation or referral to a psychiatrist is appropriate under these conditions: the PCP is not skilled in making the diagnosis or providing the recommended treatment; the diagnosis is unclear; or the treatment is unsuccessful. A non-response after 2 separate trials with two different drugs in adequate dosages and duration is an indication to refer to a psychiatrist because the longer the patient's depressive episode lasts the harder it is to treat. Other indications for referral include: the patient is suicidal; other psychological comorbidies are present that the PCP is uncomfortable with diagnosing and managing; treatment with psychotherapy, light therapy, ECT or MAOIs is indicated; patient on continuation or maintenance therapy is having breakthrough symptoms; patient has bipolar disorder or psychotic depression (Depression Guideline Panel 1993, Montano 1994).

CONCLUSION

Major depressive disorder is a very common condition in primary care and causes a huge economic burden on the society. A vast majority of patients with MDD receive care exclusively from their PCPs who fail to recognize it in a substantial proportion. The patients usually present with sleep disturbance, fatigue or multiple somatic, poorly stated or amplified complaints. They may also be judged to be difficult. The prevalence of MDD is also very high in patients with many psychiatric disorders and several chronic medical conditions. The index of suspicion should be high in these patients. Diagnosis is made by a clinical interview. A mnemonic SAD-A-FACES can help in remembering the nine cardinal symptoms of depression. The patients should be evaluated for presence of certain medical and psychiatric disorders and medications that can cause depression. The depression in this situation may resolve with management of underlying disorders. If depression persists it should be treated as a primary mood disorder. Several management strategies are available.

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APPENDIX

Instruments

Case Finding Instruments

A number of case-finding instruments have been developed over the years to detect depressive disorders. Some of the more common instruments that have been used in studies investigating the prevalence of depression in primary care patients populations are:

1. The Beck Depression Inventory (BDI) (Beck et al 1961)
2. The Center for Epidemiologic Studies Depression Screen (CES-D)(Radloff 1977)
3. The General Health Questionnaire (GHQ)(Goldberg 1979)
4. The Hopkins Symptoms Checklist (HSCL)(Derogatis et al 1974)
5. The Medical Outcomes Study Depression Screen (MOS-D) (Burnam et al 1988)
6. The Popoff Index of Depression (ID)(Popoff 1969)
7. Primary Care Evaluation of Mental Disorders (PRIME-MD)(Spitzer et al 1994)
8. Symptom Driven Diagnostic System-Primary Care (SDDS-PC)(Olfson et al 1995)
9. Zung Self-Assessment Depression Scale (SDS)(Zung 1965)
10. Two-Question Depression Scale (Whooley et al 1997)

Most of these instruments ask questions relating to:

1. The mood of the patient such as feeling blue, sad, depressed, lonely, irritated, bothered, or having crying spells.
2. Anhedonia such as loss of interest in usual activities or other people.
3. Physical symptoms such as poor appetite, weight loss, sleep problems, constipation, easy fatigability, and heart beating faster.
4. Altered psychomotor activity such as everything was an effort, could not get going, talked less than usual, felt restless.
5. Psychological symptoms such as unable to concentrate or make decision easily, feeling of worthlessness such as life has been a failure, things are not going well, can't do anything right, disappointed in self, felt hopeless, lost ambition.
6. Diurnal variation of symptoms.

The characteristics of these instruments are described in Table II. Several of these instruments were developed specifically to identify depression (BDI, CES-D, MOS-D, SDS and 2Q) while others were developed to screen for general psychiatric illness (GHQ and HSCL). Two of the instruments (Prime MD and SDDS-PC) are recently developed multi-dimensional questionnaires that have screening questions in several categories (e.g. mood, somatoform, alcohol, anxiety and eating disorders). Positive screens trigger more extensive diagnostic interviews. The response formats elicit either frequency or severity of symptoms or a yes or no response. The time frames of questions are variable and include "during the past week", "during the past month", "during the past few weeks", "recently", and "at the time of testing".

Characteristics of Case-Findings Instruments That Have Been Used to Detect Depression in Primary Care Settings*

Instrument	Scope	Items †	Response Format	Time Frame of Questions	Score Range	Usual Cut-point ‡	Sensitivity	Specificity
BDI	Depression-specific	21	4 statements of symptom severity per item	Past week	0-63	10 mild 20 moderate 30 severe	90	58
CES-D	Depression-specific	20	4 frequency ratings: "less than one day" to "most or all (5-7) days"	Past week	0-60	16 27	80	72
GHQ	Psychiatirc illness (several versions)	28	4 frequency ratings: "not alt all to "much more than usual"	Past few weeks	0-28	4	90	66
HSCL	Multiple versions and multiple components with depression category	25	4 frequency ratings: "not at all" to "much more than usual"	Past week	25-100	43	86	84
MOS-D	Depression-specific	8	Frequency ratings; same format as CES-D 2 items, yes or no	Past week	0-1 (logistic regression)	0.06	77	81
ID	Depression-specific	15	3 statements of normal, overt, or covert symptomatology	Recently	0-30	10	88	61
PRIME-MD	Multiple components with depression category	2	Yes or no	Past month	0-2	1	86	75
SDDS-PC	Multiple components with depression category	5	Yes or no	Past month	0-4	2	81	80
SDS	Depression-specific	20	4 frequency ratings: "little of the time" to "most of the time"	At the time of testing	25-100 (sum/80X 100)	50 mild 60 moderate 70 severe	88	76
2Q	Depression-specific	2	Yes or no	Past month	0-2	1	100	57

*BDI Beck Depression Inventory: CES-D = Center for Epidemiologic Studies Depression Screen: GHQ = General Health Questionnaire: HSCL = Hopkins Symptoms Checklist: MOS-D = Medical Outcomes Study Depression Screen: ID = Popoff Index of Depression: PRIME – MD = Primary Care Evaluation of Mental Disorders: SDDS-PC = Symptom Driven Diagnostic System-Primary Care: SDS = Zung Self-Assessment Depression Scale.

†Item numbers for the PRIME-MD and SDDS-PC refers to depression questions only: item numbers for the HSCL refer to depression plus anxiety questions.

‡ Cut-point is the number at or above which the test is considered positive. The Sensitivity and Specificity are given for the lowest cut-point.

The sensitivity of these instruments is excellent ranging from 77%-100% whereas the specificity is much lower ranging from 57%-84% (Mulrow et al 1995, Whooley et al 1997). Because of this poor specificity, the prevalence of depression in studies utilizing case-finding instruments only is probably falsely elevated.