Edward S. Friedman
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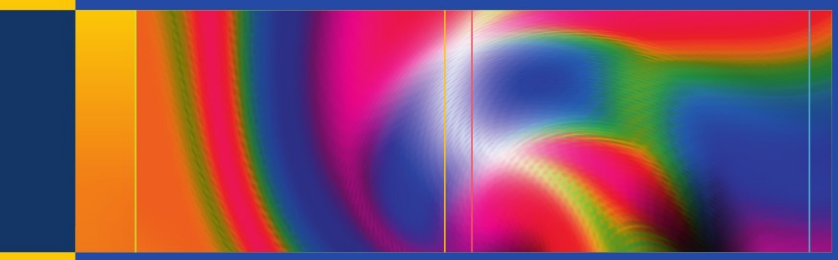

Managing Depression in Clinical Practice

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Author biographies

Edward S Friedman, MD, received his Doctor of Medicine degree from the University of Pittsburgh School of Medicine in Pittsburgh, Pennsylvania, USA. Upon graduation, he joined the faculty of the University of Pittsburgh School of Medicine Department of Psychiatry and the Western Psychiatric Institute and Clinic (WPIC) of the University of Pittsburgh Medical Center. Currently, he is the Director of the Mood Disorders Treatment and Research Program at WPIC. His research has focused on cognitive behavioral psychotherapy, pharmacotherapy, and combination treatments for major depression and bipolar illness. He has published numerous articles and book chapters on these subjects. Recently, he was the National Cognitive Therapy Director for the landmark STAR*D study. Dr Friedman is also Director of the Cognitive Therapy Residency Training Program and the Ambulatory Mood and Anxiety Disorders Residency Training Program at WPIC. Dr Friedman has participated in many mood disorders research projects, and, for example, he is currently the Pittsburgh site Primary Investigator for the National Institute of Mental Health Depression Treatment Network and the National Institute of Mental Health Bipolar Treatment Network – multicenter collaborations that have been responsible for the highly-regarded STEP-BD and STAR*D studies.

Professor Ian M Anderson is a Professor of Psychiatry at the University of Manchester and an Honorary Consultant Psychiatrist at Manchester Mental Health and Social Care Trust. He studied medicine at Cambridge University and University College Hospital Medical School, going on to training posts in general medicine and neurosurgery before training in psychiatry in Oxford. He is Director of the Specialist Service for Affective Disorders in Manchester, which he founded in 2001 as a multidisciplinary tertiary service for treatment-resistant depression and bipolar disorder. His current research interests concern the role of serotonin in the etiology and treatment of affective disorders and the use of functional brain imaging to investigate emotional processing and neurotransmitter function in depression. He is first author of the British Association for Psychopharmacology (BAP) guidelines for treating depressive disorders with antidepressants, and a co-author of the BAP guidelines for treating anxiety disorders. He was Chair of the Clinical Guideline Development Group to update the National Institute for Health and Clinical Excellence treatment guideline for depression.

Preface

Is there a need for yet another book about depression? This is the question we asked ourselves in the planning stages of this book. Given that you are now reading this preface, we obviously thought there was—but why? Developments in the field are currently evolutionary rather than revolutionary but new treatments do become available, old and new treatments are reevaluated, and patient choice and the structure of treatment delivery are increasingly emphasized. This means that there is a need for updated accessible summaries for those who need to keep abreast of current thinking and apply their knowledge in practice. As our backgrounds are from both sides of the Atlantic, we have tried to keep both perspectives in mind. We have had to be necessarily brief and emphasize areas that we believe are important. Inevitably we have had to skate over complexities, but we have tried not to oversimplify and to provide key references for further reading. Although primarily aimed at nonspecialists and students, we hope that for more experienced practitioners this book also provides a useful overview of the subject.

Chapter 1

Classification, causes, and epidemiology

Edward S Friedman

Different types of depression

The depressive disorders comprise a heterogeneous group of illnesses that are characterized by differing degrees of sad mood and associated cognitive, neurovegetative, and psychomotor alterations. Depression is currently the fourth most disabling medical condition in the world and it is predicted to be second only to ischemic heart disease with regard to disability by 2020 [1,2].

Depressive disorders

There is a broad spectrum of depressive disorders characterized by the presence of sad mood and varying degrees of other depressive symptoms [3]. According to the American Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [4], disturbance of mood is the predominant feature of mood disorders. They are further divided into the bipolar disorders (characterized by the presence of a manic or hypomanic episode – which may also include depressive episodes, hence the older term manic depression) and the depressive disorders. The latter are subdivided into major depressive disorder (MDD) and dysthymic disorder (DD), as well as a "not otherwise specified" category for subsyndromal cases that do not fulfill the criteria for MDD or DD. MDD is characterized by one or more major depressive episodes (MDEs) – a period during which an individual experiences five or more depressive symptoms to a moderate degree for 2 weeks or longer with a diminution of their previous level of functioning (see Figure 1.1). In addition, these symptoms cannot be attributed to another psychiatric or medical disorder, the direct physiologic effect of a substance, or bereavement. In circumstances where an individual presents with sad mood and clinically significant impairment, the term "depressive disorder not otherwise specified" is used.

The *International Classification of Mental and Behavioral Disorders*, 10th revision (ICD-10) [5] characterizes recurrent depressive disorder as repeated

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Characterization of a major depressive disorder

ICD-10 classification		DSM-IV classification	
Criteria symptoms: at least 2 weeks of lowered mood*, anhedonia*, reduced energy*, reduced concentration, sleep disturbances, reduced appetite, reduced self-confidence, feelings of guilt and worthlessness, psychomotor retardation or agitation, loss of libido		Criteria symptoms: at least 2 weeks of low or depressed mood*, anhedonia*, significant changes in appetite, disturbed sleeping patterns, psychomotor retardation or agitation, reduced energy levels, feelings of guilt and worthlessness, reduced concentration/decision making, ideas or acts of self harm or suicide	
* Most typical (ICD-10) or core (DSM-IV) symptoms			
Depressive episode		**Major depressive disorder, single episode**	
Mild: 4 symptoms including at least 2 of the most typical symptoms and some difficulty in continuing with usual activities	F32.0	Mild severity: few if any symptoms beyond 5 (including at least one core symptom); mild level of disability or the capacity to function normally but with substantial and unusual effort	296.21
Moderate: 5 or 6 symptoms including at least 2 of the most typical symptoms; usually considerable difficulty in continuing with usual activities	F32.1	Moderate severity: severity and disability intermediate between mild and severe	296.22
Severe: at least 7 symptoms, some severe, including all 3 of the most typical symptoms; very unlikely that that the sufferer can continue with usual activities	F32.2	Severe: several symptoms beyond 5 (including at least one core symptom); with clear-cut, observable disability	296.23
Severe with psychotic features: as F32.2, with psychotic symptoms (e.g., delusions, hallucinations and stupor)	F32.3	Severe with psychotic features: as 296.23, with psychotic symptoms (e.g., delusions or hallucinations)	296.24
		Unspecified	296.20
Other Includes atypical depression	F32.8	In partial remission: some symptoms of MDE are present but full criteria no longer met; or there are no longer any significant symptoms but period of remission is less than 2 months in duration	296.25
Unspecified	F32.9		
		In full remission: ≥2 months without any symptoms	296.26

ICD-10 classification		DSM-IV classification	
Recurrent depressive disorder		Major depressive disorder, recurrent	
Mild: at least one previous episode, current episode as F32.0	F33.0	Mild: at least one previous episode, current episode as 296.21	296.31
Moderate: at least one previous episode, current episode as F32.1	F33.1	Moderate: at least one previous episode, current episode as 296.22	296.32
Severe: at least one previous episode, current episode as F32.2	F33.2	Severe: at least one previous episode, current episode as 296.23	296.33
Severe with psychotic features: at least one previous episode, current episode as F32.3	F33.3	Severe with psychotic features: At least one previous episode, current episode as 296.24	296.34
Other	F33.8	Unspecified	296.30
Unspecified	F33.9	In partial remission: at least one previous episode, current episode as 296.25	296.35
Currently in remission: at least two previous episodes, but has had no symptoms for several months	F33.4	In full remission: at least one previous episode, current episode as 296.26	296.36

Figure 1.1 Characterization of a major depressive disorder. MDE, major depressive episode. Adapted from [4] and [5].

episodes of depression without any history of independent episodes of mood elation and hyperactivity. They subdivide the depressive episode category according to severity as being mild (at least two of the most typical symptoms of depression and two other symptoms), moderate (at least two of three most typical symptoms of depression and three or four other symptoms), or severe (all three most typical symptoms of depression and at least four other symptoms) (Figure 1.1). ICD-10 also accepts duration of symptoms of less than 2 weeks if the symptoms are unusually severe or of rapid onset.

There are several subtypes of depression that are described in the DSM-IV as specifiers to denote that they are subcategories of MDEs:

- *Dysthymia* describes a less severe, chronic, and persistent disorder. The DSM-IV diagnosis of dysthymia requires depressed mood to be present for most of the day, nearly every day, for a period of more than 2 years. The symptoms of dysthymic disorder differ from those of MDD by slower onset, longer duration and persistence, and lower severity. The mildest forms of depression are sometimes termed "subsyndromal depression."
- *Chronic* describes an MDE of more than 2 years in duration.

- *With melancholic features* describes a condition of extremely severe anhedonia – the almost complete loss of interest in and lack of reactivity to usually pleasurable activities. In addition, there must be three or more of the following features:
  - a distinct quality of depressed mood that differs from the kind of feeling following a loss
  - depression that is worse in the morning
  - early morning awakening
  - marked psychomotor agitation or retardation
  - significant appetite and/or weight loss
  - inappropriate or excessive guilt.
- *Catatonic features* describes an MDE with at least two of the following:
  - catalepsy or stupor
  - excessive and purposeless motor activity
  - postural rigidity or mutism
  - posturing, stereotyped movements, prominent mannerisms, or grimacing
  - echolalia or echopraxia.
- *Atypical features* denotes the presence of mood reactivity; i.e., the ability for the depressed individual's mood to brighten in response to actual or potential positive events, along with two or more of the following:
  - hyperphagia
  - hypersomnia
  - leaden paralysis
  - a long-standing pattern of interpersonal rejection sensitivity that results in significant social or occupational impairment (a trait with an early onset that persists throughout life).
- *Psychotic features*: the presence or absence of such features is specified according to whether they are consistent with depressive themes, termed "mood-congruent features," as opposed to mood-incongruent features, which are less common – persecutory delusions, thought insertion/withdrawal delusions, thought broadcasting, or control delusions. Furthermore, the *onset* of an MDE can be described by the presence or absence of preceding *dysthymia* or *postpartum* status if the episode begins within 4 weeks of delivery.
- *Seasonal features* describes a course of depressive illness characterized by specific onset and remission of symptoms associated with characteristic times of the year. Most commonly, depressive symptoms manifest in fall/autumn and/or winter and spontaneously remit in spring or summer. To qualify for this diagnosis, in the last 2 years there must be two MDEs

demonstrating a temporal relationship and the individual cannot have more nonseasonally than seasonally related MDEs.

Several outcomes have been described to characterize an individual's treatment trajectory (see Figure 8.1). The most serious consequence of depression is the increased risk of suicide; for example, Bostwick and Pankratz [6] examined patients with affective disorders and estimated the lifetime prevalence of suicide in those hospitalized with suicidal ideation as 8.6% and for those hospitalized without suicidal ideation as 4.0%. The lifetime suicide prevalence for mixed inpatient/outpatient populations was 2.2%, and for the nonaffectively ill population less than 0.5%. These data demonstrate that there is an increased risk of suicide with increasing intensity of suicidal ideation and suggest that suicide risk increases with depressive illness severity.

Causes of depression

Dualistic theories separating mind and brain are being replaced with more integrated models that consider the biological, psychological, and social influences that produce depression. Kandel's understanding of mind–brain interactions provides a model for understanding the nature and possible causes of depression [7], particularly:

- All mental processes derive from the brain.
- Genes and their protein products determine neuronal connections and functioning.
- Life experiences influence gene expression and psychosocial factors feed back to the brain.
- Altered gene expression that produces changes in neuronal connections contributes to maintaining abnormalities of behavior.
- Psychotherapy produces long-term behavior change by altering gene expression.

Therefore, both genetic and environmental factors are implicated in the etiology and treatment of depression. Recent advances in the study of the genetic basis of depression have produced interesting findings, such as a functional polymorphism of the serotonin transporter gene, which can be used to predict selective serotonin reuptake inhibitor (SSRI) response in the context of life stress [8]. Thus, depression can be understood to be the consequence of life stress interacting with heritable genetic and personality vulnerabilities that produce physiological and psychological dysfunction.

The prolonged exposure to stress produces characteristic alterations in brain neurotransmitter function often described as a "chemical imbalance."

This refers to alterations in the major chemical messenger systems responsible for neuronal transmission: serotonin (5HT), norepinephrine/noradrenaline (NE), and dopamine (DA). Depression has been associated with reductions in neurotransmission in these systems and currently available antidepressant medications are thought to work by reversing these deficits [9]. The alterations in these neuronal systems produce the characteristic psychological and somatic symptoms characteristic of depression (see Chapter 3).

Other theories of the etiology of depression derive from the perspectives of their discipline; e.g., the interpersonal theory examines interpersonal stress and role transition as causes of depression. The cognitive model posits that dysfunctional thoughts foster depression and reinforce behaviors that promote the depressive state. The dynamic model focuses upon unconscious psychological conflict with the goal of the individual achieving insight or needed support. One very interesting model has been proposed by Brown and colleagues (Figure 1.2), who describe mechanisms responsible for the onset, provocation, and perpetuation of depression [10]. A "severe life event" can provoke the onset of an MDE. Proximal risk factors mediate the onset of the depressive episode, and distal risk factors both mediate the proximal risk factors and foster the perpetuation of a chronic illness course.

Modeling onset and course of depressive episodes

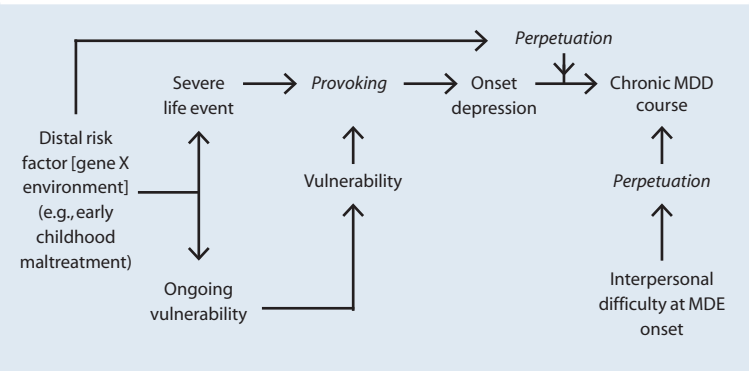

Figure 1.2 Modeling onset and course of depressive episodes. This model proposes mechanisms that are responsible for the onset, provocation, and perpetuation of depression. A "severe life event" can provoke the onset of a major depressive episode (MDE). Proximal risk factors (e.g., a poor quality interpersonal relationship) mediate the onset of the depressive episode. Distal risk factors (e.g., early childhood maltreatment) both mediate the proximal risk factors (life events and ongoing vulnerabilities) and foster the perpetuation of a chronic illness course. Adapted from [10].

In addition, there are many medical diseases that commonly manifest with symptoms of depression (Figure 1.3), and many drugs can also produce depressive symptoms as adverse effects (Figure 1.4). Several other psychiatric diseases can also present with symptoms of depression, including schizophrenia, anxiety disorders, eating disorders, and substance abuse.

Diseases commonly associated with depressive symptoms	
Brain trauma/brain tumor	Lyme disease
Cancer (especially pancreatic)	Multiple sclerosis
Cardiovascular disease	Normal pressure hydrocephalus
Dementia	Parkinson's disease
Diabetes	Pellegra
Epilepsy	Porphyria
HIV/AIDS	Rheumatoid arthritis
Huntington's disease	Stroke
Hyperthyroidism	Syphilis
Hypothyroidism	Systematic lupus erythematosus
Hyperparathyroidism	Wilson's disease
Hypoparathyroidism	

Figure 1.3 Diseases commonly associated with depressive symptoms

Drugs that may cause depression	
Anticancer agents	Hormones
Interferon-α	Estrogen
Vincristine sulfate	Progesterone
Vinblastine sulfate	
	Opioids
Antihypertensive agents	Codeine
Clonidine hydrochloride	Morphine
Guanethidine sulfate	
Methyldopa	Alcohol
Propranolol hydrochloride	
Reserpine	Anticholinergics
	Benztropine
Antiparkinsonian agents	
Amantadine hydrochloride	Barbiturates
Bromocriptine	Phenobarbital
Levodopa	Secobarbital
Levodopa and carbidopa	
	Benzodiazepines
Antituberculosis agents	
Cycloserine	
Corticosteroids	
Cortisone acetate	

Figure 1.4 Drugs that may cause depression

Epidemiology and natural history

MDD is a highly prevalent disorder. The most recent US estimates of the prevalence were 16.2% for lifetime and 6.6% for the 12 months before the survey. The age of onset varies with birth cohorts (Figure 1.5), with a fairly low risk until the teenage years, after which it rises in a linear fashion, and more steeply in more recent age cohorts. Prevalence seems to be lower outside the US and varies between countries, but global rates are still high, with one meta-analysis of 23 studies from countries across Europe, Asia, North and South America, and Australasia finding pooled rates of 6.7% lifetime prevalence and 4.1% 12-month prevalence [11]. Depressive disorders are the fourth most important cause of disability worldwide, and are expected to become the second most important cause by 2020 [1,2]. Sociodemographic correlates of increased risk of MDD in the USA include age, female gender, nonwhite race/ethnicity, employment status, not being married, having less education, lower income, and urbanicity. Nearly all MDD respondents reported at least some role impairment and three-quarters of respondents with lifetime MDD reported at least one comorbid medical disorder [12]. A recent representative clinical sample has revealed that MDD is often chronic, severe, and with substantial clinical comorbidity; for example, two-thirds of individuals in the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness study reported at least one concurrent general medical condition [13]. MDD is usually an episodic disorder with an episode occurring on average every 5 years; however, 20–33% of individuals suffer a chronic and unremitting course [14]. Those individuals who do not achieve a complete remission of symptoms are more likely to experience a relapse [13,15]. Longer depressive episodes appear to be more difficult to treat and individuals with low levels of depressive symptoms are about three times more common than individuals with MDD level symptoms [16].

Approximately 20–33% of patients who experience an MDE have a course defined by early onset and chronic dysthymic course [17]. The National Comorbidity Survey of the US population found a 12-month prevalence of 2.5% for dysthymia with a lifetime prevalence of 6.4%, and about 3% for chronic depression [18]. Individuals with chronic major depression experience an earlier age of onset, increased axis II comorbidity, likelihood of experiencing an early trauma history, and genetic familial loading for depressive illness, less effective coping strategies, more chronic stress, less social support, marked impairment in psychosocial function and work performance, and increased healthcare utilization [19–21].

MDD with melancholic features is distributed equally among men and women, and is more likely in older individuals and those experiencing psychotic features (DSM-IV). Atypical features are twice as common in women

as in men, and individuals with these features have an earlier age of onset and a more persistent, less episodic, and more chronic course (DSM-IV).

Postpartum depression is the most common complication of childbearing and occurs in 13% of women after delivery [22]. The prevalence of winter-type seasonal depression varies with increased rates with higher latitude and younger age. Women make up 60–80% of those with this disorder (DSM-IV).

Cumulative lifetime prevalence of CIDI/DSM-IV major depressive disorder by birth cohort

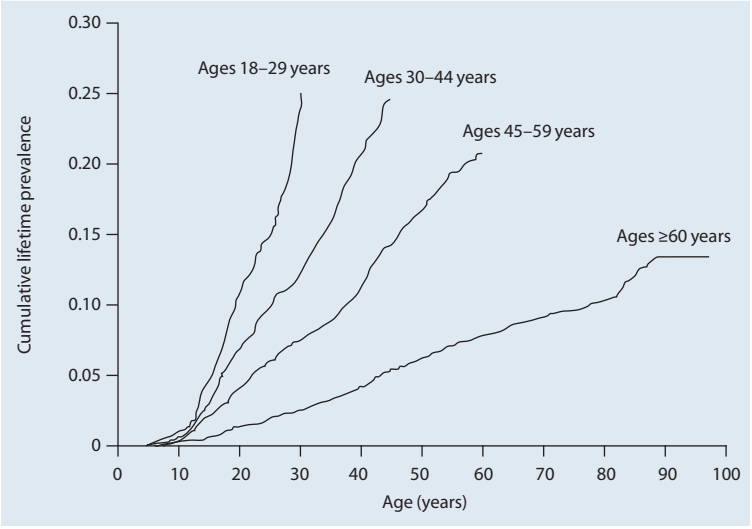

Figure 1.5 Cumulative lifetime prevalence of CIDI/DSM-IV major depressive disorder by birth cohort. CIDI, Composite International Diagnostic Interview. Adapted with permission from [12].

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Chapter 2

Depression in different types of patients

Timothey Denko and Edward S Friedman

Depression in children

Depression has been estimated to have a prevalence in children of 2.5% and in adolescents of 4–8% [1]. The presentation of symptoms of depression in young people is, to a large extent, similar to that of adults, especially with respect to the presence of neurovegetative symptoms of depression. Decline in psychosocial performance (primarily in school) and reduced interest in previously enjoyed activities may be more easily detected signs that a younger individual is experiencing symptoms of depression. In addition, irritability may be more common in depressed children and adolescents than in depressed adults.

In 2003, the UK Medicine and Healthcare products Regulatory Agency (MHRA) concluded that all SSRIs, with the exception of fluoxetine, were contraindicated in the treatment of depression in young people, due to an increase in suicidal ideation, as well as dubious efficacy. In 2004, the US Food and Drug Administration (FDA) issued a "black box warning" concerning an increased risk of suicidal ideation and behavior in people under the age of 18 treated with second-generation antidepressants.

The primary analysis of randomized controlled trials (RCTs) of SSRIs that led to the FDA "black box warning" revealed an increase over baseline of roughly 2% (placebo 2% versus 4%) in suicidal ideation or behavior in people under the age of 18 given an SSRI. No children completed suicide in the RCTs included in this analysis. The difference in suicidal ideation leads to a number needed to harm (NNH) of 50. A subsequent meta-analysis of 27 RCTs of SSRIs in children and adolescents with depression, obsessive–compulsive disorder, and other anxiety disorders [2] again found no completed suicides and a smaller increase in suicidal ideation/self harm attempts with SSRIs, corresponding to an NNH of 143. The validity of using "suicidality" (meaning suicidal behaviour, ideation, or attempts) as a surrogate for suicide, as in these studies, has been criticized [3], given the relatively high incidence of suicidality in comparison to

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completed suicide. Studies of the efficacy of SSRIs in children and adolescents suggest a number needed to treat (NNT) of 5 for fluoxetine and 9 for SSRIs overall [4]. The Texas Medication Algorithm Project (TMAP) [5] considers fluoxetine, citalopram, and sertraline to be first-line medications for treatment of depression in children and adolescents, and the relatively small increase in suicidal ideation to be less significant than the benefit from treating them with SSRIs. Fluoxetine is the most highly recommended, and is still the only FDA-approved SSRI for the treatment of depression in those aged under 18. Paroxetine should be avoided in pre-adolescents.

Second-generation antidepressants such as bupropion, venlafaxine, duloxetine, and mirtazapine have little evidence to support their use in children and adolescents, and should be considered second- or third-line choices for pharmacologic treatment: the younger the child, the less the therapeutic benefit gained from second-generation antidepressants.

Alternatively, evidence-based psychotherapies such as cognitive–behavioral therapy (CBT) are also recommended, either singly or together with medication, in the treatment of depression in younger people. The combination of fluoxetine and CBT showed the most robust response in the Treatment of Adolescents with Depression Study (TADS) when compared with CBT alone or fluoxetine alone in moderately to severely depressed adolescents [6]. Fluoxetine outperformed CBT alone in this study. However, other studies [7–9] have found the combination of CBT and an SSRI to have no greater efficacy than the SSRI alone.

Depression in elderly people

The prevalence of MDDs (i.e., meeting full DSM-IV criteria) is thought to decrease with increasing age [10]. Unfortunately, rates for completed suicide increase with advancing age, to the point that people over the age of 86 have the highest suicide rate of any age group [11]. Medical burden, loss of loved ones, decreased independence, and financial hardship are thought to contribute to the likelihood of a depressive episode in elderly people.

There are difficulties in diagnosing depression in elderly people because they tend to report somatic complaints much more readily than sad mood. Other cardinal symptoms of depression, such as sleep disturbance and/or alterations in appetite or energy, can also be nonspecific changes that are common in normal aging. Depression is often comorbid with cardiovascular disease in elderly adults, and it has been suggested that circulatory problems can actually cause depressive symptoms, possibly by affecting the flow of blood to the brain. This type of depression has been termed “vascular depression,”

although this disorder is not yet recognized by the standard guidelines. *Clinically significant depression* is a category meant to capture older adults with less than full DSM-IV depressive episodes, but still meaningful depression. This diagnosis is thought to be much more common than MDD. Symptoms that can aid in identifying the depressed older adult include decreased interest (anhedonia) and social withdrawal in individuals who were previously engaged and interested in activities. Treatment in this age group is discussed in Chapter 4.

Depression in women

Women have close to twice the lifetime prevalence of depressive disorders of men [10]. Nearly all of this increased susceptibility to depression occurs during the childbearing years, from menarche to menopause. A number of variables, both psychosocial and biological, may contribute to these disparate rates of depression. As increased rates of depression in women follow ovarian function closely, estrogen has been extensively studied as a mediator of depression in women, and is, therefore, a potential agent for the treatment of depression. To date, studies of estrogen in the treatment of depression in perimenopausal and postmenopausal women have not yielded consistent findings of benefit, and ovarian hormones are not included in standard treatment recommendations for this group [12].

Depression during pregnancy can be difficult to detect, because many of the neurovegetative signs of depression are common in pregnancy. The rate of depression in pregnant women is thought to be similar to that of nonpregnant women. *Postpartum depression* follows one in eight deliveries, and can be differentiated from the benign "baby blues" by duration and severity of symptoms, and the negative impact on maternal psychosocial function. Conversely, the "baby blues" should be limited to 10 days after delivery, and psychosocial functioning should be reasonably preserved. The treatment of postpartum depression mirrors the treatment of standard depression.

Outside the reproductive-cycle–associated increase in prevalence of depression in women, few other compelling differences have been identified when comparing depression in women and men. In the STAR*D study, clinical characteristics of 2541 outpatients with major depression were compared by gender. Two-thirds of the sample were women. Women had greater symptom severity but men had more MDEs. Women were found to have greater rates of an anxiety disorder, bulimia, and somatoform disorders, as well as more suicide attempts, whereas men showed more alcohol and substance use disorders. Irritability was equally common in men and women [13].