

Handbook of Depression

Second edition

Edward S Friedman

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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 staff of the Western Psychiatric Institute and Clinic (WPIC) of the University of Pittsburgh Medical Center. He was 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. He was the National Cognitive Therapy Director for the landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D). As Primary Investigator at the Pittsburgh site for the Bipolar Treatment Network, Dr Friedman contributed to the multi-site LITMUS and CHOICE-BP studies. Currently, Dr Friedman is an Emeritus Clinical Associate Professor of Psychiatry, University of Pittsburgh School of Medicine, Department of Psychiatry and he maintains a private practice in Pittsburgh Pennsylvania, USA.

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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 guidelines for depression.

Preface

Preface to first edition:

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.

Preface to second edition:

The second edition of the *Handbook of Depression* has been prompted by the publication of American *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) and the need to update the sections on diagnostic criteria. We have also taken the opportunity to correct mistakes that crept into the first edition and to update elsewhere where necessary, including the chapter on antidepressants. We hope that this new edition will continue to provide an up-to-date balanced summary of current thinking and knowledge about depression and its treatment.

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 affective lability 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, empty, or irritable mood and varying degrees of other somatic and cognitive changes [3]. According to the *American Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) [4], disturbance of mood is the predominant feature of mood disorders. They are further divided into major depressive disorder (MDD), disruptive mood dysregulation disorder (for children aged up to 18 years), persistent depressive disorder (dysthymia; DD), premenstrual dysphoric disorder, substance-induced depressive disorder, depressive disorder due to another medical condition, as well as other and unspecified depressive disorder categories 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 discrete period during which an individual experiences clear-cut changes in affect, cognition, and neurovegetative functions to a moderate degree for 2 weeks or longer with a diminution of their previous level of functioning (see Figure 1.1) [4,5].

Premenstrual dysphoric disorder refers to mood episodes that present during the majority of menstrual cycles over the preceding year, characterized by onset during the week before menses and improvement within a few days of the onset of menses. Women must exhibit one (or more symptoms) of:

- marked affective lability, irritability;
- marked irritability, anger, or increased interpersonal conflicts;
- marked depressed mood, feelings of hopelessness, or self-deprecating thoughts;
- marked anxiety, tension, or feelings of being "keyed-up"; and
- one (or more of the following symptoms):
 - anhedonia;
 - subjective difficulty in concentration;
 - fatigue or lethargy, lack of energy;
 - marked changes in appetite; overeating; specific food cravings
 - hypersomnia or hyposomnia
 - sense of being easily overwhelmed or out of control
 - breast tenderness, swelling, bloating, or weight gain.

Persistent depressive disorder (dysthymia) consolidates the diagnosis of dysthymia and chronic depression. These disorders are characterized by the persistence of symptoms for at least 2 years. Symptoms must include depressed mood for most of the day, more days than not, and two (or more) of the following symptoms:

- poor appetite or overeating;
- hypersomnia or hyposomnia;
- low energy or fatigue;
- low self esteem; or
- feelings of hopelessness.

Characterization of a major depressive disorder			
ICD-10 classification		DSM-5 classification	
Criteria symptoms: at least 2 weeks of lowered mood*, anhedonia*, reduced energy*, reduced concentration, sleep disturbances, reduced appetite, self-confidence reduced, 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-5) symptoms			
Depressive episode		Major depressive disorder, single episode	
Mild: Four symptoms including at least two of the most typical symptoms and some difficulty in continuing with usual activities	F32.0	Mild severity: few if any symptoms beyond five (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: Five or six symptoms including at least two 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 seven symptoms, some severe, including all three of the most typical symptoms; very unlikely that the sufferer can continue with usual activities	F32.2	Severe: several symptoms beyond five (including at least one core symptom); with clear-cut, observable disability	296.23
Severe with psychotic features: as F32.2, with psychotic symptoms (eg, delusions, hallucinations, and stupor)	F32.3	Severe with psychotic features: as 296.23, with psychotic symptoms (eg, delusions or hallucinations)	296.24
Other Includes atypical depression	F32.8	Unspecified	296.20
Nonspecified	F32.9	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
		In full remission: ≥ 2 months without any symptoms	296.26

Figure 1.1 Characterization of a major depressive disorder (continues overleaf).

Characterization of a major depressive disorder (continued)			
ICD-10 classification		DSM-5 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
Nonspecified	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 (continued). MDE, major depressive episode. DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ICD-10, International Classification of Mental and Behavioral Disorders, 10th revision Adapted from American Psychiatric Association[4] and World Health Organization [5].

Disruptive mood dysregulation represents a syndrome of irritability and frequent episodes of behavioral dyscontrol in children under 12 years of age.

Other specified depressive disorder is a category that applies to depressive episodes that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning, but do not meet the full criteria for another depressive disorder. Examples of such presentation include recurrent brief depression, short-duration depressive episodes (4–13 days), and depressive episode with insufficient symptoms.

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 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). The 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-5 as specifiers for depressive disorders. *With anxious distress* is used when two (or more) of the following symptoms are present:

- feeling keyed-up and tense; restless;
- feeling restless;
- difficulty concentrating due to worrying;
- fear that something awful will occur;
- fear of loss of control.

If 2 symptoms occur, it is mild; 3 symptoms is moderate; 4–5 symptoms is severe; and 4–5 symptoms plus motor agitation is severe.

With mixed features is used when at least 3 symptoms of manic/hypomanic episodes are present nearly every day during an MDE. These symptoms include:

- elevated/expansive mood;
- inflated self esteem or grandiosity;
- pressured speech;
- flight of ideas; racing thoughts;
- increased goal-directed activity
- increased involvement in high-risk activities;
- decreased need for sleep.

Of note, mixed features are a risk factor for developing bipolar disorder; using this specifier, when applicable, may help the clinician in treatment planning and pharmacologic monitoring for the possibility of antidepressant-induced mood switch.

With catatonia can be added to an MDE where the clinical picture is dominated by three (or more) of the following symptoms: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerism, stereotypy, agitation, grimacing, echolalia, and exchopraxia.

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 at the most severe stage of the illness:

- 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.

Atypical features denotes the presence of mood reactivity; (ie, 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).

With 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.

With peripartum: an episode of depression that occurs during pregnancy or in the 4 weeks following 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.

Specify *in partial remission* when symptoms of the MDE are present, but full criteria are not met, or there is a period lasting less than 2 months without any significant symptoms following the end of the MDE.

Specify *in full remission* when, during the past 2 months, there have been no significant symptoms or signs of MDE.

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 (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 (eg, 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.

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.

Modeling onset and course of depressive episodes

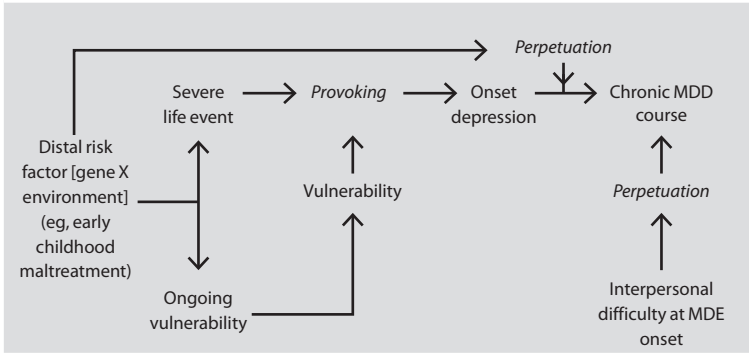


Figure 1.2 Modeling onset and course of depressive episodes. This model proposes mechanisms that are responsible for the onset, provocation, and perpetuation of depression. A “severe life event” can provoke the onset of a major depressive episode (MDE). Proximal risk factors (eg, a poor quality interpersonal relationship) mediate the onset of the depressive episode. Distal risk factors (eg, early childhood maltreatment) both mediate the proximal risk factors (life events and ongoing vulnerabilities) and foster the perpetuation of a chronic illness course. MDD, major depressive disorder. Reproduced with permission from Brown et al [10] ©Elsevier.

Common diseases associated with depression 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	Systemic lupus erythematosus
Hyperparathyroidism	Wilson's disease
Hypoparathyroidism	

Figure 1.3 Common diseases associated with depression symptoms

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, with a fairly low risk until the teenage years, after which it rises in

Drugs that may be associated with 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 be associated with depression

a linear fashion, and more steeply in more recent age cohorts [11]. Prevalence seems to be lower outside the USA 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 [12]. 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 [11].

A recent representative clinical sample has revealed that MDD is often chronic, severe, and with substantial clinical comorbidity; eg, 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 health care utilization [19–21].

MDD with melancholic features are more frequent in inpatients (as opposed to outpatients), are more likely to occur in more severe MDEs, and are more likely in those experiencing psychotic features (DSM-5).

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-5)[4].

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Depression in different types of patients

Timothy 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 selective serotonin reuptake inhibitors (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% vs 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 completed suicide. Studies of the efficacy of SSRIs in children and adolescents suggest a number needed to treat (NNT) of five for fluoxetine and nine 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 major depressive disorders (MDDs; ie, meeting full *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition [DSM-5] 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-5 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.

Premenstrual dysphoric disorder occurs in women that experience severe depressive symptoms, irritability, and tension before menstruation. The symptoms are only present in the final week before menses, show improvement within a few days after the onset, and are then minimal or completely absent in the weeks following [13].

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 major depressive episodes (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 [14].

Patients with comorbid medical conditions

Depressive disorders occur more frequently in people with chronic medical conditions, and are associated with poorer long-term outcomes [15]. Disorders of the central nervous system (CNS), such as Parkinson’s disease, dementia, cerebrovascular disease (post-stroke depression [PSD], vascular dementia), and multiple sclerosis all have strong associations

with depressive disorders. Chronic medical illnesses not directly affecting the CNS, such as human immunodeficiency virus (HIV), cancer, coronary artery disease, and autoimmune disorders have also been associated with higher rates of depressive disorders [16-18]. Identifying a mediator and a direction of association for these findings has been difficult.

PSD is estimated to occur in approximately one-third of patients within 9 months of having a cerebrovascular accident (CVA). It can be difficult to diagnose and can mimic symptoms of depression; for example, individuals with aphasia are unable to complete a clinical interview; individuals with anosognosia may be unaware of their deficits; or individuals with physical limitations that impair ability to engage in hedonic activities may seem to be anergic. PSD is related to poor functional outcomes, as well as poor cognitive outcomes, and its successful treatment is thought to lead to significant improvement in both cognition and function.

Depression has been linked to cardiovascular disease, as both a risk factor for developing heart disease and a predictor of increased mortality in patients with heart disease [17]. Mediators of such an association may include inflammatory cytokines, increases in platelet thrombus formation, or alterations in sympathetic and parasympathetic tone to the cardiac conduction system.

Depression is estimated to occur in 24% of patients diagnosed with cancer [18]. Of course, this is a highly heterogeneous group representing many types of malignancies. Pancreatic, head and neck, and breast cancer appear to have the highest rates of associated depression [19]. Factors that can affect the emergence of depressive disorders can include the severity of the illness, disfigurement, and effects of treatment – surgical, radiation, or chemotherapeutic. Conversely, as depression is thought to lower immune system function, people with depression may be at higher risk for some type of cancer [20]. Successful treatment of depression in these populations can improve quality of life as well as medical outcome.

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Diagnosis

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Signs and symptoms of depression

Depression is characterized by symptoms that generally fall into two categories: psychological, and somatic (or physical). The former are characterized by a persistent sense of sadness, termed “dysphoria,” and a persistent state of lack of usual enjoyment or pleasure in previously pleasurable activities, termed “anhedonia.” Depressed individuals with dysphoria describe themselves as being helpless and hopeless, discouraged, “blue,” “fed up,” “down in the dumps,” and “useless.” They are often easily tearful, irritable, or frustrated because they tend to have negatively biased perceptions about themselves and others to whom they relate, and a pessimistic view of their future, often manifesting as inappropriate guilt. The most serious symptom of depression with respect to mortality and morbidity is suicidal behavior [1]. The most benign type of suicidal thinking – that “life is not worth living” – is consonant with beliefs that their lives are hopeless, they are helpless and worthless, and have no chance for future betterment. Suicidal thinking with plans to harm oneself (or others) indicates a higher level of potential risk, which is greatest when the individual is contemplating acting on the plans or has demonstrated behavior in furtherance of the suicidal thinking. Proximal risk factors for suicide include agitation, current suicidal intent or plan, severe depression and/or anhedonia, instability (eg, alcohol abuse or decline in health), recent loss, and availability of a lethal agent. Distal risk factors include

current suicidal intent with plan, personal or family history of suicide, aggressive or impulsive behavioral pattern (including possible bipolar disorder, especially if associated with psychosis), poor response to treatment for depression, poor treatment alliance, a history of abuse or trauma, and/or substance or alcohol abuse [2]. The most common risk factors for suicide are summarized in Figure 3.1 [3].

Somatic symptoms of depression include alterations from normal sleep, termed “insomnia” when reduced (mild if <30 min, moderate if >30 min but <120 min, and severe if >120 min to fall asleep) and, when increased, termed “hypersomnia” (mild if >30 min, moderate if >30 but <120 min, and severe if >120 min). Insomnia is characterized by difficulties arising in the sleep cycle: difficulty in falling asleep, sleep continuity disturbance or midnight awakening, and early morning awakening. Unusual increases or decreases in appetite are common, as well as corresponding fluctuations in weight. Psychomotor changes may manifest as psychomotor activity: agitation, anxiety, and/or hyperactivity. Less frequently, individuals may present with psychomotor retardation: decreased activity, slowed thought processes, and a reduction in content and process (mutism) – termed

Risk factors for suicide: “sad person” scale	
S	Sex: more than three males for every female kill themselves
A	Age: older < younger, especially white males
D	Depression: a depressive episode precedes suicide in up to 70% of cases
P	Previous attempt(s): most people who die from suicide do so on their first or second attempt. Patients who make multiple (≥4) attempts have increased risk of future attempts rather than suicide completion
E	Ethanol use: recent onset of ethanol or other sedative-hypnotic drug use increases the risk and may be a form of self-medication
R	Rational thinking loss: profound cognitive slowing, psychotic depression, pre-existing brain damage, particularly frontal lobes
S	Social support deficit: may be result of the illness that can cause social withdrawal
O	Organized plan: always need to inquire about presence of a plan when treating a depressed patient
N	No partner: again, may be a result rather than a cause of the depressive disorder, but nevertheless absence of a partner or significant other is a risk factor
S	Sickness: intercurrent medical illnesses

Figure 3.1 Risk factors for suicide: “sad person” scale. Reproduced with permission from Preskorn [3] ©Professional Communications, Inc.

“catatonia” in its extreme presentation. Some individuals report lack of energy and persistent fatigue, often accompanied by lack of motivation and inability to initiate tasks.

The International Classification of Mental and Behavioral Disorders, 10th revision (ICD-10) system considers sad mood, anhedonia, and reduced energy leading to fatigue to be the three typical symptoms of depression [4]. The other common symptoms of depression include reduced concentration or attention, reduced self esteem and self-confidence, ideas of guilt and worthlessness, a pessimistic view of the future, thoughts of self-harm or suicide, disturbed sleep, and decreased appetite. The classification for a depressive episode in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and ICD-10 systems are summarized in Figure 1.1.

Differential diagnosis

Depressive episodes must be differentiated from other general medical conditions (DSM-5 category mood disorders due to another medical condition), substance/medication-induced mood disorders (DSM-5 substance-induced mood disorder), and other psychiatric disorders [5].

Other medical conditions that may present with symptoms characteristic of depression are listed in Figure 1.3, and include cerebrovascular, endocrine, metabolic, neurological, and infectious disorders. In addition, more than half of the depressed individuals in the ecologically valid Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study reported co-occurring general medical conditions [6]. If there is such a general medical disorder and major depressive disorder (MDD) is not judged to be the direct physiological consequence of this condition, DSM-5 suggests coding the MDD as the psychiatric disorder and the general medical condition as a medical disorder, suggesting no etiological connection between the two conditions.

Individuals may present with symptoms characteristic of depression caused by ingestion of a drug of abuse, medication, or toxin – DSM-5 substance-induced mood disorders [5]. Figure 1.4 lists common medications that can produce depressive symptoms. Individuals who present with depressive symptoms while using drugs of abuse, such as cocaine,

methamphetamine, and opioids, require detoxification to determine if there is a co-occurring depressive episode before a depressive diagnosis can be made. The very common condition of co-occurring mood and substance abuse disorders is termed “dual diagnosis.” If the depressed mood occurs only in the context of withdrawal from a substance, it is considered substance-induced mood disorder with depressive features [5].

Other psychiatric illnesses may also present with signs and symptoms associated with depression. In its acute presentation, a depressive disorder with mood-congruent psychotic features, hallucinations, and/or thought disorder may be difficult to distinguish from schizophrenia or schizoaffective disorder. Other information, such as illness history and course, the individual’s premorbid history, and family history, may aid in making a differential diagnosis. Due to cognitive impairment, dementia may also be difficult to distinguish from depression. Often, depression in elderly people can be masked by apparent dementia (ie, the pseudodementia of depression) and the prominent cognitive impairment resolves with remission of the depressive episodes. On the other hand, dementia must be ruled out in elderly people presenting with depression through medical and laboratory evaluation, an examination of the premorbid history, the commonality of onset of depressive and cognitive symptoms, the course of illness, and the response to antidepressants. Depressive episodes can also be confused with normal grief reactions and bereavement after the death of a loved one. Bereavement may resemble a major depressive episode (MDE) but may be distinguished by the variable intensity of the symptoms (versus their persistence in an MDE), the overarching feelings of loss and emptiness (versus persistent anhedonia and dysphoria), and sad thoughts focused on the deceased (versus thoughts of one’s own worthlessness and hopelessness). If intense symptoms of bereavement do persist for more than 12 months, a diagnosis of Persistent Complex Bereavement Disorder can be considered.

The patient examination and interview

A proficiently performed psychiatric interview will provide the patient and clinician with a specific and accurate diagnosis, while ideally establishing a caring relationship based on mutual respect and collaboration.

The interview should start with an empathic statement by the psychiatrist of the goals of the examination and how that will aid the patient. Inquiring after patients' reasons for the examination in their own words and determining a chief complaint in an empathic and relaxed manner may help put patients at ease and will foster cooperation, which enhances the accuracy of the clinical data obtained.

A history of the present episode should include a complete description of duration, intensity, and extent of the depressive symptoms. To aid in this process the use of clinical self-assessment instruments can be extremely helpful in gathering this information, as well as for the purposes of monitoring the progress of symptomatic improvement. Figure 3.2 presents one such instrument – the Quick Inventory of Depressive Symptomatology – Self Rated, 16 Items (QIDS-SR₁₆) [7]. Other rating scales are briefly presented in Figure 4.2. The QIDS-SR16 was used in the ecologically valid, large-scale STAR*D study [8] as a component of measurement-based care – the use of depressive measures to determine medication dosage increases and measures of side effects to determine medication dosage reductions (see the STAR*D website at www.edc.gsph.pitt.edu/stard to download the QIDS-SR16 and the FISER [Frequency, Intensity and Side Effect Rating] scale). Utilizing such tools, equally good depression outcomes were achieved by psychiatrists and family practitioners. The QIDS-SR₁₆ quantifies the somatic and psychological symptoms of

STAR*D QIDS-SR16

Choose the response to each item that best describes you for the past 7 days

1. Falling asleep (during the past 7 days)

- 0 I never take longer than 30 minutes to fall asleep.
- 1 I take at least 30 minutes to fall asleep, less than half the time.
- 2 I take at least 30 minutes to fall asleep, more than half the time.
- 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep during the night (during the past 7 days ...)

- 0 I do not wake up at night.
- 1 I have a restless, light sleep with a few brief awakenings each night.
- 2 I wake up at least once a night, but I go back to sleep easily.
- 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

Figure 3.2 STAR*D QIDS-SR16 (continues overleaf)

STAR*D QIDS-SR16 (continued)

Choose the response to each item that best describes you for the past 7 days

3. Waking up too early (during the past 7 days)

- 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
- 1 More than half the time, I awaken more than 30 minutes before I need to get up.
- 2 I almost always awaken at least 1 hour or so before I need to, but I go back to sleep eventually.
- 3 I awaken at least 1 hour before I need to, and can not go back to sleep.

4. Sleeping too much (during the past 7 days)

- 0 I sleep no longer than 7–8 hours/night, without napping during the day.
- 1 I sleep no longer than 10 hours in a 24-hour period, including naps.
- 2 I sleep no longer than 12 hours in a 24-hour period, including naps.
- 3 I sleep longer than 12 hours in a 24-hour period, including naps.

5. Feeling sad (during the past 7 days)

- 0 I do not feel sad.
- 1 I feel sad less than half the time.
- 2 I feel sad more than half the time.
- 3 I feel sad nearly all the time.

Please complete either 6 or 7 (not both)

6. Decreased appetite (during the past 7 days)

- 0 There is no change in my usual appetite.
- 1 I eat somewhat less often or lesser amounts of food than usual.
- 2 I eat much less than usual and only with personal effort.
- 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

OR

7. Increased appetite (during the past 7 days)

- 0 There is no change from my usual appetite.
- 1 I feel a need to eat more frequently than usual.
- 2 I regularly eat more often and/or greater amounts of food than usual.
- 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 8 or 9 (not both)

8. Decreased weight (within the last 2 weeks)

- 0 I have not had a change in my weight.
- 1 I feel as if I have had a slight weight loss.
- 2 I have lost 2 pounds or more.
- 3 I have lost 5 pounds or more.

Figure 3.2 STAR*D QIDS-SR16 (continues opposite)

STAR*D QIDS-SR16 (continued)

OR

9. Increased weight (within the last 2 weeks)

- 0 I have not had a change in my weight.
- 1 I feel as if I have had a slight weight gain.
- 2 I have gained 2 pounds or more.
- 3 I have gained 5 pounds or more.

10. Concentration in decision-making (during the past 7 days)

- 0 There is no change in my usual capacity to concentrate or make decisions.
- 1 I occasionally feel indecisive or find that my attention wanders.
- 2 Most of the time, I struggle to focus my attention or to make decisions.
- 3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of myself (during the past 7 days)

- 0 I see myself as equally worthwhile and deserving as other people.
- 1 I am more self-blaming than usual.
- 2 I largely believe that I cause problems for others.
- 3 I think almost constantly about major and minor defects in myself.

12. Thoughts of death or suicide (during the past 7 days)

- 0 I do not think of suicide or death.
- 1 I feel that life is empty or wonder if it is worth living.
- 2 I think of suicide or death several times a week for several minutes.
- 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General interest (during the past 7 days)

- 0 There is no change from usual in how interested I am in other people or activities.
- 1 I notice that I am less interested in people or activities.
- 2 I find I have interest in only one or two of my formerly pursued activities.
- 3 I have virtually no interest in formerly pursued activities.

14. Energy level (during the past 7 days)

- 0 There is no change in my usual level of energy.
- 1 I get tired more easily than usual.
- 2 I have to make a big effort to start or finish my usual daily activities (eg, shopping, homework, cooking, or going to work).
- 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

Figure 3.2 STAR*D QIDS-SR16 (continues overleaf)

STAR*D QIDS-SR₁₆ continued

15. Feeling slowed down (during the past 7 days)

- 0 I think, speak, and move at my usual rate of speed.
- 1 I find that my thinking is slowed down or my voice sounds dull or flat.
- 2 It takes me several seconds to respond to most questions and I am sure my thinking is slowed.
- 3 I am often unable to respond to questions without extreme effort.

16. Feeling restless (during the past 7 days)

- 0 I do not feel restless.
- 1 I am often fidgety, wringing my hands, or need to shift how I am sitting.
- 2 I have impulses to move about and am quite restless.
- 3 At times, I am unable to stay seated and need to pace around.

To score the QIDS-SR16

Enter the highest score on any one of the four sleep items (1–4 above):

Enter the highest score on item 5:

Enter the highest score on any one appetite/weight item (6–9):

Enter the highest score on item 10:

Enter the highest score on item 11:

Enter the highest score on item 12:

Enter the highest score on item 13:

Enter the highest score on item 14:

Enter the highest score on either of the two psychomotor items (15 and 16):

Total score (range: 0–27):

QIDS-SR16 scoring

6–10 = mild depression

11–15 = moderate depression

16–20 = severe depression

21 or more = very severe depression

Figure 3.2 STAR*D QIDS-SR16. STAR*D, Sequenced Treatment Alternatives to Relieve Depression. QIDS-SR16, Quick Inventory of Depressive Symptomatology – Self Rated, 16 Items. Reproduced with permission from Rush et al [7] ©Elsevier.

depression, including the presence or extent of suicidal ideation and/or planning and intent. In addition, in reviewing the circumstances around the onset of the depressive episode, it is important to inquire about recent life stresses experienced by the patient to help us better understand the psychological and social forces at play in their lives and how these may have affected the onset of the current depressive episode.

The examination should then include a detailed history of past psychiatric illness episodes. Each episode should be assessed for precipitating events, symptomatic intensity and duration, degree of lethality, suicidality, homicidality, or other self-harm behaviors, and the presence of other co-occurring illnesses or conditions. A history of substance and/or alcohol use is also essential.

A review of the patient's personal, developmental, and social history should be undertaken and information should be obtained regarding: childhood developmental delays, early trauma or abuse, and early socialization experiences with friends and in school; family circumstances (ie, custody or guardianship arrangements); financial and vocational issues; home environment issues; religious and spiritual orientation; and sexual history.

A complete and comprehensive medical history should include active medical problems, current medication(s) (including over-the-counter medications and medications for nonpsychiatric illnesses), past medical history, family medical history, and a medical review of systems.

The mental status examination is a core component of the psychiatric examination. The clinician should note and comment upon the patient's general appearance, general condition, level of motoric activity, and extent of compliance, cooperation, and collaboration in the interview.

Objective signs such as tics, tremors, eye contact, and interactive style should be described. The patterns associated with, and the extent and intensity of dysphoria and anhedonia, and the patient's range of affect, should be noted, and the rate, pattern, and content of speech and thought and the presence of abnormal perceptions described. An assessment of cognitive function is necessary and if cognitive dysfunction is exposed on cursory examination (eg, being alert and oriented to person, place, time) the use of a standardized measure, such as the Mini-Mental State Examination (MMSE) [9], can be very helpful. If indicated, a referral for formal cognitive testing may be made. Finally an assessment of the patient's insight into the illness and the quality of judgment should be noted.

Laboratory tests for co-occurring illnesses

Currently, there are no laboratory tests that can be clinically used to diagnose depression. Laboratory testing is done primarily to rule out other

co-occurring medical disorders that may present as depression. In addition, urine and serum laboratory tests are used to screen for substances of abuse or rule out some form of toxicity, which may also mimic the symptoms of depression. Laboratory tests are routinely obtained for hospital inpatient admissions and patients newly diagnosed with a depressive disorder.

Commonly used laboratory examinations and associated co-occurring medical illnesses are:

- *Complete blood count (CBC) with differential*: anemias, blood dyscrasias, inflammatory disorders, infection.
- *Serum chemistries*: electrolytes, glucose (diabetes), calcium (hyperparathyroidism, arrhythmia), magnesium (neuromuscular and renal disease), liver function tests (hepatic disease), sodium (adrenal function), creatinine, and blood urea nitrogen (renal function).
- *Thyroid function tests*: if thyroid-stimulating hormone (TSH) is abnormal, obtain triiodothyronine (T₃), thyroxine (T₄), and free hormone concentration (hyperthyroidism or hypothyroidism).
- *Rapid plasma regain (RPR) or Venereal Disease Research Laboratory (VDRL)*: syphilis.
- *Urinanalysis*: screen for renal disorders or metabolic or systemic disease.
- *Urine toxicity screen*: drug or substance of abuse toxicity.
- *Chest X-ray (patients over 35 years of age)*: arrhythmia, respiratory dysfunction.
- *Blood toxicity screen or levels of other medications taken (if indicated)*: toxicity.

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Principles of therapy

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The overriding principle behind the treatment of depression is to optimize treatment on an individual basis in order to meet the needs of the patient and to obtain the best possible clinical outcome. This involves not only careful assessment and application of the best evidence by the doctor or therapist but also sensitivity to the wishes, concerns, and beliefs of the patient. To be successful, treatment should be a mutual enterprise based on negotiation that recognizes the different roles of therapist and patient, and the patient's rights to make informed choices.

Goals of treatment

In an obvious sense, the ultimate goal of treatment is straightforward: to return the person with depression to a state of full health. However, it is important to recognize that this can be interpreted differently as the patient may have different expectations from the doctor or therapist, and goals may need to be tempered by practical considerations and unwanted effects of treatment.

Figure 4.1 shows some of the phase-specific outcomes that need to be considered. Traditionally, research and clinical practice have focused on acute phase symptomatic improvement, but other outcomes are equally important, especially to the person with depression, and include positive mental health such as optimism and self-confidence, a return to one's usual self, and a return to usual level of functioning [1].

Phase-specific treatment goals			
Outcomes	Assessment		
	Acute phase	Continuation phase	Maintenance phase
Symptoms	Response Remission	Stable remission	Stable recovery
Adverse effects	Good tolerability and safety	Good tolerability and safety	Good tolerability and safety
Function	Improved social and occupational function	Regained full social and occupational function	Maintained full social and occupational function
Wellbeing	Improved quality of life	Regained quality of life	Maintained quality of life

Figure 4.1 Phase-specific treatment goals.

The different outcomes tend to be highly correlated in uncomplicated depression, although functional improvement tends to lag behind symptomatic improvement. Factors other than depression impact on function and wellbeing, including medical and psychiatric comorbidity, and personality and social factors. However, depression has been shown to cause greater health decrements than other common chronic physical diseases [2], and effective treatment of comorbid depression can greatly improve quality of life.

It is increasingly recognized that longer-term outcomes are just as important as acute treatment [3] and the goal of achieving stable remission/recovery and preventing relapse needs to be emphasized (see Chapter 8).

Rating scales for assessment of outcomes

A variety of observer-rated and self-report measures is available to assess both severity and outcome after treatment and some of the most common are listed in Figure 4.2 [4]. Self-report measures have been seen as increasingly important but have not replaced observer-rated symptom measures as primary outcomes, especially in studies used to license drugs.

Quality of life is a subjective state and relies on self-report measures. Adverse effects, although very important for treatment adherence and quality of life, have received less systematic attention than efficacy outcomes.

Commonly used outcome measures		
Outcome	Measure	Comment
Observer rated		
Symptoms	Hamilton Depression Rating Scale (HDRS)	The HDRS has a greater emphasis on somatic symptoms compared with the MADRS. The CGI is a single overall assessment of illness severity
	Montgomery–Åsberg Depression Rating Scale (MADRS)	
	Clinical Global Impression (CGI)	
Adverse effects (AE)	Spontaneous report	Although categorization of AEs has been standardized, systematically elicited assessment is rare
Function	Global Assessment of Functioning (GAF)	GAF is a composite measure of symptom severity and function
Self-rated		
Symptoms	Beck Depression Inventory (BDI)	BDI is widely used and covers the range of depressive symptoms
	Hospital Anxiety and Depression Scale (HADS)	HADS includes anxiety assessment and omits somatic symptoms
	Patient Health Questionnaire (PHQ-9)	PHQ-9 rates how often depressive symptoms have been present rather than severity
	Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR)	QIDS-SR – see Figure 3.2
Adverse effects	Global AE questionnaires not commonly used	Questionnaires for specific AEs are sometimes used (eg, for sexual AEs)
Function	Medical Outcomes Study Short Form 36 (SF-36)	The SF-36 assesses functioning and health status
Quality of life	EuroQol 5D (EQ-5D)	A simple global health measure used in for health economic analyses

Figure 4.2 Commonly used outcome measures. Adapted with permission from Lam et al [4].

Acute treatment outcomes

Commonly reported symptomatic outcomes are:

- Response, usually defined as 50% or greater improvement in a rating scale score, especially Hamilton Depression Rating Scale (HDRS) or Montgomery–Åsberg Depression Rating Scale (MADRS).
- Remission, absent or minimal depressive symptoms, usually defined as scoring below a cut-off on a rating scale. Accepted values are <8 on the 17-item HDRS and <10 (or sometimes <13) on the MADRS.

Partial remission is used to refer to patients who continue to have significant symptoms but are below the threshold for major depression and

typically score between 8 and 13 on the 17-item HDRS. Full remission is associated with much better functional and quality-of-life outcomes compared with partial remission [5].

Figure 4.3 illustrates the relationship between response and remission. Although response is a useful measure, particularly when comparing treatments, there has been increasing emphasis on remission as the main outcome, because it relates better to the outcomes valued by depression sufferers: freedom from symptoms, and good function and well being [6].

Figure 4.3 also illustrates that depression severity improves initially over time and then plateaus. The time frame of individual studies influences the proportion of patients who will achieve response and particularly

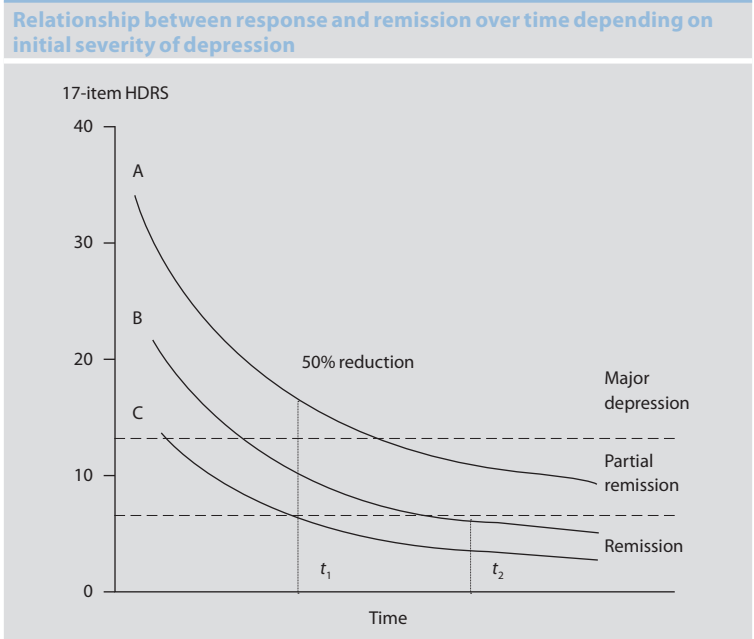


Figure 4.3 Relationship between response and remission over time depending on initial severity of depression. Patient A with severe depression still meets criteria for major depression at t_1 after improving sufficiently to have responded; by the end of the time period they are below the threshold for major depression but have still not fully remitted. Patient B with moderate depression responds and is in partial remission at t_1 , but does not achieve remission until t_2 . Patient C with mild depression meets criteria for both response and remission at t_1 . HDRS, Hamilton Depression Rating Scale.

remission in that study. There are no comparable agreed definitions for improvements in function or wellbeing measures.

Although these definitions are useful there are inevitably patients whose treatment course does not fit this clear pattern and who either do not respond sufficiently to treatment (see Chapter 7) or have a fluctuating course with unstable response and/or remission.

Medium- and long-term treatment outcomes

After the acute treatment phase with its aim of achieving full remission, there is a period of consolidation termed “continuation” treatment in order to prevent early worsening, or relapse. This has been defined in the context of patients taking antidepressants; there is less evidence about the early post-treatment period with psychological treatments, although a few booster or follow-up sessions are commonly offered. Consideration then needs to be given to whether ongoing “maintenance” or prophylactic treatment is required to prevent recurrence of a further depressive episode (see Chapter 8).

Treatment options

Nonspecific effects and placebo

One of the major problems in assessing the efficacy of treatments is the tendency for improvement to occur unrelated to specific aspects of treatment. This is best known in relation to the use of placebo tablets in drug trials but also applies to psychotherapies that posit a specific mechanism (eg, cognitive behavioral therapy [CBT]). Factors that are believed to contribute to response to placebo are given in Figure 4.4.

The placebo effect refers to the nonspecific, but genuinely beneficial, effects of engaging in a treatment. The degree of benefit and which factors contribute differ depending on the condition and the individual. Deliberately giving a placebo drug is unethical (outside a clinical trial with informed consent) and the effects are not consistent. Maximizing nonspecific beneficial effects is, however, an important (and large) part of the overall effect of treatment and should not be overlooked.

Spontaneous improvement and placebo effects are greatest in milder degrees of depression and smaller when the disorder is more severe and/or chronic. In the mildest degrees of depression, studies have shown

Factors contributing to response to a placebo treatment in drug trials	
Type	Examples
Illness factors	Spontaneous improvement
Measurement errors	Regression to the mean Observer or patient biases
Placebo (nonspecific) effects	Expectation of benefit Sharing of feelings, support, and structure Engagement of coping mechanisms and empowerment Behavioral change Neural mechanisms, such as conditioning

Figure 4.4 Factors contributing to response to a placebo treatment in drug trials.

response rates of 50–60% to placebo compared with less than 30% in moderate-to-severe depression [7–9].

Specific treatment options

The main specific treatment options in clinical use are given in Figure 4.5. Details about the individual treatments are given in subsequent chapters.

Choice of treatment

Thresholds for benefit from specific treatments

An important decision is at what stage specific treatments (such as antidepressants or CBT) are needed when an individual presents with depression. This does not mean that people with mild depression do not require, or benefit from, help, but rather directs the clinician to the type of help that is appropriate.

Placebo-controlled drug studies and the rather fewer psychological treatment studies against active control conditions indicate that little is to be gained by specific treatment over nonspecific support in milder, shorter duration states of depression because people do equally well with both. The issue is, therefore, how to maximize benefit while minimizing unnecessary treatment – for reasons of both cost and potential harm (eg, antidepressant adverse effects). For some other presentations of depressive disorders (eg, recurrent brief depression) we lack evidence as to which treatments are effective.

Types of treatment for depression	
Modality	Main groupings
Medications	Selective serotonin reuptake inhibitors Serotonin and norepinephrine reuptake inhibitors Tricyclic antidepressants Monoamine oxidase inhibitors Others including monoamine receptor-active drugs, norepinephrine/dopamine reuptake inhibitors, combined serotonin reuptake and receptor inhibitors
Psychological treatments	Nondirective therapy/counseling Directed self-help/computerized cognitive-behavioral therapy Problem-solving therapy Cognitive-behavioral therapy Behavior therapy/behavioral activation Interpersonal psychotherapy
Physical treatments	Electroconvulsive therapy Bright light therapy Experimental brain stimulation techniques
Other/complementary treatments	St John's wort Omega-3-fatty acids

Figure 4.5 Types of treatment for depression.

Severity and duration of depression are dimensions that have somewhat arbitrarily been divided into “categories” (eg, depressive episode with insufficient symptoms, different severities of major depression, short duration depressive episode, persistent depressive episode). There is no hard and fast “threshold” for clinical benefit from specific treatments over placebo with regard to increasing severity and duration of depressive symptoms, and indeed this is likely to vary between individuals.

It is important to individually tailor treatment, bearing in mind the patient’s illness history and preferences. Clinical judgment is called for rather than rigid rules in applying the evidence base to individuals [10].

Nevertheless, current clinical categories do provide some indication of potential benefit for an ‘average’ patient, so providing a starting point for treatment choice (Figure 4.6) [4]. The severity ‘threshold’ of major depression appears to be where antidepressants show benefit over placebo treatment, but there has been considerable debate about size of clinical

benefit in relationship to major depression severity. An influential analysis suggested that antidepressant-placebo differences increase with severity and only in the most severe patients is this of clinical importance [11]. Subsequent analyses of much larger data sets have not found this, nor has a recent study of combination antidepressants compared with monotherapy [12,13]. The best current evidence therefore supports the clinical benefit of antidepressants across the range of major depression, bearing in mind that most studies include at least moderately severe patients. An issue for ICD-10-defined depression is that the threshold for diagnosis of a depressive episode is lower than for the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5; see Chapter 3), so that someone with recent onset mild *International Classification of Mental and Behavioral Disorders*, 10th revision (ICD-10) depression may, on average, not routinely warrant specific treatment (eg, with antidepressants).

By definition, 2 weeks is the minimum duration for major depression, but little is known regarding how long it needs to have lasted before antidepressants have specific benefit. There is some evidence that spontaneous improvement is very common in the first 2 or 3 months [14],

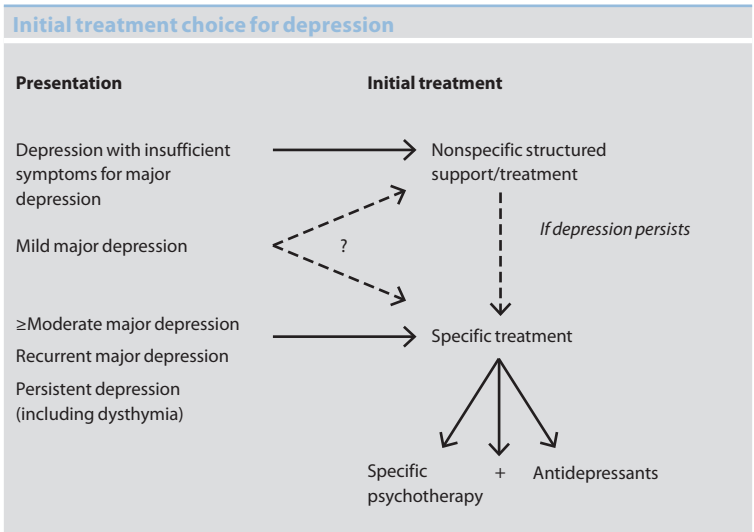


Figure 4.6 Initial treatment choice for depression.

but in practice most patients will have had persisting symptoms before presenting for help. Although recent onset depression with insufficient symptoms (for major depression) usually warrants structured supportive treatment initially, it can be very disabling and specific psychological or drug treatment should be considered if it persists (this includes dysthymia).

The best way to deliver nonspecific structured support or treatment is not known and the term “watchful waiting” has been used. However, this should not be taken to mean inaction as evidence suggests that an active approach is needed to provide benefit. Figure 4.7 suggests some approaches to providing active nonspecific support.

Choice between specific treatments

Unfortunately, there is a lack of compelling evidence allowing confident prediction of who will respond to (or tolerate) one particular specific treatment better than another, be it an antidepressant or psychotherapy. Proposed predictors have included genetic markers (eg, the serotonin transporter), gender, depression type, and comorbidities, but the evidence is generally conflicting. Evidence is accumulating that combining an antidepressant with an antipsychotic is more effective than either drug alone for psychotic depression [15,16], but others are applied pragmatically (eg, bright light therapy for seasonal affective disorder), of research interest or considered when initial treatment has failed [10].

There has been a great deal of interest in whether some antidepressants are more effective than others and how this relates to their

Examples of nonspecific structured support/treatment

Opportunity for exploration of issues and ventilation of feelings followed by defined regular monitoring

Nondirective counseling

Simple problem identification and problem-solving techniques

Guided self-help, including computerized cognitive-behavioral therapy

Support groups

Identification of regular social/recreational/exercise opportunities; provide encouragement, timetable and feedback progress at follow-up

Figure 4.7 Examples of nonspecific structured support/treatment.

pharmacology. It is generally accepted that any differences are marginal and that tolerability and side effects are the major factor in primary care. In more severe depression in secondary care, modest differences may be more important and there is some evidence that venlafaxine and amitriptyline are more effective than selective serotonin reuptake inhibitors (SSRIs), and escitalopram may be more effective than other SSRIs. Older tricyclic antidepressants (TCAs) may also be more effective than monoamine oxidase inhibitors (MAOIs) in severely ill patients [10].

Accepted predictors for response to one specific psychotherapy compared with another have not been established. In choosing between antidepressants and specific psychotherapies, the evidence at present suggests generally equal acute efficacy, although chronically depressed patients with early childhood trauma may respond better to psychotherapy than to antidepressants. There is, however, a lack of evidence for psychological therapies in very severe depression and clinical observation is that such patients commonly lack the motivation and cognitive ability to engage in them. Combining antidepressants and psychotherapy from the start of treatment may give added benefit over either alone for more severely ill patients and those with chronic depression, but not for those with mild-to-moderate depression. At the most severe end of the spectrum there is reasonable evidence that electroconvulsive therapy is the most effective treatment with significant acute benefit over medication [10].

Practicalities of treatment

Evaluation of risk, education, and agreeing treatment

Patients with depression can present a risk of suicide, occasionally harm to others (eg, a depressed mother may kill her baby), or neglect. Severe depression and suicidality can make patients reject treatment or reduce their capacity so that informed treatment choice is not possible. In these cases, careful consideration has to be given to how and where treatment can be effectively and safely initiated (eg, crisis intervention or in a hospital setting) and whether treatment needs to be given under Mental Health legislation. Most patients with mild-to-moderate depression are managed safely in primary care or outpatient settings.

An important and often overlooked aspect of managing depression is education. This consists of providing the patient with information about depression, in the context of their own history and experience. This requires the practitioner to understand depression and be able to evaluate the important factors in the patient's history. It is important in helping patients start to understand their illness and to engage nonspecific therapeutic factors (see above). It helps the therapeutic alliance and negotiation of, and engagement in, treatment. Often it can be helpful to enlist outside resources, the internet, written information, and voluntary organizations in the educational process.

It will be apparent that agreeing appropriate treatment requires evaluation of which treatments are indicated given the nature of the patient's illness (see Chapter 3), taking into account their individual characteristics, the availability of treatment, and their personal choice. This requires negotiation, with clinicians bringing their expertise and knowledge of depression, the benefits and risks of different treatments, and their availability to the situation. Patients bring their own beliefs, experience, and perceptions, which should be sensitively explored and, where necessary, misconceptions should be discussed. The aim is for patients to make an informed choice about treatment (within the bounds of what is possible). The negotiation and information given need to match the patient's wishes and ability, bearing in mind that the patient is in a vulnerable position, often desperate for help, and the depression may make absorbing and processing information difficult. It can be helpful to involve family members or care-givers in discussions, where necessary and with the patient's agreement. Figure 4.8 shows some general principles to apply in recommending particular treatments. Respecting patient choice as far as possible is very important in the therapeutic alliance and in achieving adherence to treatment, although there is surprisingly little evidence that this affects overall outcome. Figure 4.9 provides some considerations that may be helpful in recommending specific antidepressant treatments [10].

The choice between different psychotherapies has been relatively little studied and there is little evidence-based guidance possible. The therapist-patient relationship and therapist expertise (particularly in

General principles in recommending treatments	
General	<ul style="list-style-type: none"> Take into account patient choice Consider both short- and longer-term treatment needs Prioritize treatments with a sound evidence base Apply the principle of fully informed consent (requires discussion of alternative treatments, benefits, risks, off-label use of medication, etc) Provide necessary education and information about what the patient can expect from treatment and any precautions to be taken Consider practical availability of treatments
If medication is indicated	<ul style="list-style-type: none"> Match choice of antidepressant drug to individual patient requirements as far as possible In principle, choose antidepressants that are better tolerated and safer in overdose (older TCAs and MAOIs are second-line drugs) Balance potential efficacy and adverse effects, according to patient needs
If specific psychotherapy is indicated	<ul style="list-style-type: none"> Prioritize treatments with an evidence base for depression, such as CBT, BT, and IPT Recommend practitioners who have appropriate expertise/accreditation

Figure 4.8 General principles in recommending treatments. BT, behavioral therapy; CBT, cognitive-behavioral therapy; IPT, interpersonal psychotherapy; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

more severe depression) are fundamentally important and impact on the patient’s engagement in therapy. In practice, choice is usually limited by what is available locally, particularly in a public health system.

Special populations

There are specific populations where special care or special considerations are needed.

Children and adolescents

There is controversy about the use of antidepressants in younger age groups who are more likely to self-harm. The response to placebo treatment is high and appears to be responsible for the small antidepressant-placebo differences seen in adolescents and lack of clear efficacy in younger children [17]. There is also more concern that antidepressants may precipitate self-harm or suicidal behavior. For this reason there needs to be careful consideration about using antidepressants in this age group, with SSRIs being the best studied and the class with the best evidence base. TCAs and drugs more dangerous in overdose should be avoided

Choosing a specific antidepressant

Previous history of treatment response, tolerability, and adverse effects to a particular antidepressant drug/drug class

Comorbid psychiatric disorder that may indicate a particular treatment (eg, obsessive-compulsive disorder and SSRIs)

Likely side-effect profile

Low lethality in overdose if history or likelihood of overdose

Concurrent medical illness or condition that may make the antidepressant more noxious or less well tolerated

Concurrent medication that may interact with the antidepressant drug

Strong family history of differential antidepressant response

Figure 4.9 Choosing a specific antidepressant. SSRI, selective serotonin reuptake inhibitor. Adapted from Anderson et al [10].

where possible. Although psychological treatments are usually promoted as first-line treatment, it needs to be recognized that the evidence for the efficacy of specific psychotherapies over structured supportive care/treatment is not strong in this age group [10].

Elderly people

The adage “start low and go slow” when prescribing medications to elderly people remains prudent advice. Medication for older adults is complicated by altered drug pharmacokinetics compared with younger adults, increased likelihood of drug-drug interactions (owing to increased medical comorbidity that results in use of multiple medications), and increased probability of adverse effects (such as orthostatic hypotension). Metabolism and clearance of metabolites are diminished in elderly people as a result of decreases in secretion in renal tubules, hepatic mass, and function of most of the cytochrome P450 (CYP) enzymes. Decreases in albumin and other plasma proteins may impact on the protein binding of medications, further enhancing the sensitivity of older individuals to antidepressants [18].

The efficacy of antidepressants in the treatment of depression in elderly people has been studied less, and is less established than for younger adults. A recent meta-analysis found only 15 out of 74 placebo-controlled studies included patients aged over 55 years, and only six involved patients aged over 65 or 75 years [19]. The results found reduced

efficacy of antidepressants in the last group of oldest patients, but with significant variation between studies. The poorer response to antidepressants in this group may reflect a higher prevalence of predictors of poor medication response: greater neurovegetative symptoms of depression, increased medical comorbidities and cognitive dysfunction, increased medication intolerance, inadequate dosing, slower response to treatment.

Interestingly, when the FDA reviewed suicidality and SSRIs across the lifespan, seeking to clarify risks that those agents might pose in younger people, patients aged 65 years and over displayed markedly reduced suicidal ideation and behavior (odds ratio 0.37 compared with placebo-treated patients) [20].

Psychotherapy for depression in elderly people has been studied in many underpowered studies, and few compare antidepressants with psychotherapy. A meta-analysis comparing CBT with other treatment found it was more effective than treatment as usual but no different to active control, other psychotherapies or antidepressants [21].

Pregnancy and breastfeeding

Avoiding unnecessary medication in pregnancy is recommended, but, in general, TCAs and SSRIs have been used without evidence of significant adverse effects, although paroxetine is best avoided because of some concerns about cardiovascular defects. Third trimester antidepressants have been associated with a usually mild and self-limiting neonatal behavioral syndrome. Antidepressants vary in how much they are secreted in breast milk and citalopram and fluoxetine are best avoided if possible [10].

Initiating treatment

When treatment is initiated it is important to provide information about what the patient can expect with treatment. It is well recognized that there is a delay between starting treatment and noticeable benefit, but contrary to standard teaching it does appear that improvement can be detected in the first few days and the greatest rate of improvement, revealed by ratings of symptoms, occurs in the first 1 or 2 weeks. However, other aspects, such as function and sense of wellbeing, lag behind this so it is often 3 or 4 weeks before the patient feels any better. Improvement

with psychological treatment tends to be a little slower. To gain the maximum benefit from antidepressants, always aim to treat at proven therapeutic doses.

The types of side effects that might occur with medication should be explained. Studies show that most patients experience some adverse effects early in treatment (although not all are directly due to the drug, as some occur with placebo treatment – see Chapter 5 for side effects from particular antidepressants). Most side effects are mild, occur in the first 2 weeks or so, and then improve. Emphasizing that the side effects will occur before benefit is experienced and will usually diminish is important in helping patients persevere with treatment. For some treatments (eg, TCAs, reboxetine) it is helpful to titrate the dose up over about 1 or 2 weeks to minimize side effects. Other drugs (eg, most SSRIs) are started at their therapeutic dose.

A controversy with antidepressants, especially SSRIs, concerns whether or not they might provoke suicidal thoughts or actions. Whether or not this might be the case for some vulnerable groups (eg, adolescents and young adults), increased suicidality can occur during all types of treatment. Patients need to be warned that, if they experience increased agitation and/or suicidality, they should seek help immediately.

Patients often stop treatment when they start to feel better. It is important to emphasize that antidepressant treatment needs to be continued after improvement in order to prevent early relapse, as there is a high risk of this in the months after remission. In addition, they need to be warned about the risk of a discontinuation reaction if antidepressants are stopped suddenly after treatment for more than a couple of months.

Monitoring and adjusting treatment

Evidence shows that structured follow-up and monitoring are associated with better outcomes and that more frequent follow-up is better than less frequent. Early in treatment, it is advisable to make contact after 1 or 2 weeks to assess side effects and suicidality, and this can help patients to adhere to treatment.

Until recently it has been fairly rare in clinical practice to use standardized measures of mood assessment. On the analogy that a physician

would not treat a patient with diabetes without measuring plasma glucose, it can be argued that simply using a global assessment of improvement is insufficient. Self-rated standardized assessments (see Figure 4.2) are easy to use and provide helpful symptom profile information (such as suicidality), as well as engaging patients in monitoring their own symptoms [4].

A systematic scheme of monitoring allows the application of so-called “critical decision points.” These are specific points at which response to treatment is assessed and treatment changed if necessary. They have been used in medication treatment algorithms using standardized assessments and shown to produce benefit [22]. Figure 4.10 illustrates this. (See Chapter 7 for further discussion of treatment alteration for poor response.)

It is less clear how this model might apply to psychological treatments and it deserves study; for example, if insufficient improvement has occurred after four to six sessions, should alterations in treatment or adding medication be considered?

Service structure in delivery of treatment

There is good evidence that the structure of treatment delivery is important in implementing the appropriate monitoring and adjustment of treatment. In primary care, collaborative care (broadly defined as structured care

Critical decision points: guidelines in acute treatment with antidepressants			
Time (weeks)	Clinical assessment	Rating scale	Action
4	No improvement or worse	<20% improvement	Consider altering treatment*
	Some improvement	≥20% improvement	Continue current treatment
6	Insufficient improvement	<50% improvement	Consider altering treatment*
	Response	≥50% improvement	Continue current treatment
8–12	Not in full remission	> remission cut-off	Consider altering treatment*
	Full remission	< remission cut-off	Continue current treatment for at least 4–6 months

Figure 4.10 Critical decision points: guidelines in acute treatment with antidepressants.

*Options include continuing current treatment if progress still being made, increasing dose, switching antidepressant, or adding in a second agent. For partial remission after 12 weeks consider adding cognitive behavioral therapy.

involving greater use of nonmedical specialists to augment treatment) and case management (continuity of care with at least systematic monitoring of symptoms) have been shown to lead to improved outcome compared with usual treatment; at least part of this appears to result from enhanced medication adherence [23]. The best way to enhance care is not known, but a minimum appears to be a structured system of follow-up (eg, involving a case manager) and incorporating education about medication adherence.

In secondary care the structure of treatment has been less studied, but it does appear that using treatment algorithms and more intensive treatment regimens leads to better outcomes [24]. The National Institute for Health and Clinical Excellence (NICE) [25] gives a stepped care approach to treatment, which provides a structure for matching patients to the appropriate service and type of treatment.

Factors affecting response to treatment

Although most factors that might affect response cannot be changed, it is useful to consider their presence when planning treatment as some factors, such as adverse social conditions, may be amenable to intervention. Factors that are generally believed to be associated with poorer outcome of depression overall are earlier age of onset, duration and severity of depression, number of previous episodes, psychotic depression, failure of previous treatments, comorbidity with medical illness, anxiety disorders and substance misuse, some personality disorders, social factors such as ongoing social adversity, and cognitive impairment in elderly people [10,26,27].

When factors predicting response to antidepressant treatment in an episode of depression have been examined, fewer appear to influence outcome (Figure 4.11) [28]. What is important to take from this is that a range of interacting factors impacts on response to treatment, but it is difficult to predict from an individual factor what will happen in a particular patient.

There is less evidence with regard to response to treatment with psychological treatments, although one factor that came out strongly in a large study was large differences between individual therapists [29]. Although it has not been studied, it is also likely that there are clinician

Factors predicting response to antidepressant treatment	
Appears associated with poorer response	Not associated or inconsistent
Comorbid anxiety	Age
Nonresponse to treatment in current episode	Age of onset
No partner/spouse	Duration of episode
Poorer social support	Gender
Severity of illness (especially in first episode)	Number of recurrences
Significant physical illness	
Therapist factors	
Unemployed, poorer education	

Figure 4.11 Factors predicting response to antidepressant treatment. Adapted from Bagby et al [28] ©Canadian Medical Association.

factors influencing response to antidepressant treatment given the large nonspecific component to treatment.

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Medications

Ian M Anderson and Danilo Arnone

The essence of the theoretical background of antidepressant action is based on the monoamine hypothesis of depression. In the 1960s it was noted that reserpine, a catecholamine-depleting agent, induced depression and that this effect was reversed by antidepressants. The involvement of monoamines was also supported by the observations suggesting that dopamine (DA) and norepinephrine (NE; noradrenaline) were functionally deficient in depression and elevated in mania. Similarly, Ashcroft proposed that an indoleamine, now called serotonin (5HT), was deficient in depression, leading eventually to the development of selective serotonin reuptake inhibitors (SSRIs). It is widely believed that the chronic administration of SSRIs resulting in 5HT reuptake blockade is responsible for the downregulation of 5HT_{1A} receptors present on the cell bodies of serotonergic neurons. This effect reduces negative feedback, increasing 5HT neuronal firing and hence 5HT synaptic availability. This is a proposed mechanism to explain the delay between acute administration of an antidepressant and the therapeutic effect. It is unlikely to be the full explanation and does not generalize to drugs acting in different ways on the monoamine systems. It is also increasingly recognized that the onset of improvement with antidepressants is immediate, although significant clinical benefit takes some weeks to be evident. Current theories of the mechanism of action of antidepressants emphasize effects beyond the synapse such as neurotropic effects [1].

This chapter describes antidepressants prescribed in clinical practice, with tables for pharmacology and clinical details of compounds commonly used in day-to-day practice. Newer drugs do not fit easily into the classical classification of antidepressants and for simplicity we have grouped them by their main pharmacology. For more detail, readers are referred to textbooks of pharmacotherapy [1–3]. Dosage may vary according to clinical presentation and age group. Many compounds have recommended twice or even three-times-daily administration based on the elimination half-life. However, in practice, antidepressants are often given once daily and there is no evidence of benefit in giving any antidepressant more than once daily, except to reduce side effects by influencing peak plasma effects. More than once-daily administration may impair adherence, and for many drugs single nighttime administration is acceptable and tolerable [4,5]. Average dose ranges are given, but these should be taken as guidelines only and reference to manufacturer's information and/or national formulary is advisable at the time of prescribing [6,7].

Selective serotonin reuptake inhibitors

Most guidelines support the use of SSRIs as first-line pharmacological treatment for depression on the basis of their safety and tolerability. The principal mechanism of action of SSRIs is to inhibit the reuptake of 5HT into the presynaptic nerve terminal. In terms of toxicity in overdose, SSRIs are generally considered at low risk, especially if taken alone, although citalopram (and possibly escitalopram) may carry a slightly increased risk compared with other SSRIs [8]. The smallest dose likely to cause death is not clearly defined but believed to be around 1 g or 2 g. Differences in SSRI tolerability probably result largely from pharmacokinetic considerations but there are also subtle pharmacodynamic differences, with fluoxetine being the least selective for 5HT over NE, and sertraline having some DA reuptake at higher doses. Fluvoxamine appears least well tolerated at least in doses >100 mg, but may be the least likely to cause sexual dysfunction, whereas paroxetine is the most likely. Paroxetine appears the most likely to cause discontinuation symptoms, and fluoxetine the least [9]. Recently maximum dose restrictions have been introduced for citalopram and escitalopram due to concern

Pharmacology of selective serotonin reuptake inhibitors				
Drug	Active metabolite	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Citalopram	Negligible	36	Hepatic	Negligible
Escitalopram (<i>S</i> -enantiomer of citalopram)	Negligible	36	Hepatic	Negligible
Fluoxetine	Norfluoxetine	72 (200)	Hepatic	CYP2D6, 3A4, 2C19
Fluvoxamine	Negligible	25	Hepatic	CYP1A2
Paroxetine	Negligible	20	Hepatic	CYP2D6, 2C9
Sertraline	Desmethylsertraline	25 (66)	Hepatic	CYP2D6 (weak)

Figure 5.1 Pharmacology of selective serotonin reuptake inhibitors. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450; SSRI, selective serotonin reuptake inhibitor.

Clinical use of selected serotonin reuptake inhibitors			
Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Citalopram	20–40	Nausea/vomiting, agitation, akathisia, insomnia/sedation, sexual dysfunction, dizziness, convulsions (rare), increased risk of suicidality (<30years), hyponatremia (especially in the elderly), increased risk of bleeding, discontinuation syndrome, prologation of QTc at high doses	MAOIs (serotonin syndrome) Lithium (therapeutic, serotonin syndrome) L-Tryptophan (therapeutic, serotonin syndrome) St John’s wort (serotonin syndrome)
Escitalopram (<i>S</i> -enantiomer of citalopram)	10–20	As for citalopram*	As for citalopram*
Fluoxetine	20–40	As for citalopram* but insomnia and agitation more common, discontinuation syndrome less common	As for citalopram* plus: Antipsychotics (increased concentration) Opiates (increased concentration) TCAs (increased concentration)
Sertraline	50–200	As for citalopram*	As for citalopram*

Figure 5.2 Clinical use of selective serotonin reuptake inhibitors(continues overleaf).

Clinical use of selected serotonin reuptake inhibitors (continued)			
Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Paroxetine	20–40	As for citalopram* but discontinuation syndrome more common (slow discontinuation advisable)	As for fluoxetine
Fluvoxamine	100–200	As for citalopram* but nausea more common	As for citalopram* plus: Some TCAs (increased concentration) Olanzapine, clozapine (increased concentration) Warfarin (increased concentration) Propranolol (increased concentration)

Figure 5.2 Clinical use of selected serotonin reuptake inhibitors (continued). MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.*no QTc prolongation.

about QTc prolongation and risk of cardiac arrhythmias at higher doses [10]. The pharmacology and clinical use of SSRIs are summarized in Figures 5.1 and 5.2.

Combined serotonin reuptake inhibition and 5HT receptor actions

Trazodone and nefazodone are only weak serotonin reuptake inhibitors (SRIs) and their main mechanism of action is believed to be due to 5-hydroxytryptamine (5HT)₂ antagonism and possibly 5HT_{1A} partial agonism. Vilazodone has been recently licensed in the USA and is a potent 5HT reuptake inhibitor and 5HT_{1A} partial agonist. Vortioxetine has also recently been licensed in the USA and Europe and combines 5HT reuptake inhibition and multiple actions at 5HT receptors. The pharmacology and clinical use of combined SRI-5HT receptor active drugs are summarized in Figures 5.3 and 5.4.

Trazodone and nefazodone

Trazodone is a potent 5HT₂ antagonist with less strong 5HT_{1A} partial agonism and weak 5HT reuptake inhibition. Other pharmacological

Pharmacology of combined serotonin reuptake inhibitor-5-hydroxytryptamine receptor-active drugs				
Drug	Active metabolite	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Trazodone	m-Chlorophenylpiperazine	3–9 (up to 72)	Hepatic	Negligible
Nefazodone	Negligible	2–4	Hepatic	CYP3A4
Vilazodone	Negligible	25	Negligible	CYP2C8, CYP3A4/5
Vortioxetine	Negligible	66	Hepatic	Negligible

Figure 5.3 Pharmacology of combined serotonin reuptake inhibitor 5-hydroxytryptamine receptor-active drugs. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450.

Clinical use of combined serotonin reuptake inhibitor-5-hydroxytryptamine receptor-active drugs			
Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Trazodone	150–300	Sedation, dizziness, headache, nausea/vomiting, tremor, postural hypotension, tachycardia, rarely priapism	Negligible
Nefazodone	300–600	As trazodone apart from priapism; less sedative	TCA's (increased concentration) Alprazolam (increased concentration) Potential hepatotoxicity; its use is subject to monitoring of hepatic function in North America
Vilazodone	40	Diarrhea, nausea, vomiting, insomnia. Sexual dysfunction comparable to placebo	MAOIs (serotonin syndrome) Lithium (therapeutic, serotonin syndrome), L-Tryptophan (therapeutic, serotonin syndrome), St John's wort (serotonin syndrome)
Vortioxetine	10-20	Nausea, dizziness, sexual dysfunction at higher doses	As vilazodone

Figure 5.4 Clinical use of combined serotonin reuptake inhibitor 5-hydroxytryptamine receptor-active drugs. MAOI, monoamine oxidase inhibitor ; TCA, tricyclic antidepressant.

actions include $\alpha 1$ antagonism and weak antihistaminergic properties. Its metabolite m-chlorophenylpiperazine has 5HT agonist properties and

releases 5HT. Nefazodone has similar pharmacology to trazodone but lacks antihistaminergic properties. Both lack the typical effects of SSRIs and a major advantage is that they do not interfere with sexual function significantly. Nefazodone was withdrawn from the European market in 2003 due to hepatotoxicity. The use of nefazodone is subject to monitoring of hepatic function in North America and it is rarely prescribed.

Vilazodone

Vilazodone is a high affinity SSRI and a partial antagonist at 5HT_{1A} receptors. The reduced negative feedback mediated by presynaptic 5HT_{1A} autoreceptors could potentially speed antidepressant response but this has yet to be established in practice. There is little experience of its use in antidepressant combination therapy and serotonin syndrome a potential concern given the 5HT enhancement. Treatment should start at 10 mg daily and be titrated to 40 mg over two weeks. The dose should be limited to 20 mg if used with strong inhibitors of CYP3A4 which may increase vilazodone plasma concentration.

Vortioxetine

Vortioxetine is an SRI with multiple actions at 5HT receptors; 5HT_{1A} agonism, 5HT_{1B} partial agonism, 5HT_{1D}, 5HT₃ and 5HT₇ antagonism. It also binds to β ₁-receptors. It elevates levels of 5HT, NE, DA, acetylcholine and histamine in specific brain regions and has been called a multimodal antidepressant. The recommended starting dose is 10 mg, increasing to a treatment dose of 20 mg as efficacy is dose-related. The dose can be reduced to 5 mg if higher doses are not tolerated; a maximum of 10 mg is recommended if administered with drugs that inhibit CYP2D6. It is better tolerated than selective norepinephrine reuptake inhibitors (SNRIs) and the most common side effects are nausea, diarrhea and dizziness. Sexual adverse effects are more common than with placebo and dose-related, but seem less common than with SSRIs.

Serotonin and norepinephrine reuptake inhibitors

Venlafaxine, desvenlafaxine (licensed in North America), duloxetine, and milnacipran (licensed in France and Japan) are known as 'dual

action' reuptake inhibitors because of their action as selective 5HT and NE reuptake inhibitors. The pharmacology and clinical use of SNRIs are summarized in Figures 5.5 and 5.6.

Pharmacology of selected norepinephrine reuptake inhibitors				
Drug	Active metabolite	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Venlafaxine	Desvenlafaxine (O-desmethylvenlafaxine)	5 (11)	Hepatic	Negligible
Duloxetine	Negligible	12	Hepatic	CYP2D6, CYP1A2
Milnacipran	Negligible	8	Negligible	Negligible

Figure 5.5 Pharmacology of selected norepinephrine reuptake inhibitors. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450.

Clinical use of selected norepinephrine reuptake inhibitors			
Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Venlafaxine	75–225 XL 75–375	Nausea, insomnia, dry mouth, sedation, dizziness, sweating nervousness, headache, sexual dysfunction, hypertension at higher doses, discontinuation syndrome	MAOIs (serotonin syndrome) Lithium (therapeutic, serotonin syndrome) l-Tryptophan (therapeutic, serotonin syndrome) St John's wort (serotonin syndrome)
Desvenlafaxine	50	As venlafaxine, but better tolerated at recommended dose	As venlafaxine
Duloxetine	60–120	Nausea, insomnia, dizziness, dry mouth, constipation, anorexia, and increased blood pressure and heart rate	As venlafaxine plus TCAs (increased concentration) Antipsychotics (increased concentration) May cause liver damage or exacerbate pre-existing liver damage (avoid alcohol)
Milnacipran	100	Nausea, vertigo, increased anxiety, sweats, shivering, dysuria, itching, and testicle pain	As venlafaxine

Figure 5.6 Clinical use of selected norepinephrine reuptake inhibitors. MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

Venlafaxine

The efficacy of venlafaxine is similar to TCAs (eg, amitriptyline, clomipramine, and imipramine), but better tolerated. There is some evidence that its dual mechanism of action makes venlafaxine more efficacious in the treatment of more severe depressive disorders, and guidelines tend to favor its use in cases of lack of, or insufficient, response to, SSRIs. However, dual action is believed to occur only at higher doses. Reuptake of 5HT occurs at a dose of 75 mg, whereas for blockade of NE, reuptake dose is 150 mg/day and greater. At the highest doses venlafaxine may also be a DA reuptake inhibitor. Venlafaxine has typical SSRI-like side effects, including sexual dysfunction and discontinuation syndrome, as well as those attributable to effects on NE. It is contraindicated in patients at high risk of serious cardiac ventricular arrhythmia and uncontrolled hypertension. It is considered good practice to ensure that the patient is normotensive at the time of prescribing and to monitor blood pressure at doses of 300 mg/day or above. It is advisable to seek specialist supervision in case of doses reaching 300 mg/day and above. It is more toxic in overdose than SSRIs but much less than TCAs.

Desvenlafaxine

Desvenlafaxine (O-desmethylvenlafaxine) is the major metabolite of venlafaxine and has a relatively higher NE:5HT transporter inhibition ratio than its parent compound, and more similar to that of duloxetine. Unlike venlafaxine, little metabolism occurs through hepatic CYP450 pathways, reducing the risk of pharmacokinetic drug interactions; dose adjustments are not required in hepatic disease. It is well tolerated at its recommended dose of 50 mg and does not require dose titration. Doses higher than 50 mg are less well tolerated without increased efficacy.

Duloxetine

Duloxetine is a 5HT and NE reuptake inhibitor with weaker inhibition of DA than 5HT reuptake. It has been proposed to be particularly effective compared with other antidepressants for painful physical symptoms occurring in depression, but direct evidence of this is lacking. Its license includes treatment of pain syndromes such as diabetic peripheral

neuropathic pain, fibromyalgia and chronic musculoskeletal pain (the last two in the USA but not Europe). Usual dosage is in the range of 60–120 mg/day. Although the starting dose is recommended as 60 mg, it is better to titrate up from 30 mg in antidepressant-naïve patients to improve tolerability.

Milnacipran

Milnacipran is a dual reuptake inhibitor with slightly more action on NE than 5HT reuptake. Metabolism does not involve the CYP450 system, and it is excreted as a mixture of active and inactivated compound. Renal, but not hepatic, disease delays excretion. Levomilnacipran is an active enantiomer of milnacipran in clinical development.

Monoamine receptor-active drugs

The pharmacology and clinical use of monoamine receptor-active drugs are summarized in Figures 5.7 and 5.8.

Pharmacology of monoamine receptor-active drugs				
Drug	Active metabolites	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Mirtazapine	Negligible	26-37	Hepatic	Negligible
Agomelatine	Negligible	1-2	Hepatic	Negligible

Figure 5.7 Pharmacology of monoamine receptor-active drugs. CYP, cytochrome P450; $t_{1/2}$, half-life (in hours).

Clinical use of monoamine receptor-active drugs			
Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Mirtazapine	15–45	Increased appetite, weight gain, drowsiness, edema, dizziness, headache	Potiation of benzodiazepine effect (↓ excretion)
Agomelatine	25–50	Headache, nausea, fatigue, dizziness, raised liver enzymes and hepatotoxicity. Monitoring of liver enzymes required. Caution in liver disease	Negligible

Figure 5.8 Clinical use of monoamine receptor-active drugs.

Mirtazapine and mianserin

Mirtazapine's mechanisms of action include antagonism of α_2 -presynaptic receptors, which ultimately increases both NE and 5HT neurotransmission by increased cell firing and synaptic release; antagonism of postsynaptic 5HT₂ and 5HT₃ receptors, which may also improve the tolerability of mirtazapine but contribute to weight gain; and a potent antihistaminergic effect contributing to its side effects of weight gain, sedation, and anxiolytic properties. It has a low incidence of sexual side effects. It may be a little more toxic in overdose than SSRIs but much less than TCAs.

Mianserin is an older drug which has been largely superseded by mirtazapine with which it shares most of its pharmacology. However, it also antagonizes α_1 -presynaptic receptors which results in decreased presynaptic stimulation of 5HT neurons compared with mirtazapine, and hence less enhancement of 5HT release. It has similar side effects to mirtazapine but is also associated with blood dyscrasias and so complete blood count monitoring is required.

Agomelatine

Agomelatine is a melatonin agonist and 5HT₂ antagonist licensed in Europe. A proposed mechanism of action is through beneficial effects on circadian rhythms and sleep but this has yet to be definitively demonstrated. It is well tolerated with a low incidence of side effects including sexual side effects. There is an increased rate of elevated hepatic transaminases and hepatotoxicity has been reported; monitoring of liver enzymes is required.

Norepinephrine reuptake inhibitors

Reboxetine

Reboxetine is a specific reuptake inhibitor of NE licensed widely worldwide but not in the USA. There is debate about its efficacy over placebo in treating depression. Dosage is usually between 8 and 12 mg/day in twice-daily administration. Side effects include insomnia, sweating, dizziness, dry mouth, constipation, tachycardia, urinary retention, and sexual dysfunction. Dose titration may improve its tolerability. The pharmacology and clinical use of reboxetine is summarized in Figures 5.9 and 5.10.

Pharmacology of reboxetine				
Drug	Active metabolites	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Reboxetine	Negligible	13	Hepatic	CYP3A4 inhibitor (eg, erythromycin, ketoconazole) may increase its plasma concentration

Figure 5.9 Pharmacology of reboxetine. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450.

Clinical use of reboxetine			
Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Reboxetine	8–12	Insomnia, sweating, dizziness, dry mouth, constipation, tachycardia, urinary retention, sexual dysfunction	Potential of benzodiazepine effect (↓ excretion)

Figure 5.10 Clinical use of reboxetine.

Dopamine reuptake inhibitors

Bupropion (amfebutamone)

The mechanism of action of bupropion is not fully understood but the main action is thought to be the inhibition of DA reuptake, although it is also a weak NE reuptake inhibitor. Bupropion is licensed in the USA for the treatment of depression in immediate-release and delayed-release forms. Its use includes augmentation with SSRIs for treatment-resistant depression. At high doses, it may cause seizures and it is contraindicated in cases with a history of, or susceptibility to, developing seizures. Its metabolism mainly involves CYP2D6. The pharmacology and clinical use of bupropion is summarized in Figure 5.11.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are amines that inhibit the reuptake of 5HT and NE. Tertiary amines (amitriptyline, imipramine, and clomipramine) are more potent 5HT blockers, whereas secondary amines (nortriptyline, desipramine, protriptyline) are more effective on NE. Other effects are anticholinergic and antihistaminergic. Tertiary amines are metabolized to secondary amines; for example, amitriptyline to nortriptyline, imipramine to desmethylimipramine (desipramine). Desipramine has been largely

Pharmacology and clinical use of bupropion				
Drug	Active metabolites	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Hepatic enzyme inhibition
Bupropion (amfebutamone)	<i>R,R</i> -Hydroxybupropion, <i>S,S</i> -Hydroxybupropion threo-Hydrobupropion erythro-Hydrobupropion	10 (up to 26)	Hepatic	Hydroxybupropion CYP2D6 inhibitor
Medication and dose (mg)	Main adverse effects	Significant interactions		
Bupropion (amfebutamone) 300–450	MAOIs (serotonin syndrome) Carbamazepine/phenytoin (reduced concentration of bupropion) Valproate (increased concentration bupropion) Citalopram (increased concentration of citalopram)	Dry mouth, insomnia, anxiety, gastro-intestinal disturbance, sweating, hypertension		

Figure 5.11 Pharmacology and clinical use of bupropion. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450; MAOI, monoamine oxidase inhibitor.

superseded by more modern compounds but is still available in the USA. TCAs have high toxicity and fatality in overdose, particularly dosulepin, amitriptyline, and desipramine. Amitriptyline and desipramine should be prescribed with caution in cases of high suicide risk (eg, limited prescription, supervised administration) and dosulepin avoided. Lofepramine is the least toxic of all TCAs and clomipramine intermediate. The pharmacology and clinical use of TCAs are summarized in Figures 5.12 and 5.13.

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are inhibitors of MAO enzymes A and B. These enzymes are widely distributed in the CNS, but also peripherally, especially in the gastrointestinal system. MAO-A metabolizes NE, 5HT, DA, and tyramine, whereas the substrates of MAO-B are DA, tyramine, and phenylethylamine.

The inhibitory action of MAOIs results in an increased availability (storage and release) of 5HT and NE. Lack of selectivity for the CNS and irreversibility of the inhibition (for older compounds) are responsible for the most significant side effects. The most dangerous phenomenon associated with MAOIs is a hypertensive “cheese reaction” attributable to tyramine-containing foods (eg, cheese, yeast extracts, hung game, some

Pharmacology of tricyclic antidepressants						
Drug (active metabolite)	$t_{1/2}$ ($t_{1/2}$ of metabolite)	Metabolism	Comparative pharmacology			
			NE reuptake inhibition	5HT reuptake inhibition	Anticholinergic effects	Sedation
Amitriptyline (nortriptyline)	16 (36)	Hepatic	++	+++	+++	+++
Imipramine (desipramine)	16 (24)	Hepatic	++	+++	++	++
Clomipramine (desmethyl-clomipramine)	18 (36)	Hepatic	+	+++	+++	+
Nortriptyline	36	Hepatic	+++	+	++	+
Dosulepin* (northiaden)	20 (40)	Hepatic	+	+	++	++
Lofepramine (desipramine)	5 (24)	Hepatic	+++	+	+	+

Figure 5.12 Pharmacology of tricyclic antidepressants. 5HT, 5-hydroxytryptamine; CYP, cytochrome P450; NE, noradrenaline; TCA, tricyclic antidepressant; $t_{1/2}$, half-life (in hours).*Previously called dothlepin.

alcoholic drinks, broad bean pods, pickled herring), normally inactivated in the gut by MAO. Another cause is related to indirect sympathomimetic drugs such as phenylephrine (eg, nonprescription cold remedies).

Symptoms include flushing, headache, increased blood pressure, cerebral vascular accident. The most effective treatment of this condition is α -adrenergic blockade with phentolamine or chlorpromazine. MAOIs are generally contraindicated in cardio- and cerebrovascular disease, children, epilepsy, hepatic disease, pheochromocytoma, and hyperthyroidism. Irreversible MAOIs include traditional molecules (phenelzine, isocarboxazid, tranlycypromine) and selective MAO-B inhibitors (eg, selegiline). Selegiline transdermal patches have been licensed in the USA for the treatment of depression. This reduces first-pass metabolism and the risk of hypertensive reactions and food restrictions. The only available reversible MAOI is moclobemide, an MAO-A inhibitor, also called a RIMA (reversible inhibitor of MAO-A). At usual doses moclobemide does not necessitate dietary restrictions as competitive antagonism allows tyramine to displace moclobemide from MAO.

Clinical use of tricyclic antidepressants			
Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Amitriptyline	75–150*	Dry mouth, blurred vision, constipation, urinary retention, sedation, postural hypotension, tachycardia/arrhythmia, weight gain	MAOIs (toxicity) Paroxetine, fluoxetine (↑ levels of TCAs) Phenothiazines (↑ levels of TCAs) Cimetidine (↑ levels of TCAs) Antimuscarinics (enhanced effect) Alcohol
Imipramine	75–150*	As for amitriptyline but less sedative	As for amitriptyline MAOIs (toxicity, serotonin syndrome)
Clomipramine	75–150*	As for amitriptyline but less sedative	As for amitriptyline MAOIs (toxicity marked)
Nortriptyline	50–150	As for amitriptyline but less sedative, anticholinergic, and hypotensive. Constipation is common	As for amitriptyline
Dosulepin (dothiepin)†	75–225	As for amitriptyline	As for amitriptyline
Lofepamine†	140–210	As for amitriptyline but less sedative, anticholinergic, hypotensive, and low cardiotoxicity. Sweating	As for amitriptyline

Figure 5.13 Clinical use of tricyclic antidepressants. *Higher doses (eg, up to 200–300 mg are commonly used in the USA). †Not available in the USA. MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant.

As a result of the risk of adverse reactions, the traditional MAOIs should be reserved for patients failing other antidepressants and prescribed under specialist supervision. The pharmacology and clinical use of MAOIs are summarized in Figures 5.14 and 5.15.

Other drugs

Investigational compounds

Drugs targeting glutamate receptors are currently in clinical trials based on evidence that the glutamatergic dissociative anaesthetic, ketamine, has rapid antidepressant effects.

Pharmacology of monoamine oxidase inhibitors			
Drug	$t_{1/2}$ ($t_{1/2}$ of metabolite)*	Metabolism	Comparative pharmacology
Moclobemide	2–4	Hepatic	Reversible inhibitor of MAO-A
Selegiline† (desmethylselegiline, L-amphetamine, L-methylamphetamine)	3.5 (up to 14)	Hepatic	Irreversible inhibitor of MAO-B
Phenelzine	1.5	Hepatic	Irreversible, nonselective MAO-A and -B inhibitor
Tranlycypromine	2.5	Hepatic	Irreversible, nonselective MAO-A and -B inhibitor
Isocarboxazid	36	Hepatic	Irreversible, nonselective MAO-A and -B inhibitor

Figure 5.14 Pharmacology of monoamine oxidase inhibitors. *Note that for irreversible inhibitors, the half-life does not reflect the duration of pharmacological effect. †Transdermal administration reduces first pass metabolism with lower concentration of metabolites. $t_{1/2}$, half-life (in hours); CYP, cytochrome P450; MAOI, monoamine oxidase inhibitor.

Clinical use of monoamine oxidase inhibitors			
Medication	Usual daily dose (mg)	Main adverse effects	Significant interactions
Moclobemide	150–600	Sleep disturbance, headache, nausea, agitation	Other antidepressants, pethidine, alcohol, barbiturates, insulin
Selegiline* (transdermal)	6-12 every 24h	Application site reaction, insomnia, diarrhea, pharyngitis (after oral administration similar to phenelzine)	No dietary restrictions at lowest dose. Low risk transdermally. As for phenelzine with oral administration
Phenelzine	45–60	Postural hypotension, dizziness, drowsiness, insomnia, headaches, edema, anticholinergic effects, weight gain, restlessness, sexual difficulties, sweating, tremor	Tyramine in food, sympathomimetics, alcohol, opioids, antidepressants, L-dopa
Tranlycypromine	20–30	As for phenelzine. More stimulating than phenelzine	As for phenelzine but interactions more severe and it is not advisable to use in combination
Isocarboxazid	10–40	As for phenelzine	Tyramine in food, sympathomimetics, alcohol, opioids, antidepressants, L-dopa

Figure 5.15 Clinical use of monoamine oxidase inhibitors. MAOI, monoamine oxidase inhibitor. *Transdermal selegiline is not currently licensed in Europe.

Augmentation strategies

Augmentation strategies include synergistic prescribing of antidepressants and/or other compounds including lithium, T_3 , and atypical antipsychotics. Chapter 6 describes the use of augmentation strategies as next-step treatments. Their use should be supervised by mental health specialists. The clinical use of lithium is further described but for other drugs the reader is referred to the appropriate reference book, such as the *British National Formulary* [6].

Lithium (usually given as lithium carbonate) is the best-established augmentation treatment, but its popularity has decreased with the availability of new drugs and the complexities of its use. It has multiple potential actions including enhancing 5HT function. It has a narrow therapeutic range and needs regular blood tests to maintain a serum concentration in the range of 0.5–1.0 mmol/L (preferably <0.8 mmol/L to minimize side effects). Lithium is excreted by the kidneys and can interfere with thyroid hormone release and affect cardiac conduction. Pretreatment assessment of renal and thyroid function is required and, if indicated, cardiovascular status including an electrocardiography. Monitoring of renal and thyroid function is required approximately every 6 months. Adverse effects include polyuria and polydipsia, tremor, gastrointestinal symptoms, and a metallic taste in the mouth. Dehydration, sodium depletion (diarrhea, sweating), hypovolemia, and renal failure can increase serum lithium concentrations leading to lithium toxicity, which requires immediately stopping lithium, and medical assessment and intervention, including dialysis, if levels are very high.

Specific adverse effects of antidepressants

Serotonin syndrome

The serotonin syndrome is an acute neuropsychiatric condition due to increased CNS 5HT activity. Rarely, it can be an idiosyncratic reaction to a serotonergic drug but usually it results from a pharmacodynamic interaction between drugs that enhance 5HT function (eg, SSRI + MAOI). Symptoms include confusion, myoclonic jerks, hyperreflexia, pyrexia, sweating, autonomic instability, gastrointestinal symptoms, mood change,

and mania. Management is based on stopping the offending drug(s) and supportive measures [11].

Antidepressant discontinuation syndrome

The discontinuation syndrome usually occurs only after antidepressant treatment has been established for some weeks and occurs on stopping the drug, especially if it is done abruptly, with symptoms starting in the first few days. The symptoms are variable and differ between classes of antidepressants but include sleep disturbance, gastrointestinal symptoms, affective symptoms, and general somatic symptoms such as lethargy and headache. In addition, SSRIs are associated with sensory symptoms, such as electric shock feelings and paraesthesia, and disequilibrium symptoms. MAOIs may cause more severe symptoms, including worsening depression and anxiety, confusion, and psychotic symptoms. With most antidepressants, psychotic symptoms, mania, and extrapyramidal symptoms have rarely been reported. Paroxetine and venlafaxine have been associated with high rates of discontinuation symptoms, whereas fluoxetine appears to have low rates, presumably due to its long half-life.

Management is based on education and reassurance, which suffice in most cases because the course tends to be mild and self-limiting (1 or 2 weeks). In more severe cases the implicated medication can be restarted and tapered more slowly. For SSRIs and SNRIs, fluoxetine can be prescribed and then stopped because its long half-life produces a natural taper. Prevention of the discontinuation syndrome can usually be achieved by tapering down the antidepressant dose over a few weeks.

Suicidality

There has been recent concern that some antidepressants, particularly SSRIs, might cause increased suicidality in some patients. However, the evidence considered overall does not support an increased risk of completed suicide or clinically significant increased risk of suicidal behavior in adults with antidepressant use, and population studies have tended to find that antidepressants are associated with decreased suicide rates. However, individual sensitivity cannot be ruled out and

SSRIs may be associated with a very small increase in nonfatal suicidal ideation/behavior in adolescents. More important is the recognition that all patients can experience an increase in suicidality during treatment and that this needs appropriate management (see Chapter 4) [12].

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Other treatments

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Psychotherapy for depression

Several depression-focused psychotherapies [1] have been developed to be time-limited treatments. They have an explicit goal of helping the individual achieve rapid relief of depressive symptoms, inasmuch as they are treatments comparable to pharmacotherapy in time course and efficacy. Furthermore, by emphasizing short-term goals, these therapies capitalize on the acute nature of many episodes of depression. Shared features of the depression-focused psychotherapies include their specific linkage of a theoretical model of phenomenology with strategies for symptom reduction, with specification of methods to facilitate training and enhance fidelity, and with acceptance of the need to identify observable and measurable goals and outcomes. The major types of time-limited depression-focused therapies that have reliably established comparability to antidepressant medications in randomized controlled trials (RCTs) include cognitive therapy (CT) [2] and IPT [3]. The particular theoretical orientation of each model of treatment also yields predictions about specific outcomes, such as the effects of CT on measures of dysfunctional attitudes or interpersonal psychotherapy (IPT) on measures of social adjustment. Finally, these therapies share several pragmatic features, including their compatibility for use in combination with pharmacotherapy and their suitability for use by therapists with a range of backgrounds and training.

IPT aims to relieve depression through the recognition that depression occurs within an interpersonal context regardless of its severity, phenomenology, or presumed etiology. IPT therapists help patients to understand and modify interpersonal problems associated with depression. Additional long-term benefits include improved social function and prophylaxis against relapse. IPT developed from the recognition that high rates of life stressors are associated with the onset of unipolar depression. Consequently, IPT often focuses on the relationship between attachment bonds and vulnerability to depression. Helping the patient strengthen his or her intimate relationships may enhance the apparent protective or “neutralizing” role of social support. Another important aspect of the depressed person’s social milieu is his or her performance in the workplace, with friends and peer groups, and in the neighborhood or community. Attention to social role performance thus includes the individual’s current and long-term patterns of functioning in diverse situations, as well as more recent or still-evolving role transitions. IPT is a psychoeducational intervention because, in addition to the strong social emphasis, therapists teach patients about depression and its treatment. This includes providing practical advice or recommendations to help patients better tolerate the symptoms of depression and manage impairments associated with the depressive state. These efforts also serve to help lessen the demoralization and hopelessness experienced by most depressed people. The therapy may be quite active in this regard, including providing assistance to patients through the use of problem-solving strategies. IPT therapists are encouraged to identify one or more of four common interpersonal conflict situations to serve as the focus for therapeutic change: unresolved grief, role disputes, role transitions, and interpersonal deficits.

The cognitive model of depression and CT derive from the work of Aaron Beck [2]. Beck recognized that depressed patients view themselves, the world, and their future in a negative manner (*the cognitive triad*). These negative cognitions (*automatic negative thoughts*) provide the gateway for the cognitive therapist to understand the depressed patient’s phenomenological world. The patient is taught to identify and challenge dysfunctional thoughts, understand their guiding beliefs, and revise their dysfunctional attitudes. Therapists help patients discover their

unconscious attitudes through the use of Socratic questioning and guided discovery exercises. According to the CT model, depression results from unconscious dysfunctional beliefs being activated by current environmental stimuli, eliciting thoughts of helplessness, hopelessness, and worthlessness. It is believed that adverse early experiences are responsible for the individual learning inadequate coping strategies. This stress-diathesis model may explain why only some individuals become depressed after a stressor such as divorce or unemployment. The therapeutic relationship in CT is described as being one of *collaborative empiricism*, where the therapist assumes the role of a coach or teacher in addition to providing the more traditional nonspecific elements of empathy, understanding, and support. Through this model of interaction the therapist and patient develop step-wise goals to reduce symptoms, improve management of pressing day-to-day problems, and increase morale. Collaboration is explicitly fostered via the use of summarization and feedback to ensure that the patient thoroughly understands the material being covered. CT also draws heavily on the principles and methods of behavior therapy, including activity scheduling, graded task assignments, guided practice, and individualized homework assignments. Explicit, step-wise strategies are used to improve recognition of problem areas and effect changes in thoughts, behaviors, and feelings. As with other types of psychotherapy, the establishment of a strong therapeutic relationship based upon warmth, empathy, and genuineness is crucial to obtaining positive outcomes. A strong therapeutic alliance enhances learning and the mastery of targeted therapeutic tasks. Compared with the process of more traditional dynamic therapies, CT requires greater therapist activity.

Furthermore, CT differs from dynamic or experiential therapies in that affect is specifically used to identify a cognitive process by which depressed patients learn to solve problems and gain greater control over dysphoric and anhedonic moods. Like IPT, typical CT treatment of acute depression involves 12–14 therapy sessions over a 3- to 4-month period. Longer-term CT therapy can be useful for prevention of relapse of acute depressive episodes, and to revise core beliefs and dysfunctional behavioral patterns in individuals with longstanding personality or characterologic disorders.

Combination psychotherapy and psychopharmacotherapy

The goal of both psychotherapy and pharmacological treatment is to eliminate all manifestations of disorder, but individuals frequently do not achieve adequate clinical response, and relapse and recurrence are common [4]. Often referred to as “combined” or “combination” treatment, psychiatric treatment utilizing both psychotherapy and pharmacology is frequently used in practice to treat depression [1,5,6]. There are several different definitions of “combined” treatment; for example, the combination of treatment can be offered simultaneously or additively. Additive treatment can be in one of two sequential orders: psychotherapy (either individual or group) first augmented by medication or pharmacological treatment supplemented by therapy. Combined treatment can be “split” and provided by multiple providers, or integrated, with the psychiatrist providing both treatments.

Lacking a strong empirical basis, much of the existing literature discussing the pros and cons of combined treatment is based on clinical opinion and theoretical speculation. The prevailing arguments for and against combining therapy and medication are highlighted in Figure 6.1 [6]. There are a growing number of clinical trials showing combined treatment to be superior to either type of intervention used alone for depression [5,7]. Nevertheless, expert consensus panels have recommended combination treatment for the treatment of depression, especially when the illness presentation or course is complicated [8,9]. Some circumstances in which combination treatment may be helpful include the following:

- when either treatment alone, optimally given, is only partially effective
- if the clinical circumstances suggest two discrete targets of therapy (eg, symptom reduction addressed by medication and social/occupational problems addressed by psychotherapy)
- if the prior course of illness is chronic; for relapse prevention in patients achieving only a partial response to pharmacotherapy in the acute phase
- to aid in improving medication adherence and treatment compliance.

Pros and cons of combined psychotherapy and pharmacology	
Adding psychotherapy	
Pros	Cons
Helps with medication management and improves compliance	May lead therapist to ignore biological factors and place too much responsibility on the patient
May increase positive expectancy of medication (placebo effect)	Therapy could place undue stress on patients with biologically driven illness states
Decreases risk of relapse of psychiatric disorder)	
Improves social and occupational functioning	
Lessens impact of psychosocial stressors and allows patient to gain self-understanding of more adaptive coping strategies	
Adding pharmacology	
Pros	Cons
Provides symptom relief and helps patient engage better in therapy (eg, improve concentration, hyperarousal, or decrease fatigue)	Prematurely decreases target symptoms and decreases motivation for therapy or to learn new ways to cope without medication
Stabilizes ego functions to enable better psychotherapy participation	May imply to patients that they cannot handle their disease
May increase positive expectancy of therapy (placebo effect)	Elicits negative transference reactions or undercuts psychological defenses
Decreases distorted or irrational thinking that interferes with therapy progress	Medications can interfere with learning and memory or cause “state-dependent” learning in therapy
	Increases risk of relapse if discontinued, which may negatively impact on prevention efforts of therapy

Figure 6.1 Pros and cons of combined psychotherapy and pharmacology. Adapted from Szigethy et al [6].

The intriguing findings of Mayberg and colleagues demonstrating the brain regions associated with antidepressant and cognitive-behavioral therapy (CBT) activity provides an explanatory model for combined treatment. Mayberg identified the prefrontal cortex as being a target of pharmacotherapy, with the highest concentration of serotonin in the brain [10]. Goldapple and co-workers, analyzed patients treated with an selective serotonin reuptake inhibitor (SSRI; paroxetine) and CBT, and demonstrated that CBT is associated with characteristic metabolic changes in the frontal cortex, cingulate, and hippocampus rather than

the characteristic changes in the prefrontal cortex, hippocampus, and cingulate regions that result from treatment with SSRIs [11]. Mayberg and colleagues interpret these findings as indicating that CBT and medications have different primary anatomical targets of action, with cortical “top-down” effects characterizing psychotherapy effect and subcortical “bottom-up” effects accounting for the effect of medication [10]. These imaging data lend support to a theoretical position suggesting that combination treatment of depression may be synergistic in its benefits because the different modalities affect different brain regions.

There are clinician and patient factors that influence the use of combination treatments. Clinicians have theoretical biases that can influence the therapeutic process during combination treatment, some oriented by preference and training to practice a specific form of psychotherapy, such as psychoanalysis, CBT, or IPT (Figure 6.2) [12]. These clinicians may view psychotherapy as the primary treatment modality with pharmacological agents being used adjunctively. For psychoanalysts, obstacles to combination treatment may include the following:

- maintaining their theoretical orientation while assessing the benefit from adjunctive medication;
- a relative inexperience with medication treatments; and
- a lack of role models for combined treatment.

Psychological treatment for mild, moderate, or severe depression

Improving symptoms

Likely to be beneficial:

- IPT (mild-to-moderate depression)
- CT (mild-to-moderate depression)
- Combining antidepressants and psychological treatment (mild-to-moderate and severe depression)

Unknown effectiveness:

- Befriending (mild-to-moderate depression)
- Nondirective counseling (mild-to-moderate depression)
- Problem-solving therapy (mild-to-moderate depression)

Reducing relapse rate

Unknown effectiveness:

- CT (weak evidence for reduced relapse rates 1–2 years after mild-to-moderate depression)
- Relapse prevention program (no significant difference in response rates)

Figure 6.2 Psychological treatment for mild, moderate, or severe depression. CT, cognitive therapy; IPT, interpersonal psychotherapy. Adapted from Butler et al [12].

From a CBT perspective, the focus of combined treatment is the synergistic use of each modality to maximize the effect of the other modality. For a psychopharmacologically oriented psychiatrist, psychotherapy may be seen as a modality to primarily augment the use of medication. Although there may be disagreement about which approach is the most clinically efficacious, most psychiatrists agree that, optimally, combining modalities should be complementary and improve overall patient care. Another critical factor to consider in evaluating if combination treatment should be used is patient expectation and acceptance of two treatments. It is important to explore patients' understanding of treatment options, their objections to different components, and depression treatments available to them. Providing psychoeducation about combination treatment may also minimize medication noncompliance and improve treatment adherence. Thus, the examination of interpersonal, emotional, and cognitive obstacles to treatment may promote more positive pharmacological outcomes. Fostering the patient's readiness to change and strengthening the doctor–patient alliance are important factors mediating the efficacy of medication treatment. In conclusion, the delivery of combined treatment is often complicated by multiple providers, and the expectancies of patients and the providers, each bringing their own life experiences, expectations, fears, fund of knowledge, and theoretical biases to the treatment setting.

Physical treatments

In addition to pharmacological and psychological treatments of depression, there are a number of physical treatments (eg, electroconvulsive therapy [ECT], phototherapy, and acupuncture) with evidence for their use. There are also several experimental stimulation treatments for depression that are currently under study, including vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS).

Electroconvulsive therapy

ECT has been proven to be a safe and effective treatment for depression, and has been used successfully for more than 70 years [13]. Several recent, large-scale, multisite, collaborative studies have confirmed the efficacy of ECT for depression. In the Consortium for Research in ECT

(CORE) study, 217 individuals with major depression received a course of ECT; the investigators reported a remission rate of 75% at completion and 65% at 4 weeks [14]. Similarly, another multisite collaborative study of 290 depressed individuals receiving ECT reported a remission rate of 55%. In another study, the CORE investigators examined whether receiving an additional 10 treatments of ECT or continuation pharmacotherapy improved rates of relapse over 6 months of follow-up. They found no difference between the treatments, with one-third relapsing and less than half remaining well, and concluded that both treatments had limited efficacy [15].

The UK ECT Review Group (2003) performed a systematic review and meta-analysis of short-term efficacy from randomized controlled ECT trials. They report that real ECT was significantly more effective than simulated (sham) ECT (6 trials, 256 patients, standardized effect size [SES] -0.91 , 95% confidence interval [CI] -1.27 to -0.54), treatment with ECT was significantly more effective than pharmacotherapy (18 trials, 1144 participants, SES -0.80 , 95% CI -1.29 to -0.29), and bilateral electrode placement was more effective than unipolar (22 trials, 1408 participants, SES -0.32 , 95% CI -0.46 to -0.19) [16]. Another meta-analytic review of randomized controlled ECT trials compared ECT with simulated ECT, placebo, or antidepressants. They found a significant superiority of ECT in all comparisons: ECT versus simulated ECT, ECT versus placebo, ECT versus antidepressants in general, ECT versus tricyclic antidepressants (TCAs), and ECT versus monoamine oxidase inhibitors (MAOIs). In addition, they compared nonrandomized controlled ECT trials and found a significant statistical difference in favor of ECT versus antidepressants. They suggest that ECT is a valid therapeutic tool for treatment of depression, including severe and resistant forms [17].

The American Psychiatric Association (APA) Task Force on ECT [18] provides a good review of current clinical standards for the treatment, training, and privileging of ECT treatment [19]. The primary indications for treatment are a lack of response or intolerance to antidepressants, a previous good response to ECT, the need for a rapid treatment response

because of psychosis or risk of suicide, or the presence of extremely severe or chronic depression. Clinicians must review with the patient and/or family members appropriate alternative treatments, and evaluate the risks and benefits of ECT treatment for the individual. Factors associated with reduced ECT efficacy include prolonged duration of the current depressive episode, lack of response to medication, and the presence of a comorbid personality disorder [13]. There are no absolute contraindications, although those with unstable cardiac disease (eg, ischemia or arrhythmia), cerebrovascular disease (eg, recent cerebral hemorrhage or stroke), or increased intracranial pressure are at increased risk for complications [20].

Phototherapy

Phototherapy – the use of light treatment – was developed to treat, and has become the first-line treatment for, individuals with seasonal affective disorder (SAD) [21]. Meta-analysis has suggested the efficacy of light therapy in the treatment of seasonal and nonseasonal depression with effect sizes equivalent to that of most antidepressant pharmaceutical trials [22], although caution is warranted as the quality of studies included is poor and in the UK, the 2009 NICE guideline review that included better quality studies concluded that SAD should be managed in the same way as nonseasonal depression [23]. However, the guidelines acknowledge that phototherapy has been associated with an improvement in depression fatigue, sleepiness, and health-related quality of life [24]. In addition, it has shown efficacy for the treatment of premenstrual [25] and antepartum depression [26]. Three out of four SAD sufferers are women and the usual age of onset is between 18 and 30 years [27]. As is characteristic for the disorder, winter seasonal depression spontaneously remits in the spring and summer (less frequently, some individuals have a depressive pattern characterized by summer depression and spontaneous winter remission). The most common form of phototherapy is white light treatment of 2500–10,000 lux (equaling the light exposure of a bright sunny day). Phototherapy has been recommended as a first-line treatment for

SAD by some authorities [9], but not others [23]. There is also evidence that phototherapy may accelerate remission in nonseasonal depression together with medication [25].

In 1980, Lewy and colleagues were the first to recognize that melatonin could be suppressed with bright light. Melatonin is believed to regulate circadian rhythmicity and bright light appears to be responsible for melatonin suppression, the key regulatory mechanism for maintaining normal biological rhythms. Thus, phototherapy appears to aid maintenance of normal biological rhythmicity by compensating for circadian phase advances in the sleep cycle (through late afternoon exposure) and for phase delays (through early morning exposure) [28].

In addition, some investigators propose that phototherapy also affects neurotransmitter function and that this may also contribute to its antidepressant activity in vulnerable individuals [29].

Other physical treatments

Similar to ECT, these treatments use devices to introduce an electrical current that theoretically alters neuronal circuits. Positive outcomes with surgical lesion procedures since the 1940s to interrupt brain circuits (such as anterior cingulotomy and subcaudate tractotomy) suggest a role for stimulation treatments that are less invasive for severe and treatment-resistant major depressive disorders (MDDs). The stimulation treatments utilize focused excitation of brain regions to, theoretically, produce a desired behavioral alteration. Models of limbic-cortical dysfunction in MDD have been proposed that characterize the depression phenotype at the neural systems level [30] and provide a theoretical basis for neuromodulation treatments. Studies are now in progress on a number of different therapeutic neuromodulation treatments.

Vagus nerve stimulation

In 2005, VNS was approved by the FDA for individuals with treatment-resistant depression [31]. It had previously been approved for use as an adjunctive therapy for epilepsy. VNS requires a surgically implanted, battery-powered pulse generator and electrical lead wound around the left vagus nerve. This provides intermittent stimulation, typically 30

seconds on and 5 minutes off. The most common adverse effects are voice alteration during stimulation and hoarseness, dyspnea, and cough. Hypomania may be a treatment-induced adverse effect and there is a risk of surgical infection. The device is programmed using an external programming system to alter the generator output. VNS stimulation did not demonstrate acute phase efficacy in one small open-label study (18 of 59 responded positively) [32], but has shown promising results to suggest benefit to patients with low-to-moderate degrees of treatment resistance and over longer-term treatment [33]. A 12-month, nonrandomized study of similar type treatment-resistant patients compared VNS treatment plus treatment-as-usual to treatment-as-usual alone and found significantly greater symptomatic benefit in the VNS group [34]. Nahas et al reported that, after 2 years of VNS treatment, the response rate was 42% and remission rate 22%, and that 81% were still actively using the device (implying that those who did not reach response criteria still perceived a subjective benefit from the device) [35]. Currently, a large multisite study is under way to assess VNS efficacy at several different generator settings.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has been used to treat patients who have not benefited sufficiently from pharmacotherapy and psychotherapy. TMS is applied without sedation, externally delivering the stimulation to the brain through the cranium. Several small (usually single site), sham-controlled trials of TMS and meta-analysis of their results support its efficacy for the treatment of MDD [36]. Recently, a double-blind, multisite study trial of over 300 medication-free patients with major depression were randomized to active or sham TMS. Sessions were conducted five times a week for 4–6 weeks. Active TMS was significantly superior to sham TMS, with remission rates approximately two-fold higher for active TMS, and active TMS was well tolerated with a low dropout rate for adverse events (generally mild and limited to transient scalp discomfort or pain). The investigators report a small effect size with a number needed to treat (NNT) of 11 – roughly comparable to NNT values reported for antidepressant medications [37]. To date,

the existing literature suggests a potential role for TMS for depressed individuals with treatment-resistant depression, but the optimum treatment parameters remain to be established. A commercial TMS device was FDA approved for treatment of depression in the USA in October 2008, becoming the second stimulation treatment thusfar approved for depression treatment in the USA.

Deep brain stimulation

Deep brain stimulation (DBS) also has FDA approval for the treatment of epilepsy and is being studied for the treatment of depression [38]. In DBS, electrodes are surgically implanted in the subgenual cingulate area, also known as Brodmann area 25. This area of the anterior cingulate cortex has been shown to be metabolically overactive in patients with depression or in healthy individuals who are induced to feel sad. This area is thought to be involved in cortisol regulation, stress response, sleep modulation, emotional regulation of the limbic system, motivation, and drive. Mayberg and colleagues found that chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with a striking and sustained remission of depression in four of six patients participating in an open-label trial [39]. Antidepressant effects were associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites, measured using positron emission tomography. The authors suggest that disruption of focal pathological activity in limbic-cortical circuits, using electrical stimulation of the subgenual cingulate white matter, can effectively reverse symptoms in otherwise treatment-resistant depression. Such preliminary findings are promising and further, confirmatory, studies are currently under way. Adverse effects of DBS include surgical risks, such as infection, hemorrhage, and seizure, and a risk of infection from the subcutaneously planted battery and wires. Mood-related risks include induction of hypomania. Stimulation-associated adverse effects include sensorimotor changes, insomnia, autonomic changes (eg, transient increases in heart rate and blood pressure), and memory flashbacks.

Lifestyle and complementary therapies

Many individuals with mild-to-moderately severe depressive episodes seek lifestyle and complementary therapies, such as exercise, hypericum extracts (St John's wort), and omega-3-fatty acids (O-3-FA).

Exercise

There have been a few RCTs addressing the use of exercise to treat depression. Dunn and colleagues performed a randomized, placebo-controlled, 12-week study in adults (age 20–45 years) with MDDs to determine if higher total energy expenditure and frequency of exercise improved depressive symptoms and, if so, whether there is an exercise dose-response relationship [40]. They reported that increasing energy expenditure (by >17.5 kcal/kg per week) significantly reduced depressive symptoms, but there was no main effect of exercise frequency. They concluded that aerobic exercise at a dose consistent with public health recommendations is an effective treatment for MDDs of mild-to-moderate severity [38]. Blumenthal and colleagues performed a prospective RCT involving 202 adults with major depression who were treated with group-supervised exercise, home-based exercise, antidepressant (sertraline 50–200 mg daily), or placebo. After 4 months, patients who received active treatments tended ($P=0.057$) to have higher remission rates than those on placebo. These authors conclude that the efficacy of exercise seems to be generally comparable to antidepressant treatment [41]. In an earlier report, Babyak et al followed individuals who completed the above study and found that fewer in the exercise group relapsed over the next 6 months [42].

Exercise has also been examined as an augmentation treatment for depression. Trivedi and colleagues examined the use of exercise to augment SSRI treatment in 17 MDD patients with incomplete remission of depressive symptoms [43]. Patients underwent a 12-week individualized exercise program while continuing their antidepressant (unchanged in type or dose). Intent-to-treat analyses yielded significant decreases in depressive symptoms. This study provides preliminary evidence for exercise as an effective augmentation treatment for antidepressants. These

investigators suggest that exercise is a lower-cost augmentation strategy with numerous health benefits, and it may further reduce depressive symptoms in those who partially respond to antidepressants [43].

Lawlor and Hopter performed a systematic review and meta-regression analysis of RCTs of exercise as an intervention in the management of depression [44]. Hampered by poor-quality evidence they, nevertheless, found that the difference in effect sizes between exercise and CT (four studies) was not significant. Similarly, in the study comparing exercise and antidepressant, or both, there was no significant difference in outcomes between treatments. As with the case for acupuncture treatment for depression, the preliminary evidence argues for additional studies to validate these preliminary findings [44].

St John's wort

St John's wort (*Hypericum perforatum*) is the herbal therapy most commonly available worldwide for the treatment of depression. Its main active principle has not yet been identified and preparations of this compound are often unstandardized. It can interact with antidepressants acting on the 5HT system, such as SSRIs. Adverse effects are generally mild.

A number of clinical trials suggest that St John's wort may enhance 5HT function and be effective in the treatment of mild-to-moderate depression. Linde and colleagues performed a systematic review and meta-analysis to investigate if extracts of *H. perforatum* are more effective and more tolerable than placebo and antidepressants in the treatment of depression [45]. They reviewed 23 randomized trials (total of 1757 outpatients) in patients with mild or moderately severe depressive disorders. They report that *Hypericum* extracts were significantly superior to placebo and as effective as standard antidepressants, and concluded that there is evidence for *Hypericum* extracts being more effective than placebo for treatment of mild-to-moderately severe depression [45]. A more recent, double-blind RCT of *Hypericum* extract compared with fluoxetine and placebo in 135 patients with major depression found that *Hypericum* was significantly more effective than fluoxetine and tended toward superiority over placebo. However, this study was compromised

by the limitation of the dosage of fluoxetine to 20 mg/day, the low end of its recommended prescribing range (20–60 mg/day) [46].

A review of other recent trials continues to provide inconclusive evidence about Hypericum's efficacy for depression. Shelton et al studied 200 outpatients with major depression and reported Hypericum not to be effective compared with placebo [47]. This group examined the 95 patients who did not respond and found them not to be highly treatment resistant, further arguing against its efficacy versus antidepressants [48]. The Hypericum Depression Study Group trial [49] performed a multi-site study with 340 depressed individuals comparing Hypericum with placebo and sertraline; they report that this study failed to support its use. On the other hand, reports by Kasper et al [50] and Lecrubier et al [51] found it to be safe and more effective than placebo.

Omega-3-fatty acids

The family of O-3-FAs includes eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Greater dietary intakes of O-3-FAs may be beneficial for depressed mood and has generated interest in their use as an antidepressant treatment. However, at present, it is unclear whether they have a potential role [52]; for example, one randomized, double-blind, clinical trial of DHA in 36 individuals with major depression failed to find a significant effect of DHA monotherapy [52]. Another randomized trial examined the efficacy of EPA in treating depression in those with bipolar depression. In a 12-week, double-blind study, participants were randomly assigned to adjunctive treatment with placebo or two doses of EPA. They reported significant improvement with EPA compared with placebo and both doses were well tolerated [4].

Sontrop and Campbell evaluated the evidence for the efficacy of O-3-FAs in patients with unipolar and postpartum depression [53]. They note that studies in this area are confounded by a lack of power or incomplete control. In four of seven double-blind RCTs reviewed by these authors, depression was significantly improved with O-3-FA. However, although clinical significance was demonstrated, preservation of blinding may have been a major limitation, making it unclear whether O-3-FA

supplementation is effective independently of antidepressant treatment for depressed patients in general, or only for those with abnormally low concentrations of these O-3-FAs [53].

Lin and colleagues performed a systematic review and meta-analysis of clinical trials in the English literature of O-3-FA efficacy [54]. A total of 10 double-blind, placebo-controlled studies in patients with mood disorders receiving O-3-FAs for 4 weeks or longer were included. They found a significant antidepressant effect for O-3-FAs in unipolar and bipolar depression. However, significant heterogeneity among these studies and publication bias were noted, with the conclusion that it is still premature to validate this finding [54]. Similarly, Appleton et al reviewed 18 RCTs and included 12 in a meta-analysis. They concluded that the evidence examining the effects of O-3-FAs on depressed mood is limited, and difficult to summarize and evaluate because of considerable heterogeneity [55]. Furthermore, the available evidence provides little support for the use of O-3-FAs to improve depressed mood, and suggest that larger trials with adequate power to detect clinically important benefits are required to help clarify this issue.

Acupuncture

Despite its being practiced for thousands of years, there is little evidence supporting the use of acupuncture in the English-speaking medical literature, and only uncontrolled trials for acupuncture for treatments of illnesses that prominently include depression in Chinese and Russian reports [56]. Allen and colleagues examined the effectiveness of acupuncture for depression versus acupuncture treatment of nonspecific symptoms and a waiting-list condition in a small sample of 38 women with major depression. After 8 weeks of treatment, there was a statistically significant difference ($P < 0.05$) between the specific versus nonspecific acupuncture treatment, but only a marginal difference ($P > 0.12$) between the specific treatment and the waiting-list control [57]. However, effect size calculations show that the specific treatment had a large effect size ($d = 1.16$, where d is Cohen's d) compared with nonspecific treatment, which, in turn, had a moderate-to-large effect size compared with waiting

list ($d=0.61$) suggesting an effect comparable to standard treatments such as psychotherapy and pharmacotherapy [57].

Smith and Hay performed a Cochrane Database Systematic Review of acupuncture studies for depression, including all published and unpublished RCTs comparing acupuncture with sham acupuncture, no treatment, pharmacological treatment, other structured psychotherapies (CBT, psychotherapy, or counseling), or standard care [58]. The participants included men and women with depression (defined by clinical state description, or diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th edition or International Classification of Mental and Behavioral Disorders, 10th revision criteria). The primary outcomes were reduction in depression severity measured by self- or clinician-rating scales and rates of remission versus nonremission. Meta-analysis was performed using seven trials comprising 517 participants. Five trials (409 participants) included a comparison between acupuncture and medication. Two other trials compared acupuncture with a waiting-list control or sham acupuncture. Participants generally had mild-to-moderate depression. There was no evidence that medication was better than acupuncture in reducing the severity of depression (weighted mean difference 0.53, 95% CI -1.42 to $+2.47$), or in improving depression, defined as remission versus no remission (RR 1.2, 95% CI, 0.94–1.51). The authors conclude that there is insufficient evidence to determine the efficacy of acupuncture compared with medication, waiting-list control, or sham acupuncture [58].

In summary, the limitations of the current acupuncture studies (diagnostic imprecision, variation in the treatment provision, and small sample size) compromise our ability to determine its true effectiveness compared with other depression treatments, and further study is needed.

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Management of treatment nonresponse

Ian M Anderson

Inadequate treatment response is unfortunately a common problem. Approximately 50–70% of patients gain significant benefit from treatment but, of these, not all will have symptomatic remission [1]. An approximate rule of thirds applies, with one-third achieving remission, one-third being significantly better but not symptom free with partial remission, and one-third remaining depressed. These proportions depend on the duration of follow-up and the nature of the population being studied. Consideration of next-step treatments is therefore extremely important and a pessimist might say that the next step should be planned at the time of the first step. It is certainly important to plan treatment in the knowledge that further steps might be needed.

Assessment and principles of management

Assessment

If a patient has not improved sufficiently it is important to assess the stage of treatment and timing (see Figure 4.10). An important decision is whether to continue for longer with the present treatment or make a change, which depends on the trajectory of the depressive episode, likelihood of remaining symptomatic, and functional impairment and treatment history for that patient. Although the goal of remission should

always be in mind, the management is different for someone in a first episode than for someone with highly recurrent depression, a long treatment history, and incomplete interepisode recovery. In the latter case, longer periods of treatment before making changes are appropriate.

In assessing inadequate response (Figure 7.1) the aims are to re-evaluate the diagnosis and treatment goals, identify factors that may be impairing response to treatment, and identify further treatment options.

Principles of management

It is possible to get caught up in making too frequent changes in treatment because of the desire by both the clinician and the patient for the latter to get better as soon as possible. At the other extreme, patients not responding to treatment can be left for too long on the same treatment and denied potentially beneficial alternatives. There must be a happy medium so that it can be established if a treatment produces benefit before moving on to further planned treatment trials. This may require up to about 12 weeks per treatment trial.

The treatment strategies and suggested guidance for their use are outlined in Figure 7.2 and discussed in this chapter [2].

Assessment of inadequate response to treatment	
Patient and illness factors	Check diagnosis and comorbidity Exclude comorbid substance misuse Check for maintaining factors: – life events – social support – problems – avoidance behavior Check for physical illness Review current level of depression in context of depression history and realistic treatment goals (involving patient’s perspective)
Treatment factors	Adherence to treatment Treatment adequacy (dose of antidepressant, frequency of therapy) Past treatment efficacy and tolerability Treatment options not tried

Figure 7.1 Assessment of inadequate response to treatment. Adapted from Anderson et al [2].

Treatment strategies for inadequate response	
Strategy	When to consider
Continue current treatment	Possible trajectory of improvement still present, good tolerability, and resistant to previous treatments
Increase dose	Scope for dose increase, good tolerability, and possible slight improvement
Switch treatment	No improvement in spite of adequate treatment, poor tolerability
Add second treatment	Some improvement, good tolerability if second drug to be added

Figure 7.2 Treatment strategies for inadequate response.

Patient choice is important because many will have preferred options at this stage. They may be reluctant to continue the current treatment or increase dose because of side effects; alternatively, they may be reluctant to stop for fear of losing the gains made. On current evidence we have little to guide the choice of next-step treatment and there are no convincing differences in efficacy between strategies, or between most choices within a strategy. Most evidence that we have is for antidepressants and next-step treatment with psychological treatments has been little studied.

Definitions: treatment nonresponse and treatment-resistant depression

Nonresponse can be technically defined as less than 50% improvement in the initial rating scale score (see Chapter 4). This is of limited clinical use and it is better to consider the severity of continuing symptoms and functional impairment in consultation with the patient when determining what is better termed “inadequate response or improvement.”

Treatment-resistant depression (TRD) has become an accepted term and is commonly taken to mean failure to respond to two or more treatments given at an adequate dose for an adequate length of time. Exact definitions vary but the common stages are given in Figure 7.3 [3]. However, the term “TRD” is less useful than it appears at first sight: as usually applied, it does not include partial remission; it is difficult to incorporate psychological treatments into the definition; defining what counts as an adequate treatment can be difficult; and there is no natural cut-off between two or fewer treatments and three or more treatments.

Classification of treatment nonresponse/resistance

Different detailed schemes are used but in general include four stages:

1. Inadequate treatment (ie, not really resistance to treatment)
2. Nonresponse to an adequate trial of a single agent
3. Degrees of TRD (nonresponse to adequate trials of two or more agents from different classes, augmentation, ECT)
4. Chronic refractory depression (nonresponse to multiple treatments, including augmentation and ECT)

Figure 7.3 Classification of treatment nonresponse/resistance. ECT, electroconvulsive therapy; TRD, treatment-resistant depression. Adapted from Anderson et al [3].

There is also the problem of labeling patients as being treatment-resistant in an arbitrary way. What is true is that progressively fewer people respond to subsequent treatments after previous inadequate treatment response. This has been shown most clearly in Sequenced Treatment Alternatives to Relieve Depression (STAR*D), the largest sequencing study to date [4,5].

Medication strategies

Dose increase

Controlled studies have found no evidence that increasing the dose of selective serotonin reuptake inhibitors (SSRIs) is more helpful than continuing the same dose in patients who have not responded; this is consistent with their generally flat dose-response curve [6]. There is no direct evidence for other drug classes but some do appear to have some dose-response efficacy, including tricyclic antidepressants (TCAs), venlafaxine, and escitalopram [6–8]. In spite of the limited evidence, increasing the dose, provided that side effects and safety allow, may be a reasonable step, especially as there is wide interindividual variability in plasma concentration of antidepressants and associated uncertainty about what is an effective dose for an individual patient. Increasing the dose may also keep a patient in treatment to allow adequate time to respond.

In patients who have failed to respond to previous treatments, high-dose antidepressants are sometimes considered. This is usually an off-label use and must be discussed with patients. Clinical experience suggests that some patients do benefit, particularly when treated with high-dose

TCA, venlafaxine, or monoamine oxidase inhibitors (MAOIs), but caution must be exercised and adverse events monitored for (see Chapter 5).

Switching treatment

Antidepressant switching studies show widely varying response rates (25–70%) and there is very little evidence to guide drug switching. There may be marginal benefit from switching between antidepressant classes rather than to a second drug of the same class, but this may be accounted for by studies switching from an SSRI to venlafaxine, a dual noradrenaline (NE), and serotonin reuptake inhibitor. Older studies have also suggested that switching from a reuptake inhibitor to a MAOI may be effective.

To switch safely between antidepressants there is the question of whether a wash-out period is required to avoid interactions at the cost of delay in treatment and potential deterioration in depression. Immediate switching appears reasonable with drugs of similar pharmacology, but there are also reports of safe switching between class, and indeed this may reduce discontinuation symptoms from the first drug [9]. The rule of thumb is that, if two drugs can reasonably be combined, immediate switching (between modest doses) of the two drugs appears safe and well tolerated. Potentially toxic interactions need to be considered, especially when the initial drug has long-lasting effects (eg, fluoxetine to TCA, MAOIs to serotonergic drugs), and it is recommended that appropriate reference book, such as the British National Formulary (BNF) or *Maudsley Prescribing Guidelines*, are consulted [10].

Combining treatments

Adding a second agent to an antidepressant tends to be called “augmentation” when the added drug is not an antidepressant and “combination” when two antidepressants are used. The practice of combining drugs goes back to the early days of antidepressant treatment when TCAs and MAOIs were combined, a practice now viewed as without clear benefit and potentially risky.

The longest established strategy evidence remains for lithium augmentation of monoamine reuptake inhibitors, mostly TCAs [11]. However,

the studies are small and there are few recent studies, so this evidence is less secure than it once seemed. Lithium augmentation was poorly effective in the STAR*D study [4] but in other settings it does appear effective. Results with T3 augmentation suggest efficacy but it has not been extensively studied and longer-term experience with continuing treatment is lacking. It was better tolerated and nonsignificantly better than lithium in the STAR*D study. In contrast, pindolol augmentation has been shown to be an ineffective strategy and randomized controlled trials (RCTs) with buspirone also do not support efficacy [2].

Recently studies using atypical antipsychotics as augmenting agents for SSRIs have been reported, and there is now evidence for quetiapine and some for olanzapine, aripiprazole, and risperidone as effective augmenting agents, although further data are needed as well as longer-term

Efficacy and safety of drug augmentation/combination strategies		
Combination/augmentation	Efficacy	Safety/ tolerability
Lithium + antidepressant (mostly TCAs)	++	+
T3 + antidepressants (TCAs)	+	+
Pindolol + antidepressants (SSRIs)	-	+
Buspirone + antidepressants (SSRIs)	-	+
Atypical antipsychotic + antidepressants (SSRIs)	+ / ++	+
SSRI* + mirtazapine	+	+
SSRI* + bupropion (amfebutamone)	?	+
SSRI* + mianserin	(-)	+
SSRI* + reboxetine	-	+
SSRI* + trazodone	?	+
SSRI* + TCA	?	+
Venlafaxine + mirtazapine	?	+
TCA + MAOI	?	±

*SSRIs that inhibit hepatic cytochrome P450 enzymes, especially fluoxetine, paroxetine, and fluvoxamine, may elevate plasma concentrations of other antidepressants.

Figure 7.4 Efficacy and safety of drug augmentation/combination strategies. ++, good evidence from meta-analysis of randomized controlled trials (RCTs); +, some evidence from RCTs for efficacy, reasonable tolerability; -, RCT evidence of lack of efficacy; (-), conflicting evidence; ?, unknown; ± safety depends on combinations used. MAOI, monoamine oxidase inhibitors; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. Adapted from Anderson et al [2] and Rojo et al [13].

studies. They are reasonably well tolerated but there is an increased side effect burden [12].

The rationale behind combining antidepressants is to broaden pharmacological action in the hope that multiple actions will be of benefit. As Figure 7.4 shows, combining antidepressants appears to be relatively well tolerated and safe, provided that recognized dangers in combination are avoided (eg, fluoxetine and paroxetine can cause high plasma TCA levels) [13]. However, evidence for efficacy is limited.

A variety of other augmentation strategies have been used. Tryptophan augmentation of MAOIs has some support and clinically it has been used as an adjunct to lithium + MAOI and lithium + TCA combinations, with the rationale that it increased serotonin availability. There is current interest in adding treatments that might be considered “complementary” to antidepressants such as eicosapentaenoic acid, which has some preliminary evidence for efficacy [2].

The disappointing efficacy of strategies for treating depression poorly responsive to antidepressants has led to a wide variety of proof-of-concept studies based on plausible pharmacological rationales. The place for these combinations is generally in research settings.

Augmentation/combination strategies are increasingly seen as a useful addition to the options for next-step treatments, but caution is warranted to ensure that they are used safely. Many combinations involve off-label use and discussion with the patient is required and informed consent obtained. Augmentation strategies are particularly useful when current treatment has produced some benefit and stopping the current antidepressant risks losing this. They are also particularly useful when dose increase and switching strategies have failed.

Psychological treatment strategies

There is less evidence about the use of next-step psychological treatment in patients inadequately responsive to treatment. The STAR*D study found that cognitive behavioral therapy (CBT) was equally as effective as antidepressants as both a switch and an augmentation strategy after inadequate response to citalopram [14]. There is some evidence that adding CBT to the treatment of patients in partial remission after being

treated with antidepressants alone produces further improvement and may reduce the risk of relapse [15]. The finding that combined CBT and antidepressants may be more effective than either alone in moderate-to-severe depression adds weight to using this combination in patients inadequately responsive to either treatment alone [16,17]. At present we do not have evidence about the place of other psychotherapies, or sequencing psychotherapies, as next-step treatments.

Physical treatment strategies

Electroconvulsive therapy (ECT) is a very effective antidepressant treatment (see Chapter 6 for full discussion) and it is clear that patients who have failed to respond to a number of medication steps can derive significant benefit. One problem with using ECT in these patients is that, although acute efficacy is good, the relapse rate is high in the absence of effective continuation treatment, with up to 80% of patients relapsing over the next 6 months on placebo treatment [2]. In practice it is prudent to change the medication regimen from the one that failed before ECT and consideration should be given to augmentation with lithium.

Less established brain stimulation techniques such as repetitive transcranial magnetic stimulation (TMS) and vagus-nerve stimulation (VNS) (see Chapter 6) may also be useful in patients who are poorly responsive to medication, although these techniques do not seem to be as effective as ECT. One study showed that VNS is unlikely to be clinically effective if there have been more than seven previous failed treatments. Another physical therapy, deep brain stimulation (discussed in Chapter 6), is currently only an experimental treatment for depression.

Ablative neurosurgery for depression has a long clinical history but there are no RCTs. Clinical experience suggests that it can be effective for some patients refractory to all other treatments. It needs to be administered in specialist centers with effective procedures for external review.

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Continuation and maintenance treatment

Ian M Anderson

As discussed in Chapter 4, the aim of the acute phase of treatment is remission. This chapter is concerned with treatment once this aim has been achieved.

Goals of continuation/maintenance treatment

The goals of longer-term treatment are outlined in Chapter 4 and consist of continuing symptomatic and functional remission/recovery and consolidation and maintenance of wellbeing. A key point is preventing relapse/recurrence of depression and an important clinical issue is how long to advise continuing treatment beyond remission for individual patients. There are two aspects: continuing with treatment for as long as the benefits outweigh the risks/adverse effects and minimizing risk factors for relapse/recurrence.

Phases of treatment

An influential model of phases of treatment with antidepressants is that of Frank et al (Figure 8.1) [1,2]. It proposes a continuum between depressive symptoms and major depression, with phases of treatment going through response to remission, which, if stable for 4–6 months, results in recovery. A return of depression is said to be a relapse before recovery

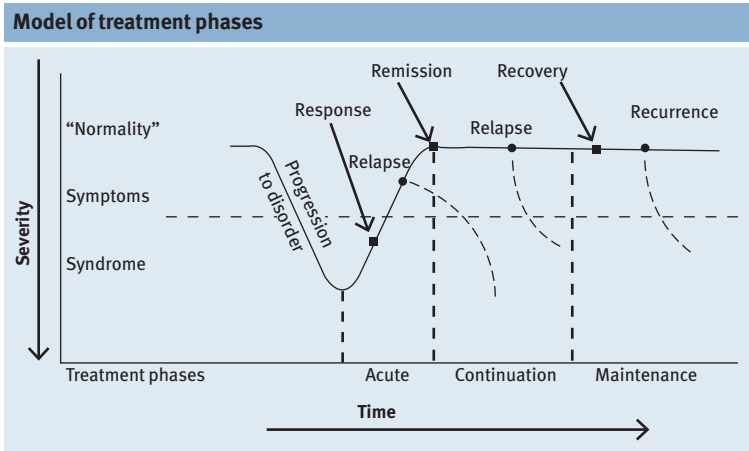


Figure 8.1 Model of treatment phases. Reproduced with permission from Kupfer [2] ©Physician Postgraduate Press.

and recurrence thereafter, and a distinction is made between continuation treatment to prevent relapse and maintenance treatment to prevent recurrence. The model has been helpful conceptually and in treatment trial design, but in practice it is not possible to know when remission becomes recovery, so it is difficult to distinguish between relapse and recurrence. This is illustrated by International Classification of Mental and Behavioral Disorders, 10th revision (ICD-10) requiring 2 months of absence of depressive symptoms to delineate different episodes, whereas Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) requires only 2 months of not meeting major depression criteria. Neither of these agrees with the model in Figure 8.1, which requires 4–6 months of remission to define recovery.

An alternative is a continuum model based on the chance of a new episode of major depression over time after achievement of remission. Prospective studies show a high early rate of relapse, which gradually flattens out but never fully plateaus. The highest risk period is in the first 3 or 4 months with much lower risk beyond 1 year, but the risk varies depending on the individual's particular risk factors [3]. This influences the benefit that patients might receive from continuing treatment and therefore when to stop it.

Medication

In patients with a relatively low risk of relapse (eg, first episode), there is compelling evidence from placebo-controlled discontinuation studies that continuing antidepressants for a further 6–9 months after prevents relapse (from approximately 50% to 20–25%) [4]. Beyond this time the risk of relapse is relatively low and the benefit from continuing antidepressants is not apparent. This is often called the continuation phase after acute treatment and applicable to all patients whose depression remits with antidepressants.

In contrast, in highly recurrent depression (usually three episodes in the last 5 years) the benefit from antidepressants continues as long as the studies continue (the longest has been 5 years). The use of antidepressants after the continuation phase for prevention of further episodes of depression is often referred to as maintenance treatment. A meta-analysis of studies with follow-up as long as 3 years found that continuing antidepressants reduced the odds of relapse by 70%, irrespective of time from remission, even though the absolute risk of relapse was lower the greater the time since remission [5]. However, patients with recurrent depression who have done well on antidepressants still have a high risk of relapse even after 18 months' remission. A 2-year, randomized, placebo-controlled discontinuation study following 6 months' remission with open venlafaxine treatment found that, over 2 years, continuing venlafaxine reduced relapse to 29% from the 47% experienced on placebo. Most striking, however, were the results in patients who had remained well on venlafaxine over the first year and were re-randomized to continue venlafaxine or placebo. In the second year only 7% of patients who remained on venlafaxine relapsed, compared with 37% on placebo [6].

The evidence for lithium being an effective maintenance treatment in unipolar depression is weaker than for antidepressants [7], but it is often used in secondary care in addition to antidepressants. If lithium has been used as an effective augmentation treatment it is usually best to continue this along with antidepressants to prevent relapse [8].

There has been debate about whether some antidepressants provide better protection against relapse/recurrence than others, in particular whether SSRIs lose efficacy. At present the evidence is lacking as to

whether this phenomenon exists or whether antidepressants differ in prophylactic efficacy. What is clear is that the treatment dose should be continued as the continuation and maintenance dose. There is no place for a lower “maintenance dose” of antidepressants because decreasing the treatment dose is associated with a higher risk of relapse [3].

Long-term treatment brings side effects more to the fore as patients who were willing to tolerate side effects to get better are usually less willing to put up with them long-term when they are feeling well, particularly when they cause impairments in functioning and quality of life. It is therefore important to consider long-term side effects (eg, sexual dysfunction and weight gain) when initially choosing treatment for patients who need maintenance treatment.

Psychological treatments

Much less is known about continuation/maintenance treatment with psychological treatments. There is some evidence that initial successful treatment with CBT does provide protection against relapse after the treatment has finished [9]. This is in contrast to antidepressant treatment where continuing with treatment is required to prevent relapse. This makes CBT an important treatment option to consider in patients with recurrent depression because it has also been shown to be effective in relapse prevention when given to patients with a high recurrence risk after remission on antidepressants [10]. The presumed mechanism is the reduction of cognitive vulnerability to relapse through the techniques learned in therapy. However, recent studies suggest that relapse is delayed rather than prevented, and eventually patients do suffer another episode.

Continuation cognitive behavioral therapy (CBT) in one study, which found that 8 months' continuation treatment reduced relapse over that period in highly recurrent patients who had responded to CBT acutely. In the highest-risk groups (early onset and unstable remission in the acute phase) this benefit was maintained to 2 years [11]. In contrast there is weaker evidence for relapse prevention with interpersonal psychotherapy and it is lacking with other forms of psychotherapy.

Physical treatments

Electroconvulsive therapy (ECT; Chapter 6) appears clinically useful as a continuation/maintenance treatment for a minority of patients who respond well to ECT but relapse occurs in spite of vigorous ongoing drug and psychological treatment [12]. In practice it is rare for patients to continue long term with ECT, but in individual cases it does not appear to cause cumulative cognitive or other adverse effects, or brain damage. The usual frequency of maintenance ECT is about monthly.

There is preliminary evidence that vagus-nerve stimulation VNS may reduce relapse in patients who have received benefits with acute treatment (see Chapter 6) [13].

Risk factors for relapse and recurrence

Figure 8.2 outlines factors that have been associated with higher risk of relapse or recurrence. The most important are probably the presence of residual symptoms, number of previous episodes, severity of index episode, and presence of treatment resistance (duration and degree of the most recent episode), but many of the factors clearly interact.

Longer-term treatment in practice

Longer-term management of depression requires careful assessment of an individual's depressive disorder and risk of relapse. In addition, it is important to consider the consequences of relapse and the timing of withdrawal of antidepressant treatment because the risk of relapse is highest in the months after stopping or reducing the dose of antidepressants. It is difficult to predict with certainty and it is important to adopt a staged approach to the assessment of the need for continuing treatment, rather than set a fixed term. It often becomes clearer over time how high the risk is, with relapse or continuing symptoms making the need for treatment clearer.

It is best to approach the risk of recurrence as a continuum, taking into account the risk factors in Figure 8.2. The risks of relapse need to be discussed with patients as well as the risks and benefits of treatment, to help them make a considered decision about ongoing treatment. It is

Risk factors associated with relapse/recurrence of depression

Shorter time since remission
 Partial remission and residual symptoms
 Number of previous episodes, especially two or more episodes in last 5 years
 Severe index episode
 Psychosis in index episode
 Duration of symptoms, including dysthymia
 Treatment resistance (duration and degree)
 Persistence of social stress/poor social adjustment/life events
 Comorbid physical illness
 Comorbid anxiety
 Female gender
 Positive family history of depression

Figure 8.2 Risk factors associated with relapse/recurrence of depression. Reproduced with permission from Anderson et al [4] ©Sage Publications.

also important to help them consider the consequences of relapse and address any remedial risk factors for relapse (eg, social stress, approaching life events, substance misuse), as well as lifestyle changes that might increase resilience to relapse (eg, stable routines, exercise). Residual symptoms and cognitive factors for relapse (eg, low self esteem, negative self-evaluation, interpersonal sensitivity) are an indication to consider a specific psychotherapy (eg, CBT) to consolidate remission. Suggested starting points with regard to ongoing treatment [3]:

- After complete remission with antidepressant treatment in a patient with relatively low risk of recurrence (eg, first episode depression in the absence of other risk factors), it is advisable to continue antidepressants for 6 months to prevent relapse.
- In patients with partial remission after antidepressant treatment or those with recurrent depression, undertaking CBT in addition to antidepressants is advisable to promote remission and reduce the risk of relapse.
- In patients with recurrent depression and unstable remission with CBT, a period of continuation CBT is advisable.
- In patients at significantly higher risk of relapse, who are in full or partial remission with antidepressant treatment, it is advisable to continue antidepressants and reassess after a minimum of 2 years'

maintenance treatment. If a significant risk of relapse continues then continuing antidepressants is advisable, if necessary indefinitely.

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