

The pharmacological management of depression

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Depressive disorders are common, recurrent, and chronic, and require treatment. A review of the symptom picture and current drug targets demonstrates the need for accurate assessment of depression severity, including suicidality. The initial focus of treatment is rapid resolution of symptoms during an acute phase, followed by continuation. Maintenance treatment is indicated if the risk of recurrence is high. The range of available medications is considerable and the benefit/risk ratio is acceptable. Depression is diagnosable across the life span and treatable at every age (although recent disagreement has arisen with regard to young patients). Comorbidity, both psychiatric and medical, need to be assessed, as does the possible presence of two subtypes of depression (psychotic and bipolar) often requiring different interventions. It is expected that the next generation of antidepressants would be associated with more specific disease and outcome biomarkers.

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Depressive disorders are common, recurrent, chronic, and require treatment. Major depressive disorder can occur across the entire life cycle and is the most common of the severe psychiatric illnesses. In the USA, the lifetime prevalence was 16.2% (32.6-35.1 million adults) and the 12-month prevalence was 6.6% (13.1-14.2 million adults) in a recent survey.¹ According to the World Health Organization's *Global Burden of Disease Report*,² major depression was the fourth leading cause of disease burden worldwide in 1990. The World Health Organization predicts that by 2020, major depression will become the second leading cause of worldwide disease burden, surpassed only by ischemic heart disease. In this review, we will focus on major depressive disorder, although we will also briefly discuss bipolar depression.

Symptom picture syndrome

The cardinal feature of major depression is persistent depressed mood or pervasive loss of interest or pleasure for a minimum of 2 weeks, accompanied by a series of somatic and cognitive changes (*Table I*). In assessing the core components of depression, it is important to note that the psychological and biological symptoms are accompanied by negative thought content, cognitive dysfunction, and suicidal ideation. These components follow the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* nosology for mood disorders, but recently there has been considerable interest in assessing not only current symptoms, but also "softer" or spectrum features, which may present lifetime signs of particular mood or mood-related spectra.^{3,4} In fact, such persistent features may relate to levels of functional impairment during episodes of depression more directly than current symptoms. Such assessment strategies raise the need for assessment of dimensional approaches to

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Selected abbreviations and acronyms

CBT	<i>cognitive behavioral therapy</i>
DA	<i>dopamine</i>
5-HT	<i>5-hydroxytryptamine (serotonin)</i>
MAOI	<i>monoamine oxidase inhibitor</i>
NE	<i>norepinephrine</i>
NNT	<i>number needed to treat</i>
SNRI	<i>serotonin and noradrenaline uptake inhibitor</i>
SSRI	<i>selective serotonin reuptake inhibitor</i>
TCA	<i>tricyclic antidepressant</i>

diagnosis, as well as the measurement of traditional categorical distinctions.⁵ Women are at twice the risk of men. Depression can and often does co-occur with another psychiatric condition or with a medical disease. Depression is a life-threatening illness for both men and women since suicide is estimated to be the cause of death in up to 6% of individuals with clinical depression.⁶

Pathogenesis and drug targets

It has been assumed that the neurobiological systems involved in the pathogenesis of depression are primarily the monoaminergic neurotransmitter systems. Considerable research has been directed toward uncovering specific defects in serotonin (5-hydroxytryptamine [5-HT]), norepinephrine (NE), and to a lesser extent dopamine (DA) neurotransmitter systems. The blockade of neurotransmitter receptors or transporters by antidepressant drugs occurs at the level of the neuronal synapse. This capacity to produce acute increases in synaptic levels of monoamines (*Table II*)⁷ has been long considered responsible for both therapeutic and adverse effects of antidepressants. However, recent advances in the neuroscience

Depressed mood or sadness	Negative thought content
Loss of interest (motivation)	• Guilt/self-blame
Loss of libido	• Worthlessness
Inability to enjoy oneself	• Low self-esteem
Irritability	• Pessimism
Anxiety	• Hopelessness
Changes in sleep	Cognitive dysfunction
Changes in appetite	• Diminished decision-making ability
Changes in energy	
Psychomotor retardation	• Poor memory
	• Poor concentration
	Suicidal ideation

Table I. Core components of major depression.

of mood regulation have pointed to the involvement of additional neurotransmitter systems and to the influence of several neuroendocrine axes; however, these discoveries have not yet led to approved treatments for depression, nor have they fundamentally changed our basic understanding of depression. Further developments in the drug treatment of depression are being actively pursued. Medications currently under testing programs include dual reuptake inhibitors, novel dopamine reuptake inhibitors, drugs combining 5-HT reuptake inhibition with 5-HT₂/5-HT₃ receptor antagonism, corticotropin-releasing factor (CRF) receptor antagonists, substance P (neurokinin) receptor antagonists, melatonergic agonists, and compounds modulating glutamatergic neurotransmission. Other novel treatment strategies are also in the pipeline.⁸ Most recently, attention has moved from intrasynaptic changes in neurotransmitter levels to changes in intracellular signaling pathways.⁹ In an important review, Manji and colleagues⁹ raise the possibility that depression may be associated with impairments in signaling pathways that are considered important for the regulation of neuroplasticity and cell survival. The heuristic value of such an approach, as highlighted in *Figure 1*, points to the wide-ranging possibilities of understanding the mechanisms of

Antidepressant	NE	5-HT	DA
Amitriptyline	+++	++++	-
Amoxapine	+++	+++	-
Bupropion	0	-	+
Citalopram	-	+++++	0
Clomipramine	+++	+++++	-
Desipramine	+++++	+++	-
Doxepin	+++	+++	0
Duloxetine	++++	+++++	+
Fluoxetine	++	+++++	-
Fluvoxamine	+	+++++	-
Imipramine	+++	+++++	-
Mirtazapine	-	0	0
Nefazodone	++	++	++
Paroxetine	+++	+++++	+
Sertraline	+	+++++	+++
Venlafaxine	+	++++	-

Table II. Antidepressant potency for blocking norepinephrine (NE), serotonin (5-hydroxytryptamine [5-HT]), and dopamine (DA) transporters. + to +++++, increasing levels of potency; -, weak; 0, no effect. Adapted from reference 7: Richelson E. The clinical relevance of antidepressant interaction with neurotransmitter transporters and receptors. *Psychopharmacol Bull.* 2002;36:133-149. Copyright © 2002. Medworks Media LLC.

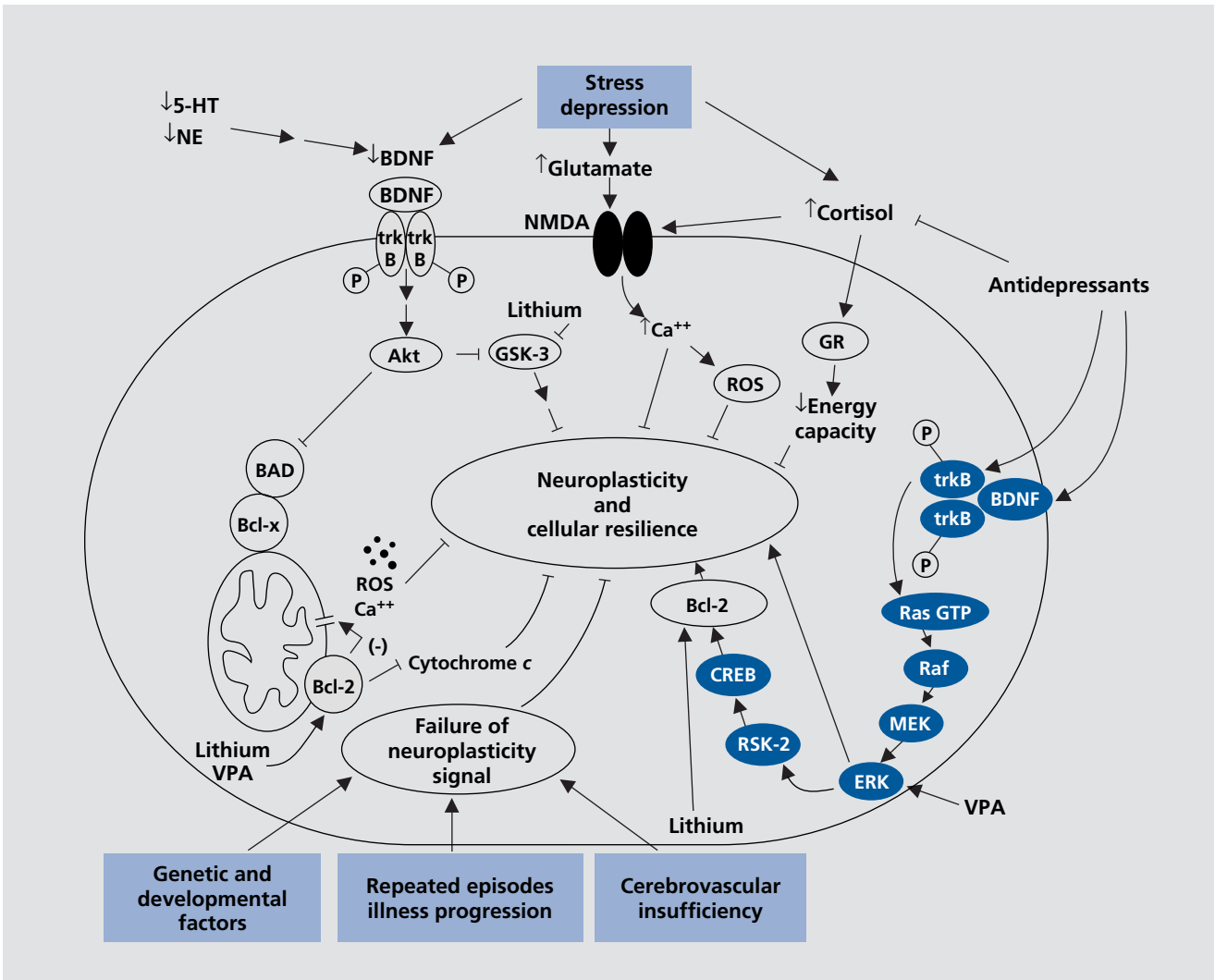


Figure 1. Neuroplasticity and cellular resilience in mood disorders: the multiple influences on neuroplasticity and cellular resilience in mood disorders. Genetic/neurodevelopmental factors, repeated affective episodes, and illness progression might all contribute to the impairments of cellular resilience, volumetric reductions, and cell death/atrophy observed in mood disorders. Stress and depression likely contribute to impairments of cellular resilience by a variety of mechanisms, including reductions in the levels of brain-derived neurotrophic factor (BDNF), facilitating glutamatergic transmission via *N*-methyl-D-aspartate (NMDA) and nonNMDA receptors, and reducing the cells energy capacity. Neurotrophic factors, such as BDNF, enhance cell survival by activating two distinct signaling pathways: the phosphatidylinositol (PI)-3-kinase pathway, and the extracellular signal-regulated kinase (ERK)-mitogen activated protein (MAP)-kinase pathway. One of the major mechanisms by which BDNF promotes cell survival is by increasing the expression of the major cytoprotective protein, Bcl-2. Bcl-2 attenuates cell death via a variety of mechanisms, including impairing the release of calcium and cytochrome c, sequestering proforms of death-inducing capase enzymes, and enhancing mitochondrial calcium uptake. The chronic administration of a variety of antidepressants increases the expression of BDNF, and its tyrosine kinase receptor (trkB). Lithium and valproic acid (VPA) robustly upregulate the cytoprotective protein Bcl-2. Lithium and VPA also inhibit glucocorticoid synthase (GSK-3b), biochemical effects shown to have neuroprotective effects. VPA also activates the ERK-MAP-kinase pathway, effects that may play a major role in neurotrophic effects and neurite outgrowth. NGF, nerve growth factor; Bcl-2 and Bcl-x, antiapoptotic members of the Bcl-2 family; BAD and Bax, proapoptotic members of the Bcl-2 family; Ras, GTP, Raf, MEK, ERK, components of the ERK-MAP-kinase pathway; CREB, cyclic adenosine monophosphate (cAMP) responsive element binding protein; Rsk-2, ribosomal S-6 kinase; ROS, reactive oxygen species; GR, glucocorticoid receptor; 5-HT, 5-hydroxytryptamine; NE, norepinephrine; P, phosphorylation.
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action of currently available medications, but raise the possibilities of new targets for future drug development. Furthermore, the review proposes roles for chronic stress. In turn, McEwen's concept of "allostatic load" may be incorporated into how recurrent depression leads to structural and functional central nervous system (CNS) impairment.¹⁰

Assessment

In assessing depression, clinicians should consider the level of symptom severity and current functional impairment of the patient, the duration of the depression, the presence of psychotic symptoms, level of suicidality, and previous illness and treatment history. Most depressed patients do not self-refer directly to a psychiatrist. Instead, they seek help from a primary care physician, often focusing on somatic disorders or energy rather than mood complaints. Recognition (sometimes more difficult in men) and appropriate diagnosis should be followed immediately by a treatment plan. If the plan includes medication, it must involve the choice of an appropriate drug prescribed at an adequate dosage and for a sufficient duration, with attention to treatment adherence by patient and family members or caretakers, if necessary.¹¹ Recognition and treatment of depression in the context of an ongoing medical disease, such as diabetes or hypertension, is very important. The primary care physician is generally in an excellent position to do so if he or she is responsible for the overall medical care of the patient. Consultation and referral to a psychiatrist is appropriate in selected cases if the primary care physician is concerned about the complexity of the case. The treating physician needs to evaluate the complexity of the symptom picture (eg, delusions, mixed manic and depressive symptoms) and dangerousness with respect to suicide or homicide at each visit. He or she should seek consultation in difficult-to-treat cases. Several forms of brief depression-specific psychotherapy, including cognitive therapy¹² and interpersonal psychotherapy,^{13,14} have been shown to have efficacy equal to that of antidepressant medication and should be considered as treatment options or adjuncts. However, a review of these treatment strategies is beyond the scope of this review.

Assessment of suicidality

Probably half of patients with major depressive episodes report death wishes, feeling that they have no reason to live, thinking they would be better off dead, thoughts of

harming or killing themselves, or actual plans to do so. Suicidal risk should be assessed not only at the initiation of treatment, but repeatedly throughout treatment. Some patients will not report suicidal ideation until they feel comfortable with the clinician, often several weeks into treatment. It is essential to ask if patients have thoughts or plans to harm themselves, whether they have a history of suicide attempts (and, if so, to determine the medical seriousness of prior attempts), and whether they have access to means. This includes specific questions about access to firearms, since half of all suicides in the USA involve handguns.¹⁵ If a patient acknowledges a plan or intent to harm him/herself, then emergency psychiatric evaluation is indicated. Up to 75% of patients who complete suicide¹⁵ have seen a primary care physician within the month prior to death, meaning that the physician has a unique opportunity to prevent suicide through appropriate intervention. Depressed patients with suicidal ideation often take longer to respond to treatment, thus necessitating a longer period of vigilance on the clinician's part.¹⁶ Due diligence includes both frequent assessments of suicidal ideation and hopelessness, aggressive treatment of the depression, and creation of a safety net involving other members of the health care team and family members or caregivers. In the USA and UK over the past 18 months, considerable furor has raged about the risk that the use of one class of antidepressants, selective serotonin reuptake inhibitors (SSRIs) may actually raise the likelihood of suicidal ideation and suicidal acts, rather than reducing the likelihood. Examination of adverse event reports for SSRIs in children and adolescents has led to "black box warnings" in the package inserts for SSRIs in the USA and considerable "official" caution in the UK about prescribing such drugs for individuals under the age of 18. These policy decisions have illustrated the need for better methodical approaches for risk assessment (see below).

Phases of treatment

In developing a treatment strategy, it is useful for the clinician to consider treatment of major depression as involving three phases: acute, continuation, and maintenance (if appropriate). The goals of the acute phase are to achieve remission (resolution of all symptoms) and restore functioning (*Table III*).^{17,18} During this period, continued follow-up visits are essential. The goal of the continuation phase is sustained remission. Unfortunately, only recently has renewed attention been devoted to the issue of

response versus remission. Failure to achieve complete remission (recovery) has major adverse consequences including the following: increased risk of relapse¹⁹ and treatment resistance; persistent functional impairment²⁰; sustained risk of suicide; worsened morbidity of other psychiatric conditions; and medical disorders. This phase should last approximately 6 months following full remission of the acute episode. Then, the patient in whom the risk for recurrence is low should be gradually tapered from treatment over a period of 1 to 3 months. Rapid discontinuation of virtually all antidepressants, including those with long half-lives, tends to be associated with symptomatic relapse. Since the majority of depressed individuals suffer from recurrent depression, the physician should consider the appropriateness of a maintenance phase. Data on long-term treatment in the psychiatric specialty sector indicate that maintenance treatment should be sustained for a minimum of 3 to 5 years. Unfortunately, there are no such²¹⁻²³ studies in primary care to determine appropriate duration of long-term treatment in this setting.

Available medications and their use in acute treatment

There is no paucity of medications approved by the Food and Drug Administration (FDA) for a depression indication. One of the two initial classes was the tricyclic antidepressants (TCAs), a family of structurally related compounds with reuptake inhibitory properties on brain monoamine metabolism. All the TCAs are potent blockers of NE reuptake (except for clomipramine which is highly serotonergic, but is approved by the FDA only for treatment of obsessive-compulsive disorder) and weak blockers of 5-HT reuptake. The second original class of drugs, the monoamine oxidase inhibitors (MAOIs), have never been widely prescribed because of real (and sometimes exaggerated) concerns about safety, despite their established efficacy in certain subtypes, especially atypical and bipolar depression.^{24,25}

A majority of the newer compounds are considered to be SSRIs. Despite a number of meta-analyses of efficacy showing no differences between TCAs and SSRIs in ambulatory studies, the more favorable adverse effect profile (including a virtual absence of overdosage lethality), ease of administration, and acceptance by physicians across specialties have led to the emergence of the SSRI as first-line treatments.^{26,27} Patients can be started on the initial dose as indicated in *Table IV* and gradually increased over

a 10- to 14-day period to the modal therapeutic dose. If the patient has not responded to this dose by 3 to 4 weeks, one should consider increasing the dose again. When the first drug in this class is not effective, experienced clinicians will often either try to augment the response with another medication or switch to another SSRI.

In *Table IV*, the starting, modal therapeutic, and maximum recommended doses are listed for the approved drugs by class. Other currently approved antidepressants are available in the USA include venlafaxine, mirtazapine, bupropion, trazodone, and nefazodone. While trazodone is often used as an adjunctive medication for sleep problems associated with depression itself or with the use of the more alerting SSRIs, of these four drugs, only venlafaxine (with presumed dual neuronal reuptake inhibition) has emerged as comparable in overall use to the SSRIs. In fact, several meta-analyses have pointed to increased efficacy when compared with fluoxetine, but not necessarily with other SSRIs (C. Nemeroff, personal communication).^{28,29}

The antidepressant market remains a highly competitive one, with a number of pharmaceutical companies introducing compounds that they hope will prove to have faster onset of action, produce a more complete remission, and reduce side-effect burden, especially weight gain and sex-

<ul style="list-style-type: none"> • Contact frequency
Weekly for the first 4 weeks of each stage, then every 2 weeks until 75% improvement is maintained for 4 weeks
<ul style="list-style-type: none"> • Assessment frequency
At each contact
<ul style="list-style-type: none"> • Duration of acute treatment
At least 75% for 4 weeks, then move to continuation phase
<ul style="list-style-type: none"> • Response
Nonresponse (<25% improvement)
Minimal response (25-50% improvement)
Partial response (50-75% improvement)
Full response (75-100% improvement)
Full remission (75-100% improvement sustained for 4 weeks)
<ul style="list-style-type: none"> • Criteria for medication change
Anything less than 75% improvement or full response may require a medication change
<ul style="list-style-type: none"> • Evaluations
At each contact, a nurse's or physician's assessment of core symptom severity, overall functional impairment, side-effect severity, and other symptoms

Table III. Depression medication algorithms. Contact may be in person or by telephone. Reproduced from Rush AJ et al (The Texas Medication Algorithm Project), personal communication.

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ual dysfunction. Escitalopram (the single-isomer form of citalopram) recently received FDA approval and duloxetine (an SNRI [serotonin and noradrenaline uptake inhibitor] with dual reuptake inhibition of 5-HT and NE) has also been approved. It is also important to point out that several antidepressant drugs approved in Europe and

Canada (eg, tianeptine, reboxetine, milnacipran, and moclobemide) are not approved for use in the USA.

Therapeutic interest in psychostimulants has led to studies suggesting that methylphenidate is generally well tolerated and modestly efficacious for medically burdened depressed elders, but should only be used in the short term.³⁰ It is also appropriate to comment on the current status of herbal remedies for depression that currently fall outside the FDA guidelines. Although there are a number of reports pointing to the efficacy of *Hypericum perforatum* (Saint John's wort) for major depression,^{31,32} two US trials comparing *Hypericum* with an SSRI and placebo have not supported this claim.³³⁻³⁵

While adverse effects are reported with all antidepressant compounds, most are transient and no major adverse effects have been reported after long-term use. In general, the TCAs are distinguished by anticholinergic and antihistaminic effects (Table V).³⁶⁻⁴¹ Drug interaction with TCAs and other medications affecting the hepatic enzyme (CYP 2D6) can lead to significantly altered TCA plasma levels. MAOIs are used sparingly, partly because of concern with hypertensive crises, as well as their interaction with other prescribed medications and beer, red wine, and foodstuffs rich in the amino acid tyramine, such as aged cheese and liver. Clinical experiences in the last 15 years have shown that the SSRIs are relatively safe, but their adverse effect profile may not be the same across the entire class. While the efficacy and adverse effect profile should be considered in selecting among the SSRIs, in usual practice these drugs do not differ dramatically in efficacy from each other or from the older classes of antidepressants. The adverse effects that most frequently influence patients' decisions to discontinue treatment are sexual dysfunction and weight gain. In inpatient settings, TCAs are still often used as first-line treatment. Not all SSRI (eg, citalopram and sertraline) have a high degree of drug-drug interaction via the cytochrome P450 (CYP) system. While nausea, sedation, appetite change, and sexual dysfunction seem approximately similar for the SSRI class, claims for reduced adverse effects on sexual functioning have been made for fluvoxamine (only approved by the FDA for obsessive-compulsive disorder),⁴² as have claims for reduced discontinuation effects for fluoxetine.⁴³ Finally, the high degree of comorbidity of depression and cigarette consumption needs to be fully understood. Tobacco smoking can induce CYP enzyme changes affecting blood levels of various antidepressants, as well as complicate drug management when smoking cessation occurs.⁴⁴

Drug name	Initial dose (mg/day)	Modal therapeutic dose (mg/day)	Maximum dosage (mg/day)
SSRIs			
• Fluoxetine*	20	20-40	60-80
• Paroxetine	20	30	50
• Sertraline	50	100	200
• Fluvoxamine* [†]	50	150	300
• Citalopram	20	30	40-60 [‡]
• Escitalopram	10	20	20 [§]
TCAs and related compounds			
• Amitriptyline*	25	150	300
• Nortriptyline*	25	50-75	100-150
• Imipramine*	25	150	300
• Desipramine*	25	100	300
• Doxepin*	25	100	300
• Clomipramine* [†]	25	100	250
• Protriptyline	10	20-30	60
• Trimipramine*	25-50	150	300
• Amoxapine	50	150-200	400
• Malprotiline	25-50	150-225	300
Mixed norepinephrine/serotonin reuptake inhibitors			
• Venlafaxine	75	150	225/375
• Mirtazapine	15	30	45-60 [‡]
Other antidepressants			
• Bupropion*	150	300	450
• Trazodone*	50	200	400-600
• Nefazodone	200	300	600
MAOIs			
• Phenelzine	15	45	90
• Tranylcypromine	10	40	60
• Isocarboxazid	20	30-40	60

Table IV. Currently available antidepressants and their recommended dosages. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor. *A generic formulation is available. [†]Approved by the Food and Drug Administration (FDA) for treatment of obsessive-compulsive disorder, but not depression. [‡]The higher dosage is approved in some countries but not in the USA. [§]A maximum therapeutic dose has not yet been established for this compound. ^{||}Even higher doses might be indicated if plasma drug concentrations are low (ie, <50 ng/mL). [¶]The maximum FDA-approved dosage of the extended-release formulation is 225 mg/day.

	SSRI	TCA	Mixed NSRI	MAOI	Bupropion	Trazodone	Nefazodone
• Anticholinergic effects							
Dry mouth	Moderate:	AMI, AMX, CLO,	MRZ>VEN	Moderate	Moderate	None	Moderate
Constipation	PAX, FLVX	PRO>DOX, DES,				significant	
Sweating		IMI, NOR;					
Urinary retention		contraindicated in glaucoma, DOX					
• CNS effects							
Sedation	Insomnia and	AMI, CLO, DOX,	Moderate	Headache	Moderate	High	Moderate
Insomnia	somnolence	IMI>AMX, DES,	sedation/ somnolence,		sedation, headache	sedation	sedation, headache, asthenia
Headache	common to all;	NOR	MRZ; headache, asthenia, VEN				
Asthenia	asthenia, SER, CIT; headache, CIT						
• GI effects							
Nausea	Nausea, diarrhea	Weight gain,	Moderate weight	Moderate	Nausea,	None	Hepatic
Weight changes	common to all	CLO	gain, appetite	weight gain	vomiting, weight gain	significant	dysfunction, nausea
Appetite changes			changes, MRZ; nausea, VEN	or anorexia			
Hepatic dysfunction							
• Cardiovascular effects							
Orthostatic hypotension	None significant	Monitor ECG in patients with history of CAD or high dose TCAs; better tolerated, DES, NOR; contraindicated in acute recovery of MI; orthostatic hypotension, IMI	Hypertension, caution in elderly or those with history of CAD with doses >200 mg/day, VEN	Hypertensive crisis; postural hypotension	None significant	Syncope	None significant
Tachycardia							
ECG changes							
• Sexual dysfunction							
Impotency	PAX, FLX,	AMI, AMX,	Abnormal	Impotency	None	Priapism	None
Abnormal ejaculation	SER>FLVX,	CLO, DES,	ejaculation,		significant		significant
Decrease libido	CIT, ECIT	NOR, PRO	impotency, VEN				
Agnorgasmia							
• Discontinuation syndrome							
Physical symptoms (ie, GI, sleep disturbances)	More common, PAX, SER;	Associated more with physical and psychological symptoms	VEN	Greater propensity, TRY	None significant	None significant	None significant
Psychological symptoms (ie, somatic, affect)	less due to longer-acting						
Sensory abnormalities (ie, paresthesia, numbness)	metabolite, FLX; all three symptom types seen						

Table V. Adverse effects of antidepressants.³⁶⁻⁴¹ SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; NSRI, noradrenaline and serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor; AMX, amoxapine; DOX, doxepine; IMI, imipramine; PRO, protriptyline; AMI, amitriptyline; ECIT, escitalopram; MRZ, mirtazapine; SER, sertraline; CIT, citalopram; FLVX, fluvoxamine; NOR, nortriptyline; TRY, tranylcypromine; CLO, clomipramine; FLX, fluoxetine; PAX, paroxetine; VEN, venlafaxine; DES, desipramine; CNS, central nervous system; GI, gastrointestinal; ECG, electrocardiogram; CAD, coronary artery disease; MI, myocardial infarction.

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Depression across the life span

While some aspects of the symptom picture may change across the life span, the core features of depression are recognizable. In children and adolescents, depression is not always characterized by sadness, but instead by irritability, boredom, or an inability to experience pleasure. Depression is present in about 1% of children and 5% of adolescents at any given time.⁴⁵ Before puberty, boys and girls are at equal risk for depression, whereas after the onset of puberty, the rate of depression is about twice as high in girls. While prepubertal depression is less prevalent than postpubertal depression, appropriate management at any age for major depression is recommended. At the other end of the life span, depressed older adults will usually be seen at medical facilities. Major depression affects 5% to 10% of older adults who visit a primary care provider⁴⁶⁻⁴⁸ and has negative implications for the prognosis of almost all co-occurring medical illnesses with which such patients may present.

Treatment of child and adolescent depression

Drug treatment for children or adolescents with depression is primarily dependent on SSRIs as first-line acute treatment. Efficacy trials have been conducted with fluoxetine, paroxetine, and citalopram.⁴⁹⁻⁵¹ The recommended practice is to start at half the usual dose of an SSRI (eg, 10 mg/day fluoxetine, paroxetine, or citalopram) for 1 week for adjustment purposes and then increase the dose to the equivalent of 20 mg/day fluoxetine for another 3 weeks.⁴⁵ It takes up to 4 weeks at steady state to determine whether a given dose will be helpful. Thus, further increases should be made at 4-week intervals. Because children and adolescents metabolize SSRI more rapidly than adults, they often require doses above the equivalent of 20 mg fluoxetine to attain a clinical response.⁵² The large National Institute of Mental Health (NIMH) multicenter contract, Treatment for Adolescents With Depression Study (TADS),⁵³ for the treatment of depression in adolescents has been recently completed, and perhaps will provide more definitive data for this population.

In a sample of 439 adolescents (aged 12 to 17 years) with major depression, four randomly assigned interventions were utilized: fluoxetine (10 to 40 mg/day) with cognitive behavioral therapy (CBT); fluoxetine alone; CBT alone; and placebo. As noted in *Table VI*, 71% responded to the

combined treatment, with 60.6% to fluoxetine alone, 43.2% to CBT alone, and 34.8% to placebo. A clinically useful manner to review these findings is to calculate number needed to treat (NNT; calculated as 1/risk difference). NNT represents the number of subjects who would have to be treated with active treatment to obtain one success that would not be obtained with the control treatment. Referring to *Table VI*, NNT for the combination treatment is 3, fluoxetine alone 4, and CBT alone 12, suggesting a medium effect size for the combination treatment and for fluoxetine alone. In addition, clinically significant suicidal thinking present in 29% of the sample at baseline improved significantly. Seven (1.6%) of 439 patients attempted suicide, but there were no completed suicides.

Treatment	Rate of response	NNT	Effect size
Fluoxetine with CBT	71%	3	0.84
Fluoxetine alone	60.6%	4	0.58
CBT alone	43.2%	12	0.20
Placebo	34.8%	–	–

Table VI. Treatment for Adolescents with Depression Study (TADS) randomized controlled trial.⁵³ NNT, number needed to treat; CBT, cognitive behavioral therapy.

Treatment of geriatric depression

In a similar fashion, SSRIs have now largely replaced TCAs and MAOIs as first-line acute treatments for late-life depression.⁵⁴ SSRIs are administered in older patients with initial dosing at half the usual effective dose and doubled after 1 week. A recent review has concluded that SSRIs are efficacious, safe, and well tolerated in older patients with depression without comorbidity, as well as in those with medical comorbidity,⁵⁵ including dementia,⁵⁶⁻⁶⁰ cardiovascular disease,⁶¹ cerebrovascular disease,⁶² stroke,^{63,64} and other medical conditions.⁶⁵⁻⁶⁹

Although most data are supportive of SSRIs as a class in the treatment of geriatric depression, experts favor the use of citalopram or sertraline over fluvoxamine and fluoxetine^{54,70} because of their favorable pharmacokinetic profiles, a lower potential for clinically significant drug–drug interaction, and data suggesting their superiority in terms of cognitive improvement.^{57,58,71,72} One placebo-controlled study with sertraline in elderly outpatients with major depression treated in both psychiatric and primary care settings further supports use of SSRIs in geriatric depression.⁷³ In the “old-old” population (≥ 75

years old) with depression, active medication (citalopram) was no more effective than placebo, except for patients with high levels of baseline severity.⁷⁴ Among the TCAs, where cardiac monitoring is recommended, nortriptyline is the most frequently used agent in the elderly, probably because it is considered the least cardiotoxic drug in this class and blood levels can be monitored. Adverse drug reactions increase dramatically in frequency and severity with advanced age.⁷⁵ Factors that may influence proper dosing include the different pharmacokinetic properties of antidepressants in elderly compared with younger patients and individual patient characteristics, such as cardiovascular or renal function. In elderly patients, antidepressant side effects of particular concern include orthostatic hypotension and anticholinergic effects (more common with TCAs), as well as extrapyramidal symptoms, and the syndrome of inappropriate antidiuretic hormone secretion.

Course of treatment

While it used to be assumed that the typical major depression was self-limiting (of 3 to 6 months duration) and associated with complete recovery, the present view is not as sanguine. Clinical trials have demonstrated that 30% to 40% of depressed patients fail to respond to first-line antidepressant treatment despite adequate adherence, dose, and duration,^{76,77} 60% to 70% fail to achieve a complete remission of symptoms,⁷⁸ up to 20% have not recovered 2 years after initiation of treatment,^{79,80} and 10% remain depressed despite multiple interventions.^{76,81} Many patients suffer from recurrent depression that requires long-term maintenance treatment to prevent future episodes of depression. Some depressive conditions, including psychotic depression, bipolar depression, and depression with psychiatric or medical comorbidity, have been associated with poor outcome and/or a higher degree of resistance to specific types of treatment or to treatment in general.⁸² Successful treatment of major depression may require more than one drug trial. A full discussion of the tactics involved in selection of the second treatment (same class, different class), choice of whether to augment the first drug with a second compound or with psychotherapy or to change treatment completely is beyond the scope of this review. Clinicians who wish to treat rather than refer these or complex patients can consult the treatment algorithms derived from the Texas Medical

Algorithm Project (TMAP).¹⁸ The goal of treatment is full remission of symptoms, but less than 50% of patients achieve this goal within 8 to 12 weeks. In general, if a patient has not shown marked improvement within 8 weeks, psychiatric consultation is recommended. Clearer guidelines for treatment augmentation and switching should be derived from the ongoing multisite NIMH contract, Sequenced Treatment Alternative to Relieve Depression (STAR*D).⁸³ This large multicenter trial (ultimately enrolling more than 4000 patients nationwide) is prospectively evaluating alternative antidepressants and augmentation strategies for patients at three stages of treatment resistance.

Psychotic depression

Psychotic depression, representing over 15% of more severely depressed cases,⁸⁴ is characterized by the presence of either delusions or hallucinations, which are often but not always congruent with the depressive themes. Psychotic depression has less than one half the likelihood of responding to antidepressant monotherapy compared with a nonpsychotic depressive disorder.⁸⁵⁻⁸⁸

Initially, TCAs, especially in the higher dose range, were used. Subsequent investigations indicated that TCAs combined with typical antipsychotics provided greater levels of efficacy (eg, amitriptyline and perphenazine).⁸⁸ Although SSRIs alone have not been used routinely to treat psychotic depression, the use of an SSRI and an atypical antipsychotic has shown efficacy greater than an SSRI alone.⁸⁹ C-1073 (mifepristone), a selective glucocorticoid receptor II (GRII) antagonist (not currently on the US market), has shown some promise in the acute treatment phase of psychotic depression.⁹⁰ In urgent situations or when other treatments have failed, electroconvulsive treatment (ECT) is warranted. While ECT is efficacious (for psychotic depression), it has many drawbacks including the requirement that the treatment must be administered under anesthesia in a hospital setting or a similarly equipped ambulatory setting.⁹¹

Bipolar depression

Bipolar depression (major depression in patients also experiencing periods of mania or hypomania) represents a major challenge to clinicians, since response to treatment is often poor and the process of achieving complete remission without a switch into mania is challenging.

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Generally, patients are already being treated with mood stabilizers. A number of investigators have pointed to the relatively poor response to traditional TCAs in this population.⁹²⁻⁹⁴ Most SSRIs demonstrate only moderate success. Recently, efforts to combine an SSRI with an atypical antipsychotic⁹⁵ have shown promising results in bipolar depression.⁹⁶ A number of atypical antipsychotic drugs are also showing some degree of antidepressant effect, perhaps similar to that of lithium.

The usual strategy is to use mood stabilizer monotherapy as the first-line therapy for bipolar depression, with the addition of an antidepressant reserved for depressed patients who do not benefit from mood stabilizer monotherapy. One hierarchy of mood stabilizer options is: (i) lithium carbonate; (ii) divalproex; (iii) olanzapine (now FDA-approved for mania and maintenance in bipolar disorder); and (iv) lamotrigine (FDA-approved for maintenance in bipolar disorder).^{95,97,98} The particular medication is chosen on the basis of the patient's history; patients known to not have responded to one monotherapy should be advanced to the next strategy. A minimum adequate trial is 4 weeks of mood stabilizer monotherapy at an optimal dose/blood level.

In contrast to the treatment of mania, pharmacological treatment of bipolar depression remains vastly understudied. Although two important placebo-controlled trials were concluded recently,^{99,100} they are the first two adequately powered studies ever conducted on this condition. Despite the severity of pediatric bipolar depression, empirical data on its treatment are limited, largely because of the relatively low prevalence of pediatric bipolar disorder. The SSRIs are the only class of medications with some level of proven efficacy in pediatric unipolar depression.^{49,101,102} Practitioners are compelled to treat depressed bipolar children and adolescents using the SSRI because the illness is so severe; however, the SSRI sometimes worsen the cyclicity of the disorder. We also lack any controlled treatment studies of bipolar depression in later life.¹⁰³

Comorbidity

Comorbidity or "co-occurrence" of either other psychiatric disorders or medical disorders is very common in major depression. Indeed, it is so common that the frequent questions raised include the heterogeneity of the depressive disorder, subgroups with specific comorbidities, and whether such nosological differences have treat-

ment and/or pathophysiological implications.⁵ For example, bipolar depression is associated often with panic-anxiety features, substance use, and cardiovascular disease, all of which have effects on immediate and long-term prognostic indicators.

Comorbidity of substance and alcohol abuse with depression is generally associated with a worse prognosis.¹⁰⁴ Several symptoms of alcohol and substance abuse, such as sleep disturbance, irritability, and dysphoria, contribute to this outcome. In fact, even moderate use of psychoactive substances such as alcohol can have a negative effect on the outcome of treatment for major depression and should be discouraged until the depression is fully remitted.¹⁰⁵ The frequent association of substance abuse with other comorbid disorders (eg, antisocial personality or anxiety disorders) may further complicate the prognosis.¹⁰⁶

Medical co-occurrence represents another major factor contributing to poor treatment response. Diseases like hypothyroidism, stroke, diabetes, coronary artery disease, Parkinson's disease, human immunodeficiency viral infection and acquired immunodeficiency syndrome, cancer, and chronic pain syndrome can play a major role in reducing treatment responsiveness, especially when the medical illness is irreversible.¹⁰⁷ Even when a reversible underlying medical condition is contributing to depression, treatment of that condition alone is not always sufficient to resolve the depression. Furthermore, some of the medications used to treat comorbid medical conditions may induce or worsen a depressive episode. Depression is a risk factor for mortality after acute myocardial infarction (MI) and a morbidity risk factor associated with slow recovery from an MI and poorer quality of life.¹⁰⁸⁻¹¹¹ Recent trials with SSRIs are pointing to these medications as safe and effective treatment for recurrent depression with recent MI or unstable angina, although a beneficial effect on the underlying cardiac disease has not been found consistently in studies to date.^{112,113} It is likely that similar findings will emerge from intervention studies in depression and other concurrent serious medical conditions.

Continuation/maintenance treatment

Clinical guidelines generally recommend that treatment should be continued for at least 6 months following remission of acute symptoms.^{114,115} However, because of the recurrent nature of depressive disorder, a question is

how long patients at risk of recurrence should remain on antidepressant medication. A recent review of data from longer-term studies¹¹⁶ pooling 31 randomized trials, demonstrated that continuing treatment reduced the odds of relapse by 70% (95% confidence interval [CI] 62% to 78%) compared to treatment discontinuation. The average rate of relapse or recurrence on placebo was 41% compared with 18% on active treatment. Most of the trials were of only 12 months' duration. Thus, the evidence on longer-term treatment requires confirmation; however, in the longer trials evaluated, the treatment effect appeared to persist for up to 36 months.

This new analysis reinforces the available findings from long-term maintenance trials conducted with TCA. The Prien et al²¹ and Frank et al²² maintenance studies with imipramine in mid-life adults, followed by the Reynolds et al²³ study in late-life depression with nortriptyline, established the efficacy of long-term maintenance treatment with antidepressants, specifically in recurrent major depression. Subsequent studies with SSRIs have pointed to similar levels of efficacy with fluoxetine, sertraline, and citalopram in mid-life patients and with citalopram in late-life patients, most of whom had experienced at least one prior episode of depression.¹¹⁷⁻¹²⁰ Furthermore, studies on long-term treatment of chronic depression (major depression with an episode lasting greater than 2 years) with the TCAs, desipramine and imipramine, and the SSRI, sertraline, have demonstrated efficacy in chronic depression.^{121,122}

While this report is not focused on psychotherapy for treatment of depression, it is noteworthy that the combination of antidepressants and specific targeted psychotherapy (interpersonal psychotherapy) has been conducted successfully in long-term trials with some suggestion in the elderly that combination treatment was better than antidepressants alone.^{22,23}

Future directions and conclusions

As discussed earlier in this review on the section on pathogenesis and drug targets, considerable efforts are being directed toward the development of new strategies for drug discovery in depression. These strategies include, as highlighted by Nestler et al¹²³ "developing better animal models of mood disorders; identifying genetic determinants of normal and abnormal mood in humans and

animals; discovering novel targets and biomarkers of mood disorders and treatments."

Biomarkers for depression have traditionally been divided into four groups⁶: peripheral, CNS neurochemical, CNS functional, and genetic biomarkers. Recent advances in functional and positron emission tomography (PET) neuroimaging, as well as pharmacogenetics, have overshadowed the previous primacy of peripheral markers. The advantages of these new methodologies are numerous, such as more direct CNS determinations, the ability to combine modalities such as cognitive neuroscience paradigms and functional magnetic resonance imaging (fMRI), and repeatability of measures over extended periods of time. However, the current limitations including ligand development, better pharmacogenetic tactics, and appropriate recruitment of large sample sizes may limit the extent of the immediate payoff for such strategies.

One final concern in the overall positive picture for advances in therapeutics for depression has been our failure to utilize the best available methodological tools to design and interpret clinical trials in depression. Insufficient planning for sample size, target population, appropriate outcome measures, multisite "assessment," and direct tactical planning for placebo effects have been associated on total focus on statistical significance, with less focus on clinical significance. Our failure to articulate clinical significance and effect size, as specified with the use of effect size determinations, is partially responsible for our weak clinical trial design strategies. Risk assessment for clinical trials to utilize tactics such as NNT for benefit (efficacy) and NNH (number needed to harm) for adverse events (risk) ratio should be conducted in all clinical trials and should be reported routinely. More attention should be given to moderator mediator analyses to identify important therapeutically responsive subgroups.¹²⁴ In summary, all the contemporary biostatistical methodological tools should be aligned with the neuroscience and genetic toolbox to increase the likelihood that newer treatments for depression will be developed in the near future. □

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El manejo farmacológico de la depresión

Los trastornos depresivos se caracterizan por ser comunes, recurrentes, crónicos y requerir tratamiento. Una revisión del cuadro clínico y de los fármacos actualmente disponibles demuestra la necesidad de una acuciosa evaluación de la gravedad de la depresión, incluyendo el riesgo suicida. El foco inicial del tratamiento se centra en la resolución rápida de los síntomas durante la fase aguda, a lo que debe seguir la fase de continuación. El tratamiento de mantención se indicará cuando el riesgo de recurrencia sea alto. La cantidad de medicamentos disponibles es considerable y la relación riesgo/beneficio es aceptable. La depresión se puede diagnosticar a lo largo de toda la vida y tratar en cada edad (aunque recientemente han surgido algunos desacuerdos en relación a los pacientes más jóvenes). También debe ser evaluada la comorbilidad, tanto psiquiátrica como médica, al igual que la posible presencia de dos de los subtipos de depresión (psicótica y bipolar) ya que habitualmente requieren de intervenciones diferentes. Se espera que la próxima generación de antidepresivos se asocie con enfermedades y con marcadores biológicos de evolución más específicas.

La prise en charge pharmacologique de la dépression

Les troubles dépressifs sont courants, récurrents, chroniques et nécessitent un traitement. Une revue de la symptomatologie et des cibles médicamenteuses actuelles met en évidence un besoin d'évaluation exacte de la sévérité de la dépression, « suicidalité » incluse. Le but initial du traitement est la résolution rapide des symptômes pendant la phase aiguë, et sa poursuite. Le traitement d'entretien est indiqué si le risque de récurrence est élevé. La gamme de médicaments disponibles est très importante et le rapport bénéfice/risque est acceptable. La dépression peut être diagnostiquée tout au long de la vie et traitée quel que soit l'âge (malgré des désaccords récents concernant les patients jeunes). La comorbidité, à la fois psychiatrique et médicale, doit être évaluée comme doit l'être la présence éventuelle de deux sous-types de dépression (psychotique et bipolaire) pour lesquels les besoins thérapeutiques sont souvent différents. On espère que la nouvelle génération d'antidépresseurs s'adressera à des troubles plus spécifiques et comportera des biomarqueurs de résultats.

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