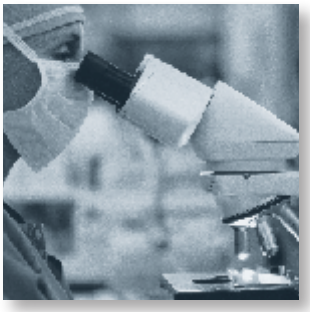
A Harvard Medical School Special Health Report

Understanding Depression






In this report:

The latest brain and genetic research

Finding the right treatment

What you should know about medications

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SPECIAL BONUS SECTION
Strategies for success: Tips for leaping common hurdles and getting good treatment

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UNDERSTANDING DEPRESSION
SPECIAL HEALTH REPORT

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ISBN 978-1-933812-50-2

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Trusted advice for a healthier life

Dear Reader,

Sadness touches all of our lives at different times, but depression can have enormous depth and staying power. It is more than a passing bout of sadness or dejection, or feeling down in the dumps. It can leave you feeling continuously burdened and can sap the joy out of once-pleasurable activities. It has physical, as well as emotional, symptoms. You may find that you can't sleep or eat, that you are fatigued, or that you have headaches or aches and pains that seem to have sprung up without a cause.

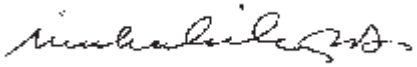
If you've ever suffered from depression or been close to someone who has, you know that this illness cannot be lifted at will or wished away. A man in the grip of depression can't solve his problems by showing a little more backbone. Nor can a woman who is depressed simply shake off the blues.

Yet too many people struggle silently with depression. Don't be among them. There are a variety of medications and treatments that can help. A recent study showed that, for those who stuck with treatment, depression lifted completely in seven out of 10 people. For many others, treatment relieves many, though not all, symptoms. Effective treatment can lighten your mood, strengthen your connections with loved ones, allow you to find satisfaction in interests and hobbies, and make you feel more like yourself again.

To get to this point, you may need patience and perseverance—which is no short order when you are feeling depressed. Some people immediately hit upon a medication or therapy that works for them. But for many others, the treatment path takes several turns and an occasional detour. You may need to adjust medications, alter a dose, or try a new therapist. Side effects, health insurance coverage, and the stigma associated with having a mood problem can be roadblocks, but as this report attests, you can circumnavigate them. The special section starting on page 36 offers a variety of tips for managing treatment problems.

In time, some of these hurdles may vanish, thanks to advances in our understanding of mood disorders. Today's scientific discoveries are paving the way for better treatment. Not only are new drugs being studied and developed, but recent genetic discoveries and a better understanding of the biology of depression will one day make more targeted, personalized treatment possible. In the meantime, we hope that this report helps you work with your doctor to find a treatment that restores your mood and brings joy into your life.

Sincerely,



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What is depression?

Depression isn't a one-size-fits-all illness. Just like a rash or heart disease, depression can take many forms. As you'll see, there's a cluster of symptoms that are typically present, but one person's experience of depression often differs from another's.

Keep in mind, too, that definitions of depression—and the therapies designed to ease this disease's grip—continue to evolve. These shifts will continue to percolate through the field as more research flows in. The standard definition for depression may change somewhat when the American Psychiatric Association revises the system for categorizing mental health disorders. The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) is scheduled to be published in 2012.

This special report addresses three main categories of depression:

- major depression
- dysthymia (a lasting, low-level depression)
- bipolar disorder, previously called manic-depressive illness.

These terms don't begin to describe the tremendous variation in people's experiences of depression. Still, while the labels sometimes seem overly simple, they do help clinicians and researchers study depression and exchange information about its various forms. The categories have many overlapping characteristics, but each has its own distinguishing features.

What is major depression?

Major depression may make you feel as though work, school, relationships, and other aspects of your life have been derailed or put on hold indefinitely. You feel constantly sad or burdened, or you lose interest in all activities, even those you previously enjoyed. This holds true nearly all day, on most days, and lasts at least two weeks. During this time, you also experience at least four of the following signs of depression:

- a change in appetite that sometimes leads to weight loss or gain
- insomnia or (less often) oversleeping
- a slowdown in talking and performing tasks or, conversely, restlessness and an inability to sit still
- loss of energy or feeling tired much of the time
- problems concentrating or making decisions
- feelings of worthlessness or excessive, inappropriate guilt
- thoughts of death or suicide, or suicide plans or attempts.

Other signs can include a loss of sexual desire, pessimistic or hopeless feelings, and physical symptoms such as headaches, unexplained aches and pains, or digestive problems. Depression and anxiety often occur simultaneously, so you may also feel worried or distressed more often than you used to.

Although these symptoms are hallmarks of depression, if you talk to any two depressed people about their experiences, you might well think they were describing entirely different illnesses. For example, one might not be able to summon the energy to leave the house, while the other might feel agitated and restless. One might feel deeply sad and break into tears easily. The other might snap irritably at the least provocation. One might pick at food, while the other might munch constantly. The two people might both report feeling sad, but the quality of their moods could differ substantially in depth and darkness. Also, symptoms may gather over a period of days, weeks, or months.

Despite such wide variations, depression does have certain common patterns. For example, depression is more prevalent in women than men (see "Differences between the sexes," page 42). And while major depression may start at any time in life, the initial episode occurs, on average, during early adulthood. Depression or

hopelessness may feel so paralyzing that you find it hard to seek help. Even worse, you may believe that treatment could never overcome the juggernaut bearing down.

Yet nothing could be further from the truth. The vast majority of people who receive proper treatment rebound emotionally within two to six weeks and then take pleasure in life once again. When major depression goes untreated, though, suffering can last for months.

Furthermore, episodes of depression frequently recur. About half of those who sink into an episode of major depression will have at least one more episode later in life. Some researchers think that diagnosing depression early and treating it successfully can help forestall such recurrences. They suspect that the more episodes of depression you've had, the more likely you are to have future episodes, because depression may cause enduring changes in brain circuits and chemicals that affect mood (see "The problem of recurrence," page 40). In addition, people who suffer from recurrent major depression have a higher risk of developing bipolar disorder than people who experience a single episode.

What is dysthymia?

Mental health professionals use the term dysthymia (dis-THIGH-me-ah) to refer to a low-level drone of depression that lasts for at least two years in adults or one year in children and teens. While not as crippling as major depression, its persistent hold can keep you from feeling good and can intrude upon your work, school, and social life. If you were to equate depression with the color black, dysthymia might be likened to a dim gray. Unlike major depression, in which relatively short episodes may be separated by considerable spans of time, dysthymia lasts for an average of at least five years.

If you suffer from dysthymia, more often than not you feel depressed during most of the day. You may carry out daily responsibilities, but much of the zest is gone from your life. Your depressed mood doesn't lift for more than two months at a time, and you also have at least two of the following symptoms:

- overeating or loss of appetite
- insomnia or sleeping too much
- tiredness or lack of energy
- low self-esteem
- trouble concentrating or making decisions
- hopelessness.

Sometimes an episode of major depression occurs on top of dysthymia; this is known as double depression.

Dysthymia often begins in childhood, the teen years, or early adulthood. Being drawn into this low-level depression appears to make major depression more likely. In fact, up to 75% of people who are diagnosed with dysthymia will have an episode of major depression within five years.

It's difficult to escape the grasp of untreated dysthymia. Only about 10% of people spontaneously emerge from it in a given year. Some appear to get beyond it for as long as two months, only to spiral downward again. However, proper treatment eases dysthymia and other depressive disorders in about four out of five people.

Mild, moderate, or severe depression?

Experts judge the severity of depression by assessing the number of symptoms and the degree to which they impair your life.

Mild: You have some symptoms and find it takes more effort than usual to accomplish what you need to do.

Moderate: You have many symptoms and find they often keep you from accomplishing what you need to do.

Severe: You have nearly all the symptoms and find they almost always keep you from accomplishing daily tasks.

What is bipolar disorder?

Bipolar disorder always includes one or more episodes of mania, characterized by high mood, grandiose thoughts, and erratic behavior. It also often includes episodes of depression. During a typical manic episode, you would feel terrifically elated, expansive, or irritated over the course of a week or longer. You would also experience at least three of the following symptoms:

- grandiose ideas or pumped-up self-esteem
- far less need for sleep than normal

- an urgent desire to talk
- racing thoughts and distractibility
- increased activity that may be directed to accomplishing a goal or expressed as agitation
- a pleasure-seeking urge that might get funneled into sexual sprees, overspending, or a variety of schemes, often with disastrous consequences.

Between episodes, you might feel completely normal for months or even years. Or you might experience faster mood swings (known as rapid cycling). Bipolar disorder actually takes many forms. For example, symptoms of depression and mania may be mixed during cycles. Or you might not have full-blown mania; instead, you could have a milder version known as hypomania.

Bipolar disorder usually starts in early adulthood. It's equally common among women and men, although certain variations of it strike one sex more than the other. Hypomania, for example, occurs more often in women. Women are also more likely to experience major depression as their first episode and to have more depressive episodes over all. Men, on the other hand, typically experience manic episodes first and tend to have more of them than depressive cycles.

Bipolar disorder is a recurring illness. Nine out of 10 people who have a single manic episode can expect to have repeat experiences. Suicide rates in people who have bipolar disorder are higher than average. Successful treatment, however, can cut down on the number and intensity of episodes and reduce suicide risk.

How common is depression?

Mood disorders—which include major depression, dysthymia, and bipolar disorder—affect 20.9 million American adults each year. This is almost 10% of the U.S. population ages 18 and older.

Major depression affects the majority of these individuals: 14.8 million Americans ages 18 and older. That translates into about one in 15 American adults.

Bipolar disorder annually affects 5.7 million American adults, or 2.6% of the U.S. population ages 18 or older.

Of the three mood disorders, dysthymia is the least common, affecting 3.3 million American adults or 1.5% of the U.S. population ages 18 and older, but there may be many people with dysthymia who never get diagnosed.

What causes depression?

It's often said that depression results from a chemical imbalance, but that figure of speech doesn't capture how complex the disease is. Research suggests that depression doesn't spring from simply having too much or too little of certain brain chemicals. Rather, depression has many possible causes, including faulty mood regulation by the brain, genetic vulnerability, stressful life events, medications, and medical problems. It's believed that several of these forces interact to bring on depression.

To be sure, chemicals are involved in this process, but it is not a simple matter of one chemical being too low and another too high. Rather, many chemicals are involved, working both inside and outside nerve cells. There are millions, even billions, of chemical reactions that make up the dynamic system that is responsible for your mood, perceptions, and how you experience life.

With this level of complexity, you can see how two people might have similar symptoms of depression, but the problem on the inside, and therefore what treatments will work best, may be entirely different.

In recent years, researchers have learned much about the biology of depression. They've identified genes that make individuals more vulnerable to low moods and influence how an individual responds to drug therapy. One day, these discoveries should lead to better, more individualized treatment (see "From the lab to your medicine cabinet," page 19), but that is likely to be years away. And while researchers know more now than ever before about how the brain regulates mood, their understanding of the biology of depression is far from complete.

What follows is an overview of the current understanding of the major factors believed to play a role in depression.

The brain

Popular lore has it that emotions reside in the heart. Science, though, tracks the seat of your emotions to the brain. Certain areas of the brain help regulate mood. Researchers believe that—more important than levels of specific brain chemicals—nerve cell connections, nerve cell growth, and the functioning of nerve circuits have a maj or impact on depression. Still, their understanding of the neurological underpinnings of mood is incomplete.

Regions that affect mood

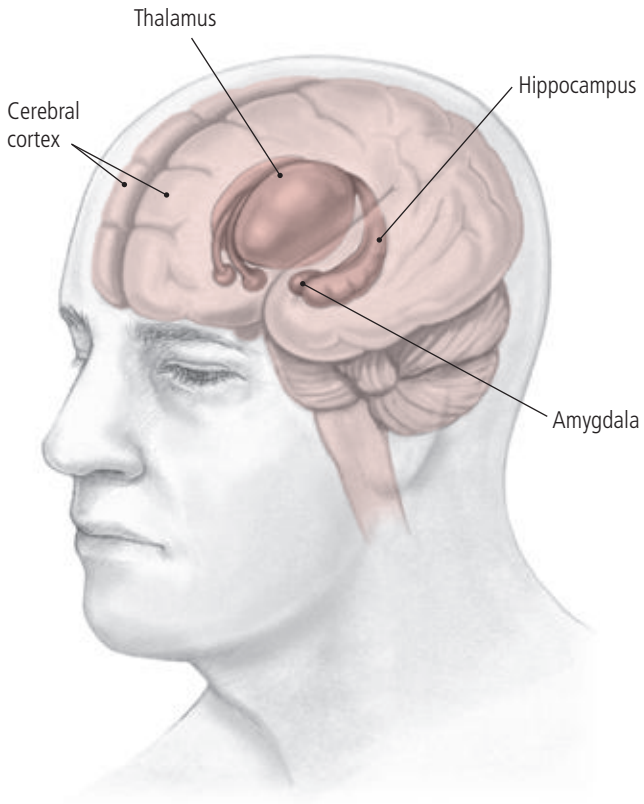
Increasingly sophisticated forms of brain imaging—such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI)—permit a much closer look at the working brain than was possible in the past. An fMRI scan, for example, can track changes that take place when a region of the brain responds during various tasks. A PET or SPECT scan can map the brain by measuring the distribution and density of neurotransmitter receptors in certain areas.

Use of this technology has led to a better understanding of which brain regions regulate mood and how other functions, such as memory, may be affected by depression. Areas that play a significant role in depression are the amygdala, the thalamus, and the hippocampus (see Figure 1).

Recent research shows that the hippocampus is smaller in some depressed people. For example, in one fMRI study published in *The Journal of Neuroscience*, investigators studied 24 women who had a history of depression. On average, the hippocampus was 9% to 13% smaller in depressed women compared with those who were not depressed. The more bouts of depression a woman had, the smaller the hippocampus. Stress, which plays a role in depression, may be a key factor here, since experts believe stress can suppress the production of new neurons (nerve cells) in the hippocampus.

Researchers are exploring possible links between sluggish production of new neurons in the hip-

Figure 1 Areas of the brain affected by depression



Amygdala: The amygdala is part of the limbic system, a group of structures deep in the brain that's associated with emotions such as anger, pleasure, sorrow, fear, and sexual arousal. The amygdala is activated when a person recalls emotionally charged memories, such as a frightening situation. Activity in the amygdala is higher when a person is sad or clinically depressed. This increased activity continues even after recovery from depression.

Thalamus: The thalamus receives most sensory information and relays it to the appropriate part of the cerebral cortex, which directs high-level functions such as speech, behavorial reactions, movement, thinking, and learning. Some research suggests that bipolar disorder may result from problems in the thalamus, which helps link sensory input to pleasant and unpleasant feelings.

Hippocampus: The hippocampus is part of the limbic system and has a central role in processing long-term memory and recollection. Interplay between the hippocampus and the amygdala might account for the adage "once bitten, twice shy." It is this part of the brain that registers fear when you are confronted by a barking, aggressive dog, and the memory of such an experience may make you wary of dogs you come across later in life. The hippocampus is smaller in some depressed people, and research suggests that ongoing exposure to stress hormone impairs the growth of nerve cells in this part of the brain.

pocampus and low moods. An interesting fact about antidepressants supports this theory. These medications immediately boost the concentration of chemical messengers in the brain (neurotransmitters). Yet people typically don't begin to feel better for several weeks or longer. Experts have long wondered why, if depression were primarily the result of low levels of neurotransmitters, people don't feel better as soon as levels of neurotransmitters increase.

The answer may be that mood only improves as nerves grow and form new connections, a process that takes weeks. In fact, animal studies have shown that antidepressants do spur the growth and enhanced branching of nerve cells in the hippocampus. So, the theory holds, the real value of these medications may be in generating new neurons (a process called neurogenesis), strengthening nerve cell connections, and improving the exchange of information between nerve circuits. If that's the case, medications could be developed that specifically promote neurogenesis, with the hope that patients would see quicker results than with current treatments.

In the meantime, recent animal research lends credence to the theory. A 2003 study in *Science* found that when neurogenesis is blocked in mice, the benefits of antidepressants seem to disappear. After receiving antidepressants for four weeks, mice exhibited less anxious or depressed behavior (they became bolder about retrieving food from a brightly lit place). These treated mice had 60% more dividing cells in the hippocampus. However, when researchers impeded new cell growth by dousing the hippocampus with x-rays, drug treatment failed to reduce anxious behavior in the mice. While more work needs to be done to determine the role of neurogenesis in depression, this is an interesting avenue of research.

Nerve cell communication

The ultimate goal in treating the biology of depression is to improve the brain's ability to regulate mood. We now know that neurotransmitters are not the *only* important part of the machinery. But let's not diminish their importance either. They are deeply involved in how nerve cells communicate with one another. And

they are a component of brain function that we can often influence to good ends.

Neurotransmitters are chemicals that relay messages from neuron to neuron. An antidepressant medication tends to increase the concentration of these substances in the spaces between neurons (the synapses). In many cases, this shift appears to give the system enough of a nudge so that the brain can do its job better.

How the system works. If you trained a high-powered microscope on a slice of brain tissue, you might be able to see a loosely braided network of neurons that send and receive messages. While every cell in the body has the capacity to send and receive signals, neurons are specially designed for this function. Each neuron has a cell body containing the structures that any cell needs to thrive. Stretching out from the cell body are short, branchlike fibers called dendrites and one longer, more prominent fiber called the axon.

A combination of electrical and chemical signals allows communication within and between neurons. When a neuron becomes activated, it passes an electrical signal from the cell body down the axon to its end (known as the axon terminal), where chemical messengers called neurotransmitters are stored. The signal releases certain neurotransmitters into the space between that neuron and the dendrite of a neighboring neuron. That space is called a synapse. As the concentration of a neurotransmitter rises in the synapse, neurotransmitter molecules begin to bind with receptors embedded in the membranes of the two neurons (see Figure 2).

The release of a neurotransmitter from one neuron can activate or inhibit a second neuron. If the signal is activating, or excitatory, the message continues to pass farther along that particular neural pathway. If it is inhibitory, the signal will be suppressed. The neurotransmitter also affects the neuron that released it. Once the first neuron has released a certain amount of the chemical, a feedback mechanism (controlled by that neuron's receptors) instructs the neuron to stop pumping out the neurotransmitter and start bringing it back into the cell. This process is called reabsorption or reuptake. Enzymes break down the remaining neurotransmitter molecules into smaller particles.

When the system falters. Brain cells usually produce levels of neurotransmitters that keep senses, learning, movements, and moods perking along. But in some people who are severely depressed or manic, the complex systems that accomplish this go awry. For example, receptors may be oversensitive or insensitive to a specific neurotransmitter, causing their response to its release to be excessive or inadequate. Or a message might be weakened if the originating cell pumps out too little of a neurotransmitter or if an overly efficient reuptake mops up too much before the molecules have the chance to bind to the receptors on other neurons. Any of these system faults could significantly affect mood.

Kinds of neurotransmitters. Scientists have identified many different neurotransmitters. Here is a description of a few believed to play a role in depression:

- Acetylcholine enhances memory and is involved in learning and recall.
- Serotonin helps regulate sleep, appetite, and mood and inhibits pain. Research supports the idea that some depressed people have reduced serotonin transmission. Low levels of a serotonin byproduct have been linked to a higher risk for suicide.
- Norepinephrine constricts blood vessels, raising blood pressure. It may trigger anxiety and be involved in some types of depression. It also seems to help determine motivation and reward.
- Dopamine is essential to movement. It also influences motivation and plays a role in how a person perceives reality. Problems in dopamine transmission have been associated with psychosis, a severe form of distorted thinking characterized by hallucinations or delusions. It's also involved in the brain's reward system, so it is thought to play a role in substance abuse.
- Glutamate is a small molecule believed to act as an excitatory neurotransmitter and to play a role in bipolar disorder and schizophrenia. Lithium carbonate, a well-known mood stabilizer used to treat bipolar disorder, helps prevent damage to neurons in the brains of rats exposed to high levels of glutamate. Other animal research suggests that lithium might stabilize glutamate reuptake, a mechanism that may explain how the drug smooths out the highs of mania and the lows of depression in the long term.

- Gamma-aminobutyric acid (GABA) is an amino acid that researchers believe acts as an inhibitory neurotransmitter. It is thought to help quell anxiety.

Genes

Every part of your body, including your brain, is controlled by genes. Genes make proteins that are involved in biological processes. Throughout life, different genes turn on and off, so that—in the best case—they make the right proteins at the right time. But if the genes get it wrong, they can alter your biology in a way that results in your mood becoming unstable. In a genetically vulnerable person, any stress (a missed deadline at work or a medical illness, for example) can then push this system off balance.

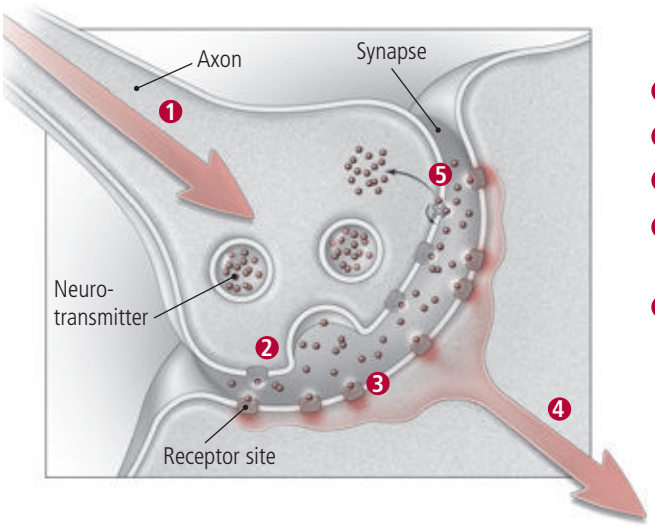
Mood is affected by dozens of genes, and as our genetic endowments differ, so do our depressions. The hope is that as researchers pinpoint the genes involved in mood disorders and better understand their functions, treatment can become more individualized and more successful. Patients would receive the best medication for their type of depression (see "From the lab to your medicine cabinet," page 19).

Another goal of gene research, of course, is to understand how, exactly, biology makes certain people vulnerable to depression. For example, several genes influence the stress response, leaving us more or less likely to become depressed in response to trouble.

A 2003 discovery supports this idea. Researchers found that people with a particular variant in a serotonin-transporter gene (5-HTT) were more likely to become depressed in response to stress. Each person inherits two copies of this gene—one from each parent. The gene comes in "short" (less efficient) and "long" (more efficient) versions. No combination of short or long variants leads directly to depression, but short versions of the gene put people at a distinct disadvantage if they experience stressful life events. In tracking more than 800 young adults over a five-year period, the researchers found that 33% of those with at least one "short" gene became depressed after a series of stressful life events, such as divorce or the loss of a job. People with two copies of the short variant fared worse than those with a single copy, and their risk of depression rose steadily as their lives became more stressful. By contrast, only 17% of those with two "longs" grew depressed in similar circumstances—and their risk of depression remained unchanged as stress levels rose.

In 2008, researchers studied a gene that influences a person's reaction to childhood abuse. This gene (CRHR1) provides the code for one of the stress hormones—corticotrophin-releasing hormone or CRH (see "How stress affects the body," at right). For this study, published in *Archives of General Psychiatry*, researchers interviewed 621 adults and tested their DNA. Among people who suffered childhood abuse,

Figure 2 How neurons communicate



1. An electrical signal travels down the axon.
2. Chemical neurotransmitter molecules are released.
3. The neurotransmitter molecules bind to receptor sites.
4. The signal is picked up by the second neuron and is either passed along or halted.
5. The signal is also picked up by the first neuron, causing reuptake, the process by which the cell that released the neurotransmitter takes back some of the remaining molecules.

those with the relatively protective versions of the CRHR1 gene had half the symptoms of depression as participants without this genetic variation. This study not only added to knowledge about protective genes, but also lent further credence to the theory that stress hormones play an important role in depression.

Another interesting discovery is the identification of a variation in the DNA sequence named G1463A. People with this atypical DNA sequence are more likely to have major depression than those who don't. (See "From the lab to your medicine cabinet," page 19.)

Perhaps the easiest way to grasp the power of genetics is to look at families. It is well known that depression and bipolar disorder run in families. The strongest evidence for this comes from the research on bipolar disorder. Half of those with bipolar disorder have a relative with a similar pattern of mood fluctuations. Studies of identical twins, who share a genetic blueprint, show that if one twin has bipolar disorder, the other has a 60% to 80% chance of developing it, too. These numbers don't apply to fraternal twins, who—like other biological siblings—share only about half of their genes. If one fraternal twin has bipolar disorder, the other has a 20% chance of developing it.

The evidence for other types of depression is more subtle, but it is real. A person who has a first-degree relative who suffered major depression has an increase in risk for the condition of 1.5% to 3% over normal.

One important goal of genetics research—and this is true throughout medicine—is to learn the specific function of each gene. This kind of information will help us figure out how the interaction of biology and environment leads to depression in some people but not others.

Stressful life events

At some point, nearly everyone encounters stressful life events: the death of a loved one, the loss of a job, an illness, or a relationship spiraling downward. Some must cope with the early loss of a parent, violence, or sexual abuse. While not everyone who faces these stresses develops a mood disorder—in fact, most do not—stress plays an important role in depression.

As the previous section explained, your genetic makeup influences how sensitive you are to stressful life events. When genetics, biology, and stressful life situations come together, depression can result.

Stress has its own physiological consequences. It triggers a chain of chemical reactions and responses in the body. If the stress is short-lived, the body usually returns to normal. But when stress is chronic or the system gets stuck in overdrive, changes in the body and brain can be long-lasting.

How stress affects the body

Stress can be defined as an automatic physical response to any stimulus that requires you to adjust to change. Every real or perceived threat to your body triggers a cascade of stress hormones that produces physiological changes. We all know the sensations: your heart pounds, muscles tense, breathing quickens, and beads of sweat appear. This is known as the stress response.

The stress response starts with a signal from the part of your brain known as the hypothalamus. The hypothalamus joins the pituitary gland and the adrenal glands to form a trio known as the hypothalamic-pituitary-adrenal (HPA) axis, which governs a multitude of hormonal activities in the body and may play a role in depression as well.

When a physical or emotional threat looms, the hypothalamus secretes corticotropin-releasing hormone (CRH), which has the job of rousing your body. Hormones are complex chemicals that carry messages to organs or groups of cells throughout the body and trigger certain responses. CRH follows a pathway to your pituitary gland, where it stimulates the secretion of adrenocorticotropic hormone (ACTH), which pulses into your bloodstream. When ACTH reaches your adrenal glands, it prompts the release of cortisol.

The boost in cortisol readies your body to fight or flee. Your heart beats faster—up to five times as quickly as normal—and your blood pressure rises. Your breath quickens as your body takes in extra oxygen. Sharpened senses, such as sight and hearing, make you more alert.

CRH also affects the cerebral cortex, part of the amygdala, and the brainstem. It is thought to play a major role in coordinating your thoughts and behaviors, emotional reactions, and involuntary responses. Working along a variety of neural pathways,

it influences the concentration of neurotransmitters throughout the brain. Disturbances in hormonal systems, therefore, may well affect neurotransmitters, and vice versa.

Normally, a feedback loop allows the body to turn off "fight-or-flight" defenses when the threat passes. In some cases, though, the floodgates never close properly, and cortisol levels rise too often or simply stay high. This can contribute to problems such as high blood pressure, immune suppression, asthma, and possibly depression.

Studies have shown that people who are depressed or have dysthymia typically have increased levels of CRH. Antidepressants (see "Medications for depression," page 21) and electroconvulsive therapy (see page 30) are both known to reduce these high CRH levels. As CRH levels return to normal, depressive symptoms recede. Research also suggests that trauma during childhood can negatively affect the functioning of CRH and the HPA axis throughout life.

Temperament shapes behavior

Genetics provides one perspective on how resilient you are in the face of difficult life events. But you don't need to be a geneticist to understand yourself. Perhaps a more intuitive way to look at resilience is by understanding your temperament. Temperament—for example, how excitable you are or whether you tend to withdraw from or engage in social situations—is determined by your genetic inheritance and by the experiences you've had during the course of your life. Some people are able to make better choices in life once they appreciate their habitual reactions to people and to life events.

Cognitive psychologists point out that your view of the world and, in particular, your unacknowledged assumptions about how the world works also influence how you feel. You develop your viewpoint early on and learn to automatically fall back on it when loss, disappointment, or rejection occurs. For example, you may come to see yourself as unworthy of love, so you avoid getting involved with people rather than risk losing a relationship. Or you may be so self-critical that you can't bear the slightest criticism from others, which can slow or block your career progress.

Yet while temperament or world view may have a hand in depression, neither is unchangeable. Therapy and medications can shift thoughts and attitudes that have developed over time.

Early losses and trauma

Certain events can have lasting physical, as well as emotional, consequences. Researchers have found that early losses and emotional trauma may leave individuals more vulnerable to depression later in life.

Childhood losses. Profound early losses, such as the death of a parent or the withdrawal of a loved one's affection, may resonate throughout life, eventually expressing themselves as depression. When an individual is unaware of the wellspring of his or her illness, he or she can't easily move past the depression. Moreover, unless the person gains a conscious understanding of the source of the condition, later losses or disappointments may trigger its return.

The British psychiatrist John Bowlby focused on early losses in a number of landmark studies of monkeys. When he separated young monkeys from their mothers, the monkeys passed through predictable stages of a separation response. Their furious outbursts trailed off into despair, followed by apathetic detachment. Meanwhile, the levels of their stress hormones rose. Later investigators extended this research. One study found that the CRH system and HPA axis got stuck in overdrive in adult rodents that had been separated from their mothers too early in life. This held true whether or not the rats were purposely put under stress. Interestingly, antidepressants and electroconvulsive therapy relieve the symptoms of animals distressed by such separations.

The role of trauma. Traumas may also be indelibly etched on the psyche. A small but intriguing study in the *Journal of the American Medical Association* showed that women who were abused physically or sexually as children had more extreme stress responses than women who had not been abused. The women had higher levels of the stress hormones ACTH and cortisol, and their hearts beat faster when they performed stressful tasks, such as working out mathematical equations or speaking in front of an audience.

Many researchers believe that early trauma causes subtle changes in brain function that account for symptoms of depression and anxiety. The key brain regions involved in the stress response may be altered at the chemical or cellular level. Changes might include fluctuations in the concentration of neurotransmitters

or damage to nerve cells. However, further investigation is needed to clarify the relationship between the brain, psychological trauma, and depression.

Medical problems

Certain medical problems are linked to lasting, significant mood disturbances. In fact, medical illnesses or medications may be at the root of up to 10% to 15% of all depressions.

Among the best-known culprits are two thyroid hormone imbalances. An excess of thyroid hormone (hyperthyroidism) can trigger manic symptoms. On the other hand, hypothyroidism, a condition in which your body produces too little thyroid hormone, often leads to exhaustion and depression.

Heart disease has also been linked to depression, with up to half of heart attack survivors reporting feeling blue and many having significant depression. Depression can spell trouble for heart patients: it's been linked with slower recovery, future cardiovascular trouble, and a higher risk of dying within about six months. Although doctors have hesitated to give heart patients older depression medications called tricyclic antidepressants because of their impact on heart rhythms, selective serotonin reuptake inhibitors seem safe for people with heart conditions.

The following medical conditions have also been associated with mood disorders:

- degenerative neurological conditions, such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease
- stroke
- some nutritional deficiencies, such as a lack of vitamin B_{12}
- other endocrine disorders, such as problems with the parathyroid or adrenal glands that cause them to produce too little or too much of particular hormones
- certain immune system diseases, such as lupus
- some viruses and other infections, such as mononucleosis, hepatitis, and HIV
- cancer
- erectile dysfunction in men.

When considering the connection between health problems and depression, an important question to address is which came first, the medical condition or

Seasonal affective disorder: When winter brings the blues

Many people feel sad when summer wanes, but some actually develop depression with the season's change. Known as seasonal affective disorder (SAD), this form of depression affects about 1% to 2% of the population, particularly women and young people.

SAD seems to be triggered by more limited exposure to daylight; typically it comes on during the fall or winter months and subsides in the spring. Symptoms are similar to general depression and include lethargy, loss of interest in once-pleasurable activities, irritability, inability to concentrate, and a change in sleeping patterns, appetite, or both.

To combat SAD, doctors suggest exercise, particularly outdoor activities during daylight hours. Exposing yourself to bright artificial light may also help. Light therapy, also called phototherapy, usually involves sitting close to a special light source that is far more intense than normal indoor light for 30 minutes every morning. The light must enter through your eyes to be effective; skin exposure has not been proven to work. Some people feel better after only one light treatment, but most people require at least a few days of treatment, and some need several weeks. You can buy boxes that emit the proper light intensity (10,000 lux) with a minimal amount of ultraviolet light without a prescription, but it is best to work with a professional who can monitor your response.

There are few side effects to light therapy, but you should be aware of the following potential problems:

- Mild anxiety, jitteriness, headaches, early awakening, or eyestrain can occur.
- There is evidence that light therapy can trigger a manic episode in people who are vulnerable.
- While there is no proof that light therapy can aggravate an eye problem, you should still discuss any eye disease with your doctor before starting light therapy. Likewise, since rashes can result, let your doctor know about any skin conditions.
- Some drugs or herbs (for example, St. John's wort) can make you sensitive to light.
- If light therapy isn't helpful, antidepressants may offer relief.

For information on a possible cause of SAD, see page 13.

Table 1 Medications that may cause depression

Antimicrobials, antibiotics, antifungals, and antivirals	Tranquilizers, insomnia aids, and sedatives
acyclovir (Zovirax); alpha-interferons; cycloserine (Seromycin); ethambutol (Myambutol); levofloxacin (Levaquin); metronidazole (Flagyl); streptomycin; sulfonamides (AVC, Sultrin, Trysul); tetracycline	barbiturates such as phenobarbital (Solfoton) and secobarbital (Seconal); benzodiazepines such as diazepam (Valium) and clonazepam (Klonopin)
Heart and blood pressure drugs	**Miscellaneous**
beta blockers such as propranolol (Inderal), metoprolol (Lopressor, Toprol XL), atenolol (Tenormin); calcium-channel blockers such as verapamil (Calan, Isoptin, Verelan) and nifedipine (Adalat CC, Procardia XL); digoxin (Digitek, Lanoxicaps, Lanoxin); disopyramide (Norpace); methyldopa (Aldomet)	acetazolamide (Diamox); antacids such as cimetidine (Tagamet) and ranitidine (Zantac); antiseizure drugs; baclofen (Lioresal); cancer drugs such as asparaginase (Elspar); cyclosporine (Neoral, Sandimmune); disulfiram (Antabuse); isotretinoin (Accutane); levodopa or L-dopa (Larodopa); metoclopramide (Octamide, Reglan); narcotic pain medications (e.g., codeine, Percodan, Demerol, morphine); withdrawal from cocaine or amphetamines
Hormones	
anabolic steroids; danazol (Danocrine); glucocorticoids such as prednisone and adrenocorticotropic hormone; estrogens (e.g., Premarin, Prempro); oral contraceptives (birth control pills)	

the mood changes. There is no doubt that the stress of having certain illnesses can trigger depression. In other cases, depression precedes the medical illness and may even contribute to it. To find out whether the mood changes occurred on their own or as a result of the medical illness, a doctor carefully considers a person's medical history and the results of a physical exam.

If depression or mania springs from an underlying medical problem, the mood changes should disappear after the medical condition is treated. If you have hypothyroidism, for example, lethargy and depression often lift once treatment regulates the level of thyroid hormone in your blood. In many cases, however, the depression is an independent problem, which means that in order to be successful, treatment must address depression directly.

Medications

Sometimes, symptoms of depression or mania are a side effect of certain drugs, such as steroids or blood pressure medication. Be sure to tell your doctor or therapist what medications you take and when your symptoms began. A professional can help sort out whether a new medication, a change in dosage, or interactions with other drugs or substances might be affecting your mood.

Table 1 lists drugs that may affect mood. However, keep in mind the following:

- Researchers disagree about whether a few of these drugs—such as birth control pills or propranolol—affect mood enough to be a significant factor.
- Most people who take the medications listed will not experience mood changes, although having a family or personal history of depression may make you more vulnerable to such a change.
- Some of the drugs cause symptoms like malaise (a general feeling of being ill or uncomfortable) or appetite loss that may be mistaken for depression.
- Even if you are taking one of these drugs, your depression may spring from other sources.

An out-of-sync body clock may underlie SAD and other mood disorders

Research into one form of depression—seasonal affective disorder (SAD)—has uncovered another potential factor in mood disorders: an internal body clock that has gone awry.

Experts don't fully understand the cause of SAD, but a leading theory has been that the hormone melatonin plays a role. The brain secretes melatonin at night, so longer periods of darkness in the winter months may spur greater production of this hormone. Some researchers believe light therapy has been helpful in treating SAD (see page 11) because exposure to light artificially lengthens daytime and decreases melatonin production.

But in the last couple of years, a new theory has emerged: that SAD stems, at least partly, from an out-of-sync body clock. The researchers who propose this idea suggest that light therapy works because it resets the body's internal clock.

Each of us has a biological clock that regulates the circadian (meaning "about a day") rhythm of sleeping and waking. This internal clock—which is located in a small bundle of brain cells called the suprachiasmatic nucleus and gradually becomes established during the first months of life—controls the daily ups and downs of biological patterns, including body temperature, blood pressure, and the release of hormones. Although the clock is largely self-regulating, it responds to several cues to keep it set properly, including light and melatonin production.

When researchers expose people to light at intervals that are at odds with the outside world, this resets the subjects' biological clocks to match the new light input. Likewise, melatonin affects the body clock. It's produced in a predictable daily rhythm by the pineal gland, with levels climbing after dark and ebbing after dawn. Scientists believe this daily light-sensitive pattern helps keep the sleep/wake cycle on track.

Not keeping proper time

In 2006, a group of researchers presented findings that support the theory that SAD symptoms may stem from a body clock that isn't keeping time properly. They suggested that these rhythms can be thrown off by the late dawn and early dusk of winter.

The researchers tracked sleep patterns and depressive symptoms in 68 SAD patients. By examining healthy subjects, the researchers determined that circadian rhythms are synchronized when melatonin is secreted roughly six hours before the midpoint of sleep. In about 70% of the individuals with SAD, the interval was shorter than six hours, meaning they produced melatonin late, perhaps because of the later winter dawn. About 30% of the study's participants had the opposite problem: the interval between melatonin production and the midpoint of sleep was longer than the ideal six hours.

The SAD patients were split randomly into three groups: two that received low doses of melatonin (one group in the morning and the other in afternoon) and one that received a placebo. In this way, the circadian clock in some individuals was reset properly, and in others it remained out of sync.

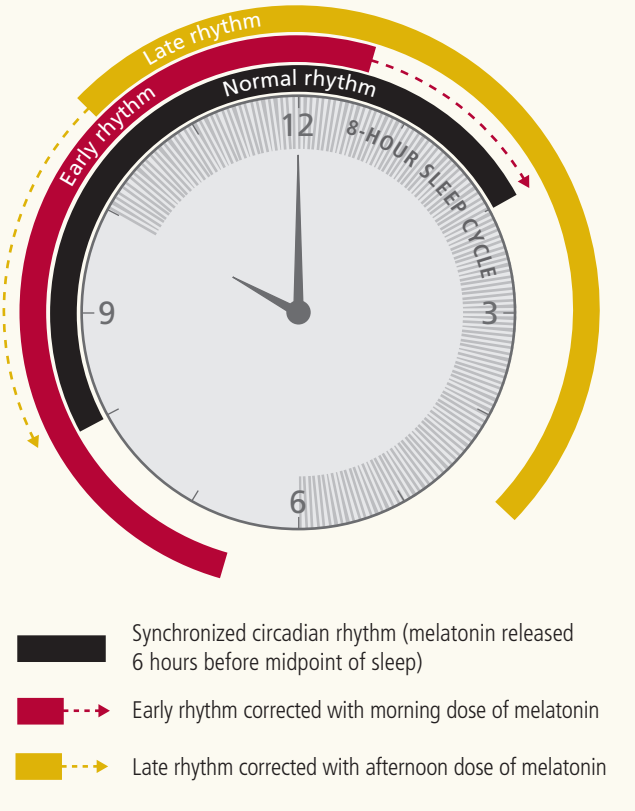
Researchers found that depressive symptoms lifted when the cycles were synchronized. Taking melatonin at the correct time of day—afternoon for people with a late rhythm and morning for those with an early rhythm—more than doubled their improvement in depression scores, compared with taking the hormone at the wrong time or taking a placebo.

This study casts doubt on the theory that light therapy is beneficial because it reduces melatonin levels. If that were the case, the participants receiving melatonin shouldn't have shown improvement, but many did. Still, the debate is not over. Researchers still have much to learn about how light exposure and melatonin secretion interact with the brain's mood-regulating function.

Beyond SAD

A case is being made that circadian rhythms influence other mood disorders as well. Studies have uncovered out-of-sync circadian rhythms among people with bipolar disorder, schizophrenia, borderline personality disorder, or night eating disorder.

Figure 3 Getting back in sync



Suicide: Recognizing the risk

Most people who commit suicide are depressed, but what triggers this irrevocable step varies from person to person. Suicide may stem from intense feelings of anger, despair, hopelessness, or panic. Sometimes it's carried out under the sway of a highly distorted or psychotic idea. If you think you might harm yourself, seek help. If you believe a friend or loved one might become self-destructive, urge him or her to do the same.

A number of factors can put someone at a higher risk for suicide in the short term, including the following:

- an episode of depression, psychosis, or anxiety
- a significant loss, such as the death of a spouse or the loss of a job
- loss of social support, for example, because of a move or when a close friend relocates
- a personal crisis or life stress, especially one that increases a sense of isolation or leads to a loss of self-esteem, such as a separation or divorce
- an illness or medication that triggers a change in mood.

None of these circumstances necessarily leads to suicide. In fact, most people in these circumstances do not commit suicide, and there is no way to predict who will. But any blow that upsets a person's life can set a vulnerable individual on a self-destructive course. Treatment can help you or someone you care about change that course.

Other grounds for concern

Mental health experts also observe that many cases of suicide involve some of the following factors. Although these circumstances can't reveal states of mind or predict actions, they should be taken seriously. Family members and health care professionals may be able to reduce the chances of suicide by watching for these factors and taking action if they notice them.

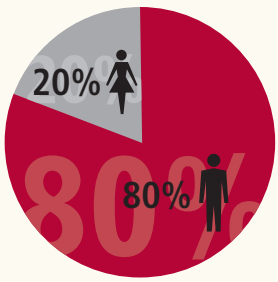
Family history. People with a biological relative with a history of suicide or suicide attempts have a risk of suicide that is much higher than average. For example, the child of a person who attempts suicide has six times the average risk of committing suicide. And 13% of people with an identical twin who commits suicide take their own lives, compared with less than 1% among fraternal twins. Some research indi-

Suicides in the United States

Reliable statistics on suicide aren't easy to compile because reporting is not always candid and records are not always thorough. Family members and others may have many reasons for denying that a death is suicide, and official sources cannot always distinguish suicide from accidents in cases like drunk driving and drug overdoses. Still, despite these limitations, we know that suicide is an important public health problem. Here is a look at some of the figures that are available:

- Suicide is the 11th leading cause of death in the United States.
- In 2005, the number of known suicide deaths in the United States was 32,637.
- For every suicide death, there are an estimated eight to 25 attempted suicides. Men and older adults are more likely to complete suicide than are women, children, and young adults.
- The risk of suicide rises with age, and older Americans are disproportionately likely to die by suicide. In 2005, of every 100,000 people ages 75 and older, about 17 died by suicide. Compare that with the general population, where the annual rate is nearly 11 suicides per 100,000 people.

Most suicides are by men



Can antidepressants trigger suicide?

Suicidal thoughts (although no suicides) were first reported in people taking selective serotonin reuptake inhibitors (SSRIs) in 1990, shortly after the drugs were introduced. An FDA committee rejected the association, and most mental health professionals accepted the committee's conclusion, but the issue was never fully resolved.

The debate was revived as a result of an increase in the number of children and adolescents receiving prescriptions for antidepressants. In 2003, British drug authorities announced a possible connection between the antidepressant paroxetine (Paxil) and thoughts of suicide in some teenagers and children. The FDA performed its own review of these medications, and in 2004 it began requiring that drug manufacturers include a warning on all antidepressants. This warning now applies to children and young adults up to age 24.

This "black box" warning—the FDA's strongest available measure short of withdrawing a drug from the market—is placed on package inserts for all commonly used antidepressants. The warning mentions the risk of suicidal thoughts, hostility, and agitation in both children and adults.

Although results from many subsequent studies have varied, there is a consistent trend. When compared with a placebo, all antidepressants, including SSRIs, seem to double the risk of suicidal thinking, from 1% to 2% up to 2% to 4%, in both children and adults.

Even so, these studies did not report any cases of completed suicides. However, because many drug studies purposely exclude the most depressed individuals, the study samples do not necessarily accurately represent that important subgroup of people.

As antidepressant use falls, suicides rise

Not only is there no evidence so far from controlled research that links suicide to antidepressant use, studies suggest that just the opposite is true—that antidepressant treatment reduces the risk of suicide. Several studies have found that higher rates of SSRI use coincided with lower suicide rates.

But since the black box warning appeared, fewer prescriptions for SSRIs are being given to youths. A 2007 study in *The American Journal of Psychiatry* found that before the warning was issued, SSRIs were given for 59% of depressive episodes in children, but by 2005 the rate had sunk to 28%. The same study found that depression was being diagnosed less frequently as well, and some experts are concerned that many youngsters with depression aren't getting the care they need.

Even more sobering, the youth suicide rate in the United States spiked 8% in 2004—the biggest increase in 15 years. Rates rose among girls ages 10 to 14, and among both boys and girls ages 15 to 19. In general, prior to 2003, the suicide rates for these youngsters were dropping. There is speculation that the two events—an increase in suicides and a decrease in the use of antidepressants—are linked.

Why the increase in suicidal thoughts?

Researchers are still trying to ascertain why antidepressants increase suicidal thoughts in some people. Depression in itself increases the risk of suicide, and self-destructive and impulsive behavior is common in adolescence, so it's hard to know what to make of the data. Ongoing studies on this subject may shed more light.

A person's genetic makeup may play a role. Researchers have identified two genes that code for receptors for the neurotransmitter glutamate. In 2007, researchers analyzing data from the Star*D study (see "What if my depression doesn't go away?" on page 26) noted that people taking the SSRI citalopram (Celexa) who had certain versions of these two genes were more likely to have suicidal thoughts. While having either gene version increased the likelihood of suicidal thoughts, having both raised the chances even more. Over all, 6% of the participants reported suicidal thoughts while on medication, but 36% of the people with both suspected gene versions had suicidal thoughts. Interestingly, neither version seemed to increase the chances of attempting suicide.

Certainly, other factors also play a role in suicidal thinking, and several theories may explain this phenomenon. For example, in a small percentage of patients, antidepressants may have the paradoxical effect of making moods worse. Self-injury may result from an antidepressant side effect known as akathisia—an extremely uncomfortable form of restlessness. Or perhaps severely depressed people recover the energy to act on suicidal thoughts before their mood improves or hope returns. In addition, giving an antidepressant to a person with bipolar disorder may trigger mania or irritability, increasing the risk of self-destructive behavior.

Close monitoring recommended

Regular follow-ups and close monitoring by a doctor are the best ways to avoid medication-related suicide. Experts recommend that all people starting on or changing their dose of an antidepressant—either increasing or decreasing—be closely monitored. Watch for signs that the depression is worsening or that suicidal thoughts or behaviors have emerged. Careful monitoring is particularly important in the first month or two.

If you feel worse after beginning treatment or if you develop uncomfortable symptoms (like anxiety or restlessness), let your doctor know. The same advice holds true for children: if your child's symptoms seem to worsen or you notice any signs of suicidal thinking or behavior, contact the child's doctor immediately.

cates that this apparent inherited vulnerability may be the product of common genes that cause neurotransmitters to act in a way that predisposes a person toward rage and impulsive behavior. However, the gene studies are preliminary, and neurotransmitter levels are not simply hereditary but vary with a person's state of mind.

Access to handguns. In the United States, although not in other countries, most suicides are by gunshot. Studies have found that suicides are more common in homes that have handguns, and that the suicide rate is among the highest in those states where gun ownership is highest and among the lowest in those states with the fewest gun owners. The American Academy of Pediatrics has urged parents to keep guns and ammunition out of the house if a child might be depressed or suicidal. The same recommendation holds true for adults.

Substance abuse. The combination of depression and alcohol or drug use can be deadly because these substances can erase inhibitions and anxiety that might help keep suicide at bay. Or, as the more pleasing effects of such self-medication wear off, hopelessness may take hold.

Previous attempts. When someone has survived one or more attempted suicides, friends and relatives may take further attempts less, rather than more, seriously. But people with a history of a suicide attempt are about 40 times more likely to commit suicide than those who haven't attempted it before.

Setting affairs in order. Individuals who have decided on suicide may sort out their finances, give away mementos, or call or visit loved ones. People who have been agitated or depressed may seem calmer and happier. But rather than being a sign of returning health, this shift may stem from their relief at having made a final decision. Although this phenomenon is usually noted only in hindsight, friends and family members may be in the position to recognize it before a doctor or counselor does.

Help is available

If you or a loved one feels suicidal, there are many places to turn for help. Experts recommend these steps:

- Talk with your doctor or a mental health professional. Very often, treatment eases or entirely eliminates suicidal urges. In some cases, hospitalization is necessary until a sense of equilibrium returns.
- Call 800-273-TALK (8255) or a local hotline and speak with a crisis counselor.
- Discuss your feelings with trusted family members, friends, or religious advisers who can assist you in getting help.

How is depression diagnosed?

Although depression is by no means a silent disease, it is seriously underdiagnosed. Experts estimate that only 34% of people with depression seek help, and only one-third of those who have major depression get the help they need.

When people do reach out for help, doctors typically diagnose depression by asking about feelings and experiences. They may also use screening tools and look for possible medical causes by performing a physical exam and sometimes ordering lab tests.

A physical exam and medical history may offer clues that point to depression caused by medication or an underlying illness. In these cases, blood tests or x-rays may confirm the problem. Often, when people are unable or unwilling to recognize their own depression, their initial complaints are medical. Headaches, stomach problems, sexual difficulties, and lack of energy are among the more common medical complaints.

If your symptoms suggest depression and medical causes seem unlikely, your doctor will be interested in hearing whether you've had any feelings of sadness or hopelessness and whether you've noticed any changes in your appetite, sex drive, or sleep patterns. He or she may also ask these questions:

- Have you or anyone in your family ever suffered from depression or another mental disorder? If so, how was it treated?
- Do you get satisfaction and pleasure from your life?
- Do you ever have thoughts about suicide or have you attempted suicide?
- Do you drink alcohol? If so, how often and how much?
- Do you use any drugs such as marijuana, cocaine, crack, or heroin to get high or relax? If so, which drugs and how often?

Your caregiver might ask you to complete a checklist that may pick up some symptoms or subtle mood changes that otherwise might not be identified. Alternatively, the clinician may complete a similar scale based on his or her observations; such scales are slightly better at detecting depression than self-reports.

Because you may minimize symptoms or may not even be aware of them, your doctor or therapist may want to speak to someone close to you. Where a child or teen is concerned, the doctor may interview parents and, when possible, teachers or a guidance counselor.

When other tests may be useful

Recent years have brought great advances in our understanding of the biological underpinnings of depression. One day these discoveries may lead to the development of genetic or other tests for mood disorders, but right now no such lab test is available. Doctors who want to determine whether someone is depressed generally order tests only when they note a potential health problem during a physical exam or medical history.

Most doctors do not embark on a battery of lab tests for many reasons. Tests can be costly and may not be covered by insurance. In some cases, results point the doctor in the wrong direction, leading to more tests and unnecessary anxiety. Usually, self-reports of symptoms combined with the clinical skills of a doctor or therapist are enough to begin treatment of depression or bipolar disorder.

Sometimes, however, you may need more tests to confirm a diagnosis, tease out information, or distinguish depression from other psychological or neurological problems. Your doctor may ask you to take any of the following:

- Psychological tests, during which you answer questions, respond to pictures, or perform tasks like sorting cards or drawing pictures. These tests can give your doctor a better sense of your coping mechanisms, your temperament, or your ability to organize and plan.
- Tests that look at the brain, such as an EEG or MRI, which can help identify causes of dementia or some rare causes of depression. Both tests are painless. During an EEG, electrodes taped to your scalp pick up electrical signals. An MRI uses magnets, a radio wave transmitter, and a computer to pick up small changes in energy in hydrogen molecules in your brain and process the data to make a detailed scan of your brain.
- Tests for biological causes of depression, such as a blood test to check thyroid function.

Treating depression

If we were all carbon copies of one another, identifying the causes of depression and its proper treatment would be simpler. But unique differences in life experience, temperament, and biology make treatment a complex matter. No single treatment works for everyone. However, research suggests that many people benefit from a combination of medication and therapy (see "Drugs and therapy: A winning combination?" on page 20).

Often, treatment is divided into three phases. Keep in mind, though, that there are no sharp lines dividing the phases, and very few people take a straight path through them.

- In the acute phase, the aim is to relieve your symptoms. Generally, this occurs within six to 12 weeks, but it may take longer depending on your response to the first treatments you try.
- In the continuation phase, you work with your doctor to maximize your improvements. Further treatment adjustments, such as modifying the dosage of a medication, can help. This period takes another four to five months.
- In the maintenance phase, the aim is to prevent relapse. Ongoing treatment is often necessary, especially if you have already experienced several depressive episodes, have chronic low mood, or have risk factors that make a recurrence more likely.

What you should know about medications

Often, medications are the first choice in treatment, especially if you're experiencing a severe depression or suicidal urges. Controlled studies have found that about 65% to 85% of people get some relief from antidepressants, compared with 25% to 40% of people taking a placebo (a pill with no biologically active ingredient). But the very same drug that works wonders for a friend may fail to ease your symptoms. You may need to try a few different medications to find the one that works best for you with as few side effects as possible. In some cases, a doctor may prescribe a combination of antidepressants or an antidepressant along with a drug to treat anxiety or distorted thinking. A drug combination may be more effective than either drug alone.

Doctors usually first prescribe medications from a class of drugs known as selective serotonin reuptake inhibitors (SSRIs). SSRIs include fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft). Although the side effects of each drug vary slightly from person to person, you have an equal chance of success on any

Who should you see for treatment?

On your road to treatment, your primary care doctor may be your first stop. A good primary care doctor can assess your symptoms with an eye to whether you have any underlying medical problems. If your doctor believes that depression is the main problem, he or she may suggest an antidepressant. Sometimes the initial response to the medication is good. If so, you may not need to go further.

However, if you don't respond well to the first medication, your doctor may refer you to a mental health professional, such as a psychiatrist, psychologist, social worker, or psychiatric nurse. Most primary care doctors aren't equipped to do a more detailed review of the mood problem or to take treatment further with psychotherapy or different medications.

You can also find a mental health professional through a local clinic or hospital or through recommendations from family members or friends. While some insurance plans leave the choice of therapist up to you, others limit you to professionals enrolled in their networks. Therefore, it's worthwhile to check with your insurer before choosing a doctor.

Since states have different requirements about who may hang out a shingle as a therapist, inquire about the therapist's training, and opt only for one who has been formally trained and certified (see "10 questions to ask when choosing a therapist," page 29).

From the lab to your medicine cabinet: How today's scientific discoveries may lead to better, more individualized treatment

Some people find that the first medication they try delivers great results: their depression lifts, they feel more like themselves, and they have few or no side effects. But for many others, finding the right medication is a frustrating exercise in trial and error.

What if a simple test could tell you what medication is right for you? Right now, such a test doesn't exist. But as researchers uncover which genes influence mood and clarify their function, the hope is that these discoveries will make this kind of testing possible and will eliminate some of the guesswork involved in prescribing antidepressants.

In effect, depression may be many diseases, not a single one. Scientists have found that dozens of genes affect mood, and as our genetic endowments differ, so do our depressions. That may be more apparent when symptoms differ—for example, when one person experiences depression as profound sadness and another primarily feels listless and takes pleasure in nothing. But even when symptoms are similar, the underlying causes may vary—and thus the same drug that works marvelously for one person may have little effect on another.

If gene- and protein-based work being done in labs today fulfills its promise, future patients will receive different medicines for different types of depression. Researchers are pursuing the goal of targeting medication more effectively one "snip" at a time. Those snips, or SNPs, are single nucleotide polymorphisms—small variations in the DNA sequence that can have big consequences.

An example is the SNP code-named G1463A. People with G1463A produce very low levels of serotonin. This aberrant SNP shows up more often in people who have major depression than those who don't. And depressed people with G1463A are relatively resistant to SSRI antidepressants like Prozac and Zoloft, which act on serotonin. Someday doctors may be able to test for this variant to determine whether an individual is a good candidate for treatment with an SSRI or if another medication is a better fit.

In 2008, scientists discovered another gene variation that seems to influence how well patients respond to treatment. People who have certain variations in the TREK1 gene are more likely to have treatment-resistant depression, meaning that they failed to respond to initial and sometimes subsequent medications.

Not only is current research adding to our understanding of why people respond differently to antidepressants, it's also paving the way for blood tests that can help your doctor track how well you are responding to a medication. Scientists have discovered that levels of a protein called beta-arrestin-1 are low in depressed people, but return to normal after treatment with an antidepressant. One day, doctors may be able to monitor a patient's progress on a given treatment by measuring levels of this protein.

These kinds of tests are still possibilities, not realities, but in the years to come, it's likely that today's scientific discoveries will significantly reshape how depression is treated.

of these drugs. If you don't have a good response to the first drug you try, you and your doctor may decide to switch to another.

Improvement may take time

Although in a few cases people report a change for the better as quickly as one or two weeks after beginning medication, more often it takes from two to six weeks for antidepressants to ease depression. The lag may reflect the time it takes the medications to affect processes inside the nerve cells and in brain circuits. It's frustrating but true that side effects may appear before the benefits of a drug become obvious. Once you start to feel better, though, it's important to take the medication for as long as it's prescribed to get a full response and avoid a relapse.

While you are using medications, the doctor prescribing them should regularly monitor the dosage and your response. All medical treatments have advantages and disadvantages, and a doctor cannot predict an individual's response to a given medication. While there's a good chance that an antidepressant will relieve your symptoms, there's also a possibility that you'll encounter side effects. So when you're about to embark on treatment, it's important to weigh the potential benefits against the risks. Thankfully, most side effects can be managed or reversed.

Poor response to an antidepressant is often due to an inadequate dose. If the medication doesn't seem to be working during the first phase of your treatment, your doctor may suggest increasing the prescribed amount.

Not everyone who takes a drug will be bothered by side effects. If you do experience some, the first step is to report them to your doctor. Your doctor may be able to suggest simple, helpful adjustments (see "Man-

aging side effects," page 38). Many side effects disappear once your body becomes accustomed to the medication. Or, if necessary, you can try a different dosage or drug.

Antidepressants are not habit-forming or addictive. However, if you are about to stop taking these medications, your body needs to readjust slowly, so your doctor may instruct you to reduce the dosage gradually. Even if you do this, you may experience uncomfortable or disturbing symptoms. Sometimes these symptoms are mistaken for a recurrence of the illness (see "Is it a relapse or not?" on page 40).

While many antidepressants can be safely combined, some cannot. If you switch medications, you may need a washout period (a stretch of several weeks of taking no drugs) in order to prevent dangerous interactions between a new drug and the lingering effects of the previous one.

Drugs and therapy: A winning combination?

No single treatment—whether a drug or a style of therapy—can beat depression in every case. But would you be better off with a combination of drugs and therapy? Research suggests the answer is yes.

A review of several studies considered data collected on nearly 600 people treated for major depression. The investigators found recovery was quicker and more likely to occur with therapy plus an antidepressant compared with therapy alone.

A study of 439 teens with major depression found similar results: treatment with the antidepressant Prozac along with cognitive behavioral therapy worked better than either treatment alone. In that study, 18 weeks after treatment began, 85% of those on combination therapy improved, compared with 69% of those taking only Prozac and 65% of those doing only cognitive behavioral therapy.

At the 36-week mark, the numbers were more similar, but combination therapy still edged out the other treatments. Combination therapy helped about 86% of the individuals using this treatment, while the response rate for Prozac alone and cognitive behavioral therapy alone was 81% each.

Combination therapy may also help ward off recurrences. A three-year study reported in the *Journal of the American Medical Association* tracked recurrences of major depression in about 200 people ages 60 or older. Of those who received monthly interpersonal therapy and the medication nortriptyline, 80% avoided a recurrence. In contrast, only 57% of those who received the drug alone, 36% of those given just therapy, and a mere 10% in the placebo group did as well.

A 2004 study found that one reason therapy and medication may complement each other is that they have effects on different parts of the brain.

However, if your depression is mild, research suggests that combination therapy is no better than cognitive behavioral therapy or interpersonal therapy alone.

Of course, it always makes sense to mull over all of your options. If one type of treatment alone isn't helping you, consider trying combination treatment.

Choosing a medication

One day it may be possible to use biological markers and other indicators to predict exactly which antidepressant will work best for each person (see "From the lab to your medicine cabinet," page 19). Right now, though, psychiatrists and doctors who prescribe antidepressants choose a particular drug and dosage based on many factors, including the following:

Diagnosis. Certain drugs work better for specific symptoms and types of depression. For example, some antidepressants may be better when insomnia is an issue. The severity of your illness or the presence of anxiety, obsessions, or compulsions may also dictate the choice of one drug over another.

Age. As you age, your body tends to break down drugs more slowly. Thus, older patients may need a lower dosage. For children, only a few medications have been studied carefully.

Health. If you have certain health problems, it's best to avoid certain drugs. For this reason, it's important to discuss medical problems with a primary care doctor or psychiatrist before starting an antidepressant.

Medications, supplements, and diet. When combined with certain drugs or substances, antidepressants may not work as well, or they may have worrisome or dangerous side effects. For example, taking an SSRI with another type of antidepressant known as a monoamine oxidase inhibitor (MAOI) can be fatal. Combining the herbal remedy St. John's wort with an SSRI or an MAOI could lead to serious side effects, because this herb boosts serotonin. Likewise, mixing St. John's wort with other drugs—including certain drugs to control HIV infection, cancer medications, and birth

control pills—might lower their effectiveness. Eating certain foods, such as cheeses and pickles, while taking an MAOI can raise your blood pressure to dangerously high levels.

Alcohol or drugs. Alcohol and other substances can cause depression and make antidepressants less effective. Doctors often treat alcohol or drug addiction first if they believe either is causing the depression. In many instances, simultaneous treatment for addiction and depression is warranted.

Mental health and medication history. Depending on the nature and course of your depression (for example, if your depression is long-lasting or difficult to treat), you may need a higher dosage or a combination of drugs. This may also be true if an antidepressant has stopped working for you, which may occur after you've used it for some time or after you've stopped and restarted treatment with it.

Medications for depression

More medications are available to treat depression than ever before. Some antidepressant classes have fallen out of favor, while others have risen in popularity. Currently, the most commonly prescribed antidepressants are drugs that have been developed since the mid-1980s. SSRIs lead the list in popularity. Some commonly prescribed medications don't fall into one class. They include bupropion (Wellbutrin), mirtazapine (Remeron), venlafaxine (Effexor), and duloxetine (Cymbalta). Two older classes of antidepressants, tricyclic antidepressants (TCAs) and MAOIs, are still very useful—some people take them without being bothered by side effects—but on average their side effects have made them less appealing as a first-line treatment.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs stepped into the spotlight in the late 1980s. The serotonin system involves many regions of the brain and affects mood, arousal, anxiety, impulses, and aggression. SSRIs slow the reuptake of serotonin—that is, they keep it from being quickly reabsorbed by the neurons that released it. By blocking reuptake, they permit serotonin to work for a longer time at receptor sites. SSRIs also appear to change the number and sensitivity of receptors and to indirectly influence other neurotransmitters, including norepinephrine and dopamine.

Prozac, the first SSRI introduced, quickly became a celebrity. Not only did it relieve depressive symptoms in many people, but it also appeared to help with a wide variety of problems, including anxiety, shyness (social phobia), obsessions (obsessive-compulsive disorder), and eating disorders (anorexia or bulimia). Other SSRIs have since been introduced to the market (see Table 2, page 24).

SSRIs have several advantages over the TCAs and MAOIs that came before them. Unlike TCAs, they rarely cause side effects like dry mouth, constipation, or dizziness. Nor are they likely to disrupt heart rhythms, a potentially fatal side effect of an overdose of TCAs. And with SSRIs, you don't have to worry about dietary restrictions, as you would if you took MAOIs.

On the other hand, SSRIs do have their own problems. The best known of these are sexual side effects. It's fairly common for men taking these medications to have problems sustaining an erection. Both sexes may find that the drugs dampen desire or make it difficult to reach orgasm (see "Sexuality and SSRIs," page 23).

Other side effects include nausea, insomnia, and a slight increased risk of excessive bleeding, particularly if taken with aspirin or the blood thinner warfarin (Coumadin). Ironically, SSRIs can also increase the risk of suicidal tendencies in a small percentage of adults and children taking them (see "Can antidepressants trigger suicide?" on page 15 and "Treating depression in teens and children" on page 45).

In addition, SSRIs can interact with certain antihistamines, anticonvulsants, other antidepressants, drugs used to quell mood disorders and herbal supplements. For example, one such problem, called the serotonin syndrome, can occur when St. John's wort is taken along with SSRIs. This condition is marked by a racing heart, fever, sweating, high blood pressure, trembling, and confusion. Potentially, at least, it can also occur when an SSRI is combined with lithium or the herb St. John's wort.

Although these side effects may seem daunting, keep in mind that some of the older antidepressants also can be dangerous. The main advantage of SSRIs and other

newer antidepressants isn't necessarily that they cause fewer side effects or less discomfort, but that the most dangerous side effects tend to occur less frequently.

Newer types of antidepressants

Since the early 1990s, many newer antidepressants have joined SSRIs in supplanting MAOIs and TCAs as treatment options. The change reflects a number of factors—for example, the newer antidepressants have less severe side effects, are easier to prescribe, and have been promoted with intense marketing campaigns. In any case, having more treatment options available increases the likelihood that people who are depressed will find one that works for them.

These newer medications, which don't fall neatly into a single class, often work through mechanisms that differ from those of the older classes of antidepressants. For example, bupropion (Wellbutrin) affects the neurotransmitters norepinephrine and dopamine, and mirtazapine (Remeron) affects norepinephrine and serotonin. On the other hand, venlafaxine (Effexor) and duloxetine (Cymbalta) work in part by slowing the reuptake of serotonin, like SSRIs do, but they also slow the reuptake of norepinephrine. Because of their twofold action, they are designated as dual serotonin and norepinephrine reuptake inhibitors.

Side effects vary from medication to medication (see Table 2). Because these medications are fairly new, much isn't known yet about long-term side effects, but none are apparent at this time.

In general, studies haven't found that the newer medications are more or less effective than older ones like SSRIs. But, as mentioned previously, individuals respond differently to different antidepressants. So while a newer medication may not work better for all—or even most—people, some individuals may find it more helpful or may tolerate it better than another drug.

Doctors are still inclined to prescribe an SSRI first. They have more experience with SSRIs, since these drugs have been available longer and more research has been done using them. People have tolerated them well. Many are now available in cost-effective generic form. However, newer drugs are good second choices and may become more common as first choices in time.

Tricyclic antidepressants (TCAs)

TCAs, named for their three-ring molecular structure, have been used since the 1960s. Doctors believe TCAs lift depression mainly by increasing the availability of both norepinephrine and serotonin. TCAs do this by slowing the reabsorption of these neurotransmitters into the neurons that released them.

At the same time, though, TCAs influence another neurotransmitter, acetylcholine, which can lead to dizziness, constipation, blurred vision when reading, and trouble urinating (see Table 2). These drugs can also cause weight gain. But their most serious side effect is a dangerously abnormal heart rhythm, so they aren't the first choice of antidepressants for people with heart disease. While TCAs are generally safe for people with healthy hearts, a two-week supply of pills could fatally disrupt heart rhythms if a person were to attempt suicide by taking them all at once.

Monoamine oxidase inhibitors (MAOIs)

The neurotransmitters norepinephrine and serotonin are members of a class of compounds called monoamines. They are normally broken down in the body by the enzyme monoamine oxidase. MAOIs block this enzyme, raising the levels of norepinephrine and serotonin in the brain. That can relieve mood problems, anxiety, and other hallmarks of depression.

The two most commonly used MAOIs are tranylcypromine (Parnate) and phenelzine (Nardil). These drugs may be especially helpful if your depression includes features that are considered atypical, such as oversleeping rather than insomnia or weight gain rather than weight loss. They can also relieve the extreme anxiety of panic attacks.

As with other antidepressants, MAOIs have a variety of side effects (see Table 2). They can cause sedation, insomnia, and weight gain. MAOIs can also leave you feeling stimulated or restless. Dizziness sometimes occurs, which is particularly troublesome to older adults who are more prone to disabling falls. In addition, a relatively small number of people taking MAOIs develop liver damage.

But the greatest source of inconvenience—and occasionally danger—is that people taking MAOIs must avoid eating a substance called tyramine. Normally,

monoamine oxidase breaks down tyramine. If you are taking an MAOI, however, tyramine does not get broken down and can build to unsafe levels. In high concentrations, tyramine can cause a dangerous and rapid increase in blood pressure, and on rare occasions leads to a stroke. Therefore, if you take MAOIs, you must avoid foods that contain tyramine—such as yogurt, aged cheese, pickles, beer, and red wine.

Adding mood stabilizers

People who have problems with depression may also experience mood swings—like the ups and downs seen in various forms of bipolar disorder—so a mood stabilizer, such as lithium (Eskalith, Lithane, and others) or valproate (Depakote), may be added to treatment. Even if you don't have a tendency toward mood cycling, these medications can sometimes build on the effects of an antidepressant, improving your response.

Medications for bipolar disorder

Lithium is the most widely known medication used to treat bipolar disorder. Lithium helps stabilize moods. Other medications also have this effect—for example, some anticonvulsants (which are often used to combat seizures) also have mood-stabilizing properties. These mood stabilizers tend to be mainstays for treating bipolar disorder, but your doctor may recommend other medications as well. Depending on the nature of your illness, you may receive antipsychotic, antidepressant, or anti-anxiety medications.

You may need to stay on some medication or combination of medications indefinitely to keep your

Sexuality and SSRIs

One drawback to SSRIs is that they frequently dampen sexual response. Sexual side effects are a possibility with other antidepressants, too, but they are much more common with SSRIs. One study suggested that as many as half of all people taking these medications may experience some sexual problems. In addition to reducing interest in sex, SSRIs can make it difficult to become aroused, sustain arousal, and reach orgasm. Some people taking SSRIs aren't able to have an orgasm at all.

If you experience any sexual problems while taking an SSRI, talk with your doctor or therapist. Studies have found that about 35% to 50% of people with untreated major depression experience some type of sexual dysfunction. So in some cases, sexual difficulties may stem not from the medication, but rather from the underlying depression.

If medication is the problem, sexual side effects sometimes subside with time, so it's worth waiting a while to see if problems diminish. This is a particularly good strategy if the medication is easing your depression significantly. If side effects persist, your doctor or therapist may suggest one of the following strategies:

- **Lowering the dose.** Sexual side effects may subside at a lower, although still therapeutic, dose.
- **Scheduling sex.** Your medication may produce more pronounced side effects at particular times of the day, for example, within a few hours of taking it. If so, you can try scheduling sexual activity for the time when side effects are least bothersome—or take the drug at a different time.
- **Taking a drug holiday.** Depending on how long the drug usually remains in your body, you might stop taking it for a few days before a weekend, if that's when you hope to have sex. This is hardly spontaneous, but it can work if you carefully follow your doctor's directions about how to stop and resume your medication. However, there is always a chance that this might cause a relapse, especially if it is one of the drugs that leaves your system more rapidly.
- **Switching to a different drug.** Certain antidepressants, such as bupropion (Wellbutrin), mirtazapine (Remeron), TCAs, and MAOIs, are less likely to cause sexual problems. Bupropion can sometimes improve sexual response (see below).
- **Adding a drug.** Studies have found that sildenafil (Viagra) and tadalafil (Cialis) can alleviate SSRI-induced erectile dysfunction in men. For women, these drugs haven't proven very helpful. However, men and women may both benefit from adding bupropion to their treatment. This medication has been found to counter SSRI-induced sexual dysfunction, boost sexual drive and arousal, and increase the intensity or duration of an orgasm. Another drug, buspirone (BuSpar), can restore the ability to have an orgasm and increase libido.
- **Meeting with a therapist.** Even when physical issues or medication are at the root of sexual problems, psychological issues often become interwoven. For example, a few episodes of erectile dysfunction may cause a man to withdraw from sex and his partner to feel rejected. These issues can lead the couple to retreat further from intimacy. Working with a qualified sex therapist or general therapist can help couples explore their sexual concerns, learn to better communicate their needs, and expand their repertoire of sexual activities.

Table 2 Medications used for depression and bipolar disorder

GENERIC NAME (BRAND NAME)	SIDE EFFECTS
Selective serotonin reuptake inhibitors (SSRIs)	
citalopram (Celexa)	Nausea; diarrhea or constipation; weight loss or gain; anxiety; insomnia (occasionally drowsiness); headache; sweating; dry mouth; and sexual problems (see "Sexuality and SSRIs," page 23). Bleeding problems are uncommon, but do sometimes occur.
escitalopram (Lexapro)	
fluoxetine (Prozac)	
fluvoxamine (Luvox)	
paroxetine (Paxil)	
sertraline (Zoloft)	
Newer antidepressants	
bupropion (Wellbutrin)	Anxiety; dry mouth; sweating; loss of appetite; sleep problems Can trigger seizures and psychosis in people who have an underlying condition that makes them vulnerable to these problems
duloxetine (Cymbalta)	Nausea; dry mouth; dizziness; sexual problems; anxiety; loss of appetite; at higher doses, rise in blood pressure
mirtazapine (Remeron)	Drowsiness or sedation; constipation; dry mouth; increased appetite; weight gain
venlafaxine (Effexor)	Nausea; insomnia; dry mouth; dizziness; sleep problems; sexual problems; blurred vision; anxiety; loss of appetite; at higher doses, rise in blood pressure
Tricyclic antidepressants (TCAs)	
amitriptyline (Elavil, Endep)	Dry mouth; blurred vision; dizziness when changing postures (for example, going from sitting to standing); drowsiness; weight gain; constipation; trouble urinating; disturbance of heart rhythm (arrhythmia)
clomipramine (Anafranil)	
imipramine (Tofranil)	
nortriptyline (Aventyl, Pamelor)	
Monoamine oxidase inhibitors (MAOIs)	
isocarboxazid (Marplan)	Dizziness when changing postures; diarrhea; nervousness or trembling; drowsiness; mild headache; weight gain, with cravings for sweets; disturbed sleep Rarely: dangerously high blood pressure if foods containing tyramine are eaten; abnormal liver function
phenelzine (Nardil)	
tranylcypromine (Parnate)	
Note: All antidepressants may cause agitation and restlessness; involuntary movements, such as tics and tremors; and suicidal thoughts or behaviors, particularly in the first weeks of treatment. These side effects are rare.	
Mood stabilizers	
lithium carbonate (Eskalith, Lithonate)	Excessive thirst; frequent urination; memory problems and poor concentration; tremors; weight gain; drowsiness; diarrhea; occasional low-thyroid problems or, more rarely, heart or kidney problems over time
carbamazepine (Tegretol)	Fatigue; nausea; dizziness; unsteadiness; double or blurred vision Rarely: lowered blood cell counts; impaired liver function
gabapentin (Neurontin)	Coordination problems; abnormal dreams or thinking; anemia; irregular heartbeat; agitation or nervousness
lamotrigine (Lamictal)	Fatigue; rash; headache; blurred or double vision; dizziness; nausea; memory or concentration problems Rarely: lowered blood cell counts; impaired liver function
topiramate (Topamax)	Lack of coordination; dizziness; abdominal pain; fatigue; memory difficulties; nervousness; drowsiness; speech problems; nausea; tremors; sensations such as tingling, burning, or hypersensitivity; rapid movement of the eyes; upper respiratory infections; mood problems Rarely: abdominal pain; weight loss
valproate (Depakote)	Nausea, indigestion, vomiting, or diarrhea; tremors; sedation; hair loss; increased appetite and weight gain Rarely: impaired liver function; lowered blood cell counts; inflamed pancreas

GENERIC NAME (BRAND NAME)	SIDE EFFECTS
Antipsychotics	
clozapine (Clozaril)	Drowsiness; excess salivation; dry mouth; blurred vision; constipation; dizziness; transient fever; rapid heartbeat; seizures at higher doses; potentially dangerous drop in white blood cell counts, which requires frequent, regular monitoring
olanzapine (Zyprexa)	Drowsiness; weight gain; dry mouth; dizziness; weakness; upset stomach or constipation; anxiety or agitation; headache; fast heartbeat Rarely: movement disorders; seizures; very low blood pressure
quetiapine (Seroquel)	Headache; drowsiness; dizziness; constipation; dry mouth; weight gain; rapid heart rate or low blood pressure; upset stomach; altered liver or thyroid function Rarely: movement disorders; low blood cell counts; seizures
risperidone (Risperdal)	Drowsiness; anxiety; dizziness; constipation or diarrhea; nausea or stomach upset; rapid heart rate; increased dreaming; visual disturbances; weight gain Rarely: movement disorders
Anti-anxiety medications	
Benzodiazepines, including alprazolam (Xanax), clonazepam (Klonopin), lorazepam (Ativan)	Clumsiness or unsteadiness; drowsiness; cognitive impairment; dizziness; headache; tolerance may develop
buspirone (BuSpar)	Chest pain; dizziness; headache; nausea
Note: For precautions regarding the use of these medications during pregnancy, see "Information for expectant and new mothers," page 43.	

mood stable. The likelihood of having a relapse when you go off medications is great, especially if you've had two or more episodes of mania or depression. Experts now believe that the more episodes of depression or mania you've experienced, the more intense and frequent your subsequent episodes may be. Therefore, for people with bipolar disorder, maintenance therapy is the best strategy.

Mood stabilizers

Stabilizing mood is the chief goal of any treatment for bipolar disorder. By preventing manic and depressive episodes, these medications smooth out the highs and lows of this illness.

Lithium. Lithium is one of the oldest drugs used in psychiatry. Since the 1960s, it has proved very effective in preventing the mood swings of bipolar illness.

Common side effects of lithium include thirst, nausea, and tremors. While this medication can alter laboratory measures of kidney, heart, or thyroid function, studies of people who have taken lithium for many years are reassuring. Significant damage to the kidneys is quite rare, and changes to the heart noted on electrocardiograms are almost always benign. Long-term lithium use can cause thyroid problems in up to half the people who use it, but these problems can be treated.

There is a narrow dose range in which lithium is effective. Since doses that are too high can rapidly become toxic, doctors use periodic blood tests to monitor lithium levels in people taking this drug. Dehydration and diuretics (which are taken for high blood pressure) can increase the concentration of lithium in the blood, making the risk of toxicity greater. Early symptoms of toxicity include diarrhea, vomiting, drowsiness, weakness, and loss of coordination. Without treatment, toxicity can lead to confusion, agitation, unstable blood pressure, stupor, or coma. But these problems are quite rare if you know the risk and your doctor monitors your blood levels regularly.

Because lithium takes days or weeks to become effective in someone who is going through a manic phase, doctors often prescribe additional medications to help in the meantime.

While lithium has some drawbacks, a survey conducted by two large health plans indicates that it's better at preventing suicide than valproate, a newer drug that is increasingly replacing it in the treatment of bipolar disorder (see "Anticonvulsants," page 26). According to research appearing in the *Journal of the American Medical Association* in 2003, patients taking valproate had a 70% greater risk of a serious suicide attempt and nearly three times the risk of death by suicide. The difference

amounted to one completed suicide per 1,000 patients annually. Valproate is at least as effective as lithium for mania, but lithium provides better protection against depression, the state in which bipolar patients are most likely to commit suicide. Other research shows that when patients stop taking lithium, the suicide rate rises for several months, although the effect can be minimized by lowering the dose gradually.

Anticonvulsants. Anticonvulsant drugs are named for their ability to treat seizure disorders, but doctors have recognized their value in treating mania and stabilizing moods.

One such drug, valproate, is so effective that some doctors turn to it first when treating bipolar disorder. While it isn't more effective than lithium, some doctors and patients find that its side effects seem easier to tolerate, and the dose is easier to adjust. For most people, blood tests are needed less frequently, and it isn't as toxic as lithium in overdose. It also may be better for some types of bipolar disorder—for example, when a person has very frequent mood cycles. However, as mentioned above, there is evidence that lithium is better than valproate at lowering the risk of suicide for people with bipolar disorder.

Common side effects include nausea, sedation, and weight gain. People who have liver disease should not take valproate without having their liver function carefully monitored.

What if my depression doesn't go away?

Until doctors have a way to test people ahead of time to see which treatment will work for each individual, finding the right approach is a matter of trial and error.

What might be a typical course of treatment if your depression doesn't respond well to the initial choice? If the first medication you try doesn't work after six to 12 weeks of treatment, your doctor may increase your dosage. If that doesn't work, he or she may suggest that you switch to another drug in the same class or a drug in a different class. Your doctor may also recommend adding psychotherapy (see page 28) if that hasn't been part of your treatment plan.

If you still don't respond to these therapies, your doctor may prescribe an additional medication, such as lithium (see page 25), to be taken with the antidepressant. The next step may be trying electroconvulsive therapy (see page 30) or light therapy (see "Seasonal affective disorder," page 11). Newer therapies, such as vagus nerve stimulation (see page 31) or repetitive transcranial magnetic stimulation (see page 31), are other options for you and your doctor to discuss.

Having to go through all of these steps may sound discouraging, but finding the treatment that works for you will be worth the effort.

Lessons from the STAR*D study

The STAR*D trial, the largest and longest study designed to evaluate depression treatments, took a close look at how people respond to "real world" treatment, where they try a series of treatments until finding one that works. The study had four treatment episodes, and patients moved on to subsequent treatments if they didn't respond well to a previous one.

The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study evaluated 2,876 people, ages 18 to 75, who had at least moderate depression. Here's the process used:

- Level 1—individuals were given the SSRI citalopram (Celexa) for 12 to 14 weeks. If a person went into remission—meaning that he or she didn't just have a reduction in symptoms but was actually free of all symptoms—he or she moved on to maintenance therapy. But if remission didn't occur or side effects were intolerable, the person moved on to Level 2.
- Level 2—participants could switch or add on to treatment. Those who wanted to switch treatments were randomly assigned to receive either sertraline (Zoloft), bupropion-SR (Wellbutrin), or venlafaxine-XR (Effexor). The people who wished to add on to treatment were given either bupropion-SR (Wellbutrin) or buspirone (BuSpar), an anti-anxiety medication that can boost the response to an antidepressant. People could also switch to, or add, cognitive behavioral therapy, but results are not yet available from this portion of the study. Once again, if a person became symptom-free, he or she maintained the treatment. All others moved on to Level 3.
- Level 3—individuals could switch or add on to their medications. Those who wanted to switch were randomly given either mirtazapine (Remeron) or the tricyclic nortriptyline (Aventyl or Pamelor) for up to 14 weeks. Those who chose to add on received either the mood stabilizer lithium or the thyroid hormone triiodothyronine (T3). Either may increase the effectiveness of antidepressants. If symptoms disappeared, maintenance treatment was undertaken; otherwise, participants moved on to Level 4.
- Level 4—all medications were stopped and participants were randomly given one of two treatments: the MAOI tranylcypromine (Parnate) or a combination of extended-release venlafaxine-XR (Effexor) and mirtazapine (Remeron).

Other anticonvulsants, including carbamazepine (Tegretol), lamotrigine (Lamictal), topiramate (Topamax), and gabapentin (Neurontin), have also proved useful in treating some people with mood disorders. (For more on these medications, see Table 2.) In addition, doctors commonly combine different mood stabilizers to treat people whose episodes are not controlled by a single drug; for example, a person might take two anticonvulsants, or an anticonvulsant along with lithium.

Antipsychotics

Antipsychotic medications play a role in treating bipolar illness in one of two ways. An antipsychotic can be helpful if distorted or psychotic thinking occurs as part of an episode of mania. And even in the absence of a thought disorder, the addition of an antipsychotic may help if you've tried mood stabilizers alone without great success.

Risperidone (Risperdal), olanzapine (Zyprexa), and quetiapine (Seroquel) are among the antipsychotics most often chosen (see Table 2). A newer medication pairs olanzapine with the antidepressant fluoxetine (see "A combination pill," page 28).

In some cases, the drug clozapine (Clozaril) is most helpful. But because it sometimes suppresses white blood cells that the body uses to fight infection, doctors offer clozapine only to people who haven't responded to other treatments.

The researchers found that people whose treatment relieved them entirely of symptoms (remission) were less likely to relapse than those who had lingering symptoms. While people who didn't respond well to one or more treatments could eventually find relief, researchers learned that as more treatments failed, the chances of remission decreased. Not unexpectedly, the more failed treatments a person encountered, the more likely he or she was to drop out of the study. Withdrawal rates were 21% after level 1, 30% after level 2, and 42% after level 3.

As for how individual medications stacked up against each other, the following is a summary of some of the findings.

Level 1

- About 33% of the participants became symptom-free on Celexa. Another 10% to 15% showed improvement but had some lingering symptoms.
- It took about six weeks for benefits to appear.

Level 2

- About 25% of the participants who switched became symptom-free.
- All three of the medications used as alternatives—sertraline (Zoloft), bupropion-SR (Wellbutrin), or venlafaxine-XR (Effexor)—performed equally well in terms of effectiveness and side effects.
- About 33% of the add-on group became symptom-free. However, these results can't be directly compared to the switch results because patients weren't randomly assigned to switch or add drugs; they chose which strategy they wanted. Also, the people who switched medication tended to be those who'd had more side effects with citalopram.
- Bupropion caused fewer difficult side effects and improved symptoms slightly more than buspirone.

Level 3

- Among participants who chose to switch drugs, approximately 12% to 20% became symptom-free.
- Mirtazapine (Remeron) and the tricyclic nortriptyline (Aventyl or Pamelor) performed equally well in reducing symptoms and causing side effects.
- In the add-on group, 20% of participants became symptom-free.
- While lithium and T3 seemed equally effective in reducing symptoms, side effects were less of a problem with T3.

Level 4

- About 7% to 10% of participants became symptom-free.
- The venlafaxine-mirtazapine combination reduced symptoms more than tranylcypromine did, and people taking tranylcypromine were more likely to stop treatment due to side effects.

This study provides an argument to keep trying different treatment options. It also demonstrates that no two people and no two forms of depression are alike.

Note that more than half of the people who participated in the study went into remission after two treatment levels. Over all, 70% of all the people who didn't withdraw from the study got relief from all their symptoms of depression.

Keep in mind that there are some things you can do to improve your chances for successful treatment, including making sure you take medication as directed and keeping up with therapy appointments (see "Sticking with treatment," page 37).

Antidepressants

Because people with bipolar disorder are as likely to experience depression as mania, doctors may also prescribe antidepressants (see Table 2). One problem with using antidepressants to treat bipolar illness is that they can trigger a manic episode or cause a more rapid cycling of episodes. However, antidepressants can be helpful, and SSRIs and bupropion have been used safely for this purpose. Doctors have found that the mood stabilizer lamotrigine works well for people with bipolar disorder who are showing signs of depression. It tends not to cause the problems that antidepressants sometimes do.

A combination pill. A bipolar medication called Symbyax, introduced in early 2004, combines two medicines in one pill: the antidepressant fluoxetine and the antipsychotic drug olanzapine. The pill is touted as offering greater convenience, since some patients would have fewer pills to take. Plus, combining an antidepressant with an antipsychotic drug may be helpful for bipolar disorder, because antidepressants alone sometimes trigger mania in susceptible people. The addition of an antipsychotic drug can reduce that risk. However, some experts point out that this particular preparation has several drawbacks. Symbyax pills combine 6 milligrams (mg) or 12 mg of olanzapine with 25 mg or 50 mg of fluoxetine. These fixed amounts limit a doctor's ability to adjust the dose of each medication freely and make it harder to find the smallest effective dose for each drug. In addition, if a patient develops certain side effects, like weight gain or drowsiness, it won't be clear which drug is causing the problem. And since olanzapine alone comes in 5-mg doses and fluoxetine in 20-mg pills, it's not easy to convert to the combination pill after individual doses are established.

Finally, and perhaps most importantly, most patients who are treated for bipolar disorder aren't given these two medications in combination. In most cases, patients receive valproate or lithium alone. Then an antidepressant is added if those medications don't produce the desired effect. Combining an antidepressant with an antipsychotic is much less common.

Anti-anxiety medications

Doctors may also prescribe anti-anxiety medications to help with the jitteriness, racing thoughts, and overall worry and distress that often accompany manic episodes. Typical choices are either an SSRI, buspirone (BuSpar), or one of the benzodiazepines, such as alprazolam (Xanax), clonazepam (Klonopin), or lorazepam (Ativan). Each of these benzodiazepines may differ slightly in how quickly it is absorbed by the body and how long its effects last. For more information on these medications, see Table 2 and talk to your doctor.

Psychotherapy for depression and bipolar disorder

Depression can bring everything in your life—work, relationships, school, and even the most minor tasks—to a grinding halt, or, at the very least, gum up the works. The aim of psychotherapy is to relieve your symptoms and to help you manage your problems better and live the healthiest, most satisfying life you can.

Some evidence suggests that by encouraging more constructive ways of thinking and acting, psychotherapy makes future bouts of depression less likely. Three schools of psychotherapy—cognitive behavioral therapy, interpersonal therapy, and psychodynamic therapy—play a primary role in combating depression.

Which type of psychotherapy works best? There's no simple answer. Just as people respond differently to different drugs, you might do better with one type of therapy than with another. Many people find that a blended approach—one that draws on elements of different schools of psychotherapy—suits them best.

Cognitive behavioral therapy

Cognitive behavioral therapy aims to correct ingrained patterns of negative thoughts and behaviors. To accomplish this, you are taught to recognize distorted, self-critical thoughts, such as "I always screw up"; "People don't like me"; "It's all my fault." During cognitive behavioral therapy, your therapist may ask you to judge the truth behind these statements, to work to transform such automatic thoughts, and to recognize events that are beyond your control.

Along with cutting down on the number of negative thoughts, cognitive behavioral therapy also fo-

cuses on breaking jobs into smaller, more manageable pieces that set you up for success. You rehearse new ways of coping with problems and practice social skills that can help wean you from actions that provide a fertile breeding ground for depression, such as isolating yourself. Your therapist may assign you tasks to reinforce your learning. For example, you might keep a log of thoughts that occur as you try out your new skills. As negative patterns become clearer, you can learn to redirect them.

Interpersonal psychotherapy

Interpersonal psychotherapy concentrates on the thornier aspects of your current relationships, both at work and at home. Weekly sessions over three or four months will help you identify and practice ways to cope with recurring conflicts. Typically, therapy centers on one of four specific problems:

- grief over a recent loss
- conflicts about roles and social expectations
- the effect of a major life change, such as divorce or a new job
- social isolation.

Psychodynamic therapy

Psychodynamic therapy focuses on how life events, desires, and past and current relationships affect your feelings and the choices you make. In this type of therapy, you and your therapist identify the compromises you've made to defend yourself against painful thoughts or emotions, sometimes without even knowing it. For example, someone with an overbearing parent may unconsciously find it difficult to risk developing intimate relationships, out of fear that all close relationships will involve a domineering partner. By becoming aware of links like this, you may find it easier to overcome such obstacles.

You and your therapist may talk about disruptions in your early life—perhaps the death of a parent, your parents' divorce, or other disappointments—to determine their effect on you. While the duration of psychodynamic therapy can be open-ended, a variation called brief dynamic therapy is limited to a specific amount of time (generally 12 to 20 weeks). It applies a similar lens to a specific emotional problem.

Not just for individuals

Group, family, or couples therapy may also be part of a plan for treating depression or bipolar disorder. Group therapy draws on support generated from people in the group and uses the dynamics among them, along with the leader's help, to explore shared problems. Family therapy and couples therapy also delve into human interactions. Like group therapy, the aim is to define destructive patterns—such as scapegoating one

10 questions to ask when choosing a therapist

Whether you get a recommendation for a therapist from your primary care doctor, a friend, or your insurance company, finding out about his or her background and training can help you feel comfortable with your choice. Here are some questions to ask before settling on a therapist:

1. What's your training (i.e., what certification or degrees do you hold)?
2. How long have you worked in this field?
3. What kinds of treatment or therapy do you think might help me?
4. What are the advantages and disadvantages of the different approaches, including medication?
5. How does the treatment work?
6. What are the chances that treatment will succeed?
7. How soon should I start feeling better?
8. How will we assess my progress?
9. What should I do if I don't feel better?
10. How much will treatment cost?

It's hard for a therapist to give precise answers to some of these questions, because no single therapist or type of treatment is best for everyone. But there are some general responses you should be looking for. The therapist should have formal training and certification. There's a tendency for mental health professionals to offer the particular type of psychotherapy that they do best. It's good if the person can describe the merits and drawbacks of different types of treatment, including ones they don't do.

The therapist should also let you know how he or she will monitor your progress. If you don't feel there's been improvement after several months, consider getting a second opinion.

family member or enabling a spouse's alcohol abuse—and replace them with healthier ones. These therapies can uncover hidden issues and establish lines of communication. Family therapy is especially useful when one person is struggling with emotions that spill over into the family.

The ingredients of good therapy

There are many different approaches to psychotherapy, but all good therapy shares some common elements. To start with, make sure that your therapist has a state license. While psychotherapy isn't always comfortable, you should feel reasonably at ease with your therapist. In the best case, the two of you will be, or will become, a good match. Of course, both of you must respect ethical and professional boundaries.

It's important that therapy provide some relief. Your therapist should not only offer reassurance and support, but also suggest a clear plan for how the therapy will proceed. You and your therapist should agree upon realistic goals for the therapy early on. While well-defined problems might be addressed relatively quickly, you may need to approach more difficult problems from many angles, which will take longer.

Since mood disorders can have a broad influence on relationships, work, school, and leisure activities, therapy should address these areas when—or if possible before—they become a problem. Therapy isn't just for uncovering painful thoughts, although that's part of the work. Good therapy also addresses how you can adjust, adapt, or function better. And it helps you understand the nature of your distress. You should feel that your therapist approaches the important issues in your life in a way that's unique to your needs, not from a one-size-fits-all perspective. Pertinent issues springing from your culture, sex, and age, as well as individual differences, should shape the direction therapy takes.

If a doctor other than your therapist prescribes antidepressants for you, the two should communicate. If they don't do so on their own, you may want to encourage collaboration by asking your therapist and doctor to speak regularly. Your therapist ought to understand the medication portion of your treatment, encourage you to take medications as prescribed, and help monitor your response.

Although it's not uncommon to feel stuck at times, don't persist for months with that feeling. Some difficult problems take a long time to unravel, but you should sense progress. If you don't, it's a sign that the match between you and either the technique or the therapist isn't right. If four to six months have gone by and you don't feel better, it's a good idea to consult another therapist.

Electroconvulsive therapy

Reality often fails to jibe with movies and books. While psychotherapy and antidepressants have garnered some positive fictional portrayals, electroconvulsive therapy (ECT) typically evokes only frightening pictures. More than 30 years after *One Flew Over the Cuckoo's Nest* won its Academy Awards, the images from the film linger in many people's minds. Yet ECT remains one of the most effective treatments for severe depression, with response rates of 80% to 90% for people with major depression. ECT may also be used to treat mania when a person fails to respond to other treatments.

Despite its effectiveness, doctors usually reserve ECT for situations in which several drugs have failed. That's partly because of its technical complexity, and partly because of its negative image.

How ECT works

The discomfort of ECT is roughly equivalent to that of a minor surgical procedure. The purpose of ECT is to induce a seizure, which acts as the therapeutic agent. Before receiving treatment, a person is given general anesthesia. Then the doctor places electrodes on the patient's scalp and administers an electric current in a brief pulse that causes a seizure. Medicine is given to prevent the muscular effects of the seizure, so there are no obvious convulsions. The seizure is evident only because it registers on an electroencephalographic monitor. The procedure takes a few minutes, after which the person is roused from the anesthesia.

On average, six to 12 treatments are given over several weeks. Contrary to what some people might expect, when there is a good response, the improvement occurs gradually over the course of treatment, rather than all at once. Generally, the response occurs faster than with medications, making ECT a good treatment for severely depressed people who may be at very high risk for suicide.

In the best-case scenario, a prospective patient is well educated about ECT. Usually, doctors and nurses explain the treatment in detail, and often patients watch videotapes of the procedure. Sometimes other people who have had ECT explain what the experience is like to further demystify it. Patients decide if they want to try ECT only after they have been fully

informed about how the procedure works and what its risks and benefits are. Most states have clear safeguards against involuntary ECT treatment.

ECT and memory

The most commonly discussed side effect of ECT is memory loss. Routinely, patients lose memories of events that occurred just before and soon after treatment. After the treatment concludes, some people will have difficulty remembering things that occurred during the course of treatment. Once all the treatments have ended, relatively few people have persistent memory problems. However, ECT may exaggerate problems in people already having memory trouble.

Other side effects are also fleeting. Some people feel a bit sedated or tired on the day of the procedure, or they might have a mild headache or nausea. However, these symptoms might come from the anesthesia rather than ECT itself. To date, no study has shown that ECT causes brain damage.

One drawback to ECT is a relapse rate of about 50% in people treated for severe depression. It may be even higher with so-called double depression (the combination of depression and dysthymia). To help avoid a relapse, a person who responds to ECT might also take an antidepressant medication or mood stabilizer. If dual treatment doesn't work, some people receive maintenance ECT on an outpatient basis about once a month. Some people with severe depression have done very well with this approach.

Newer approaches

Two newer treatments are geared toward people who haven't responded well to other, more traditional approaches. While they are somewhat similar to ECT, in that they rely on delivering impulses (electrical or magnetic) to achieve results, neither has the proven track record of ECT.

Vagus nerve stimulation

In the summer of 2005, the FDA approved a device known as a vagus nerve stimulator for use in treating adults with depression who haven't responded to four or more other therapies. Extending from the brain through the chest to the abdomen, the vagus nerve helps control your breathing and is linked to the amygdala, hypothalamus, and other parts of the brain that regulate mood and anxiety.

A vagus nerve stimulator is a surgically implanted device similar to a pacemaker that delivers a small electrical impulse to this nerve for about 30 seconds every five minutes. The surgeon implants the electric pulse generator in the chest and attaches it to a tube containing electrodes, which is wrapped around the vagus nerve where it passes through the neck. Although vagus nerve stimulation (VNS) was initially developed as a method for controlling epilepsy, researchers found that it improved mood in some people.

The FDA based its approval on research showing that VNS was safe and effective. One study cited in the FDA approval documents showed that 31% of people getting VNS responded well to the treatment in the first 12 weeks of therapy and 45% did after one year. Few other studies have been conducted on VNS, but those that are available have turned up different results. One showed no clear benefit at 10 weeks, and another showed that patients who continued with VNS improved gradually over the course of a year.

The most common side effects are cough and neck pain. Many people also find that their voice often becomes hoarse while the stimulator is delivering its impulse. Between impulses, though, the person's voice returns to normal.

VNS is a relatively untested treatment that has not yet been proved effective by randomized, controlled trials. For the most part, this treatment should be reserved for exceptional cases where many other therapies have been tried without success.

Repetitive transcranial magnetic stimulation (rTMS)

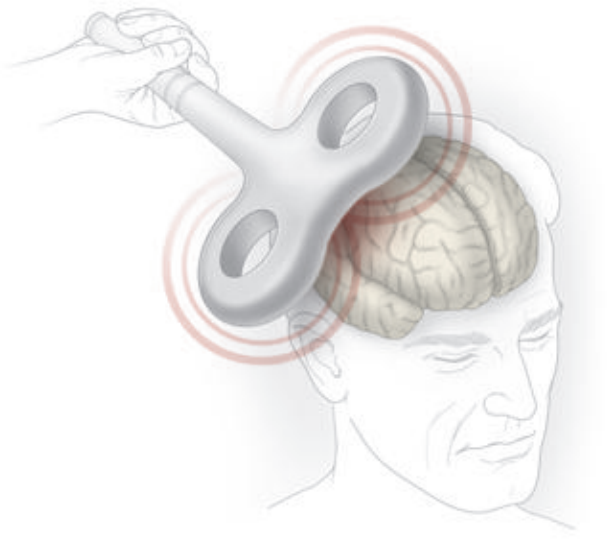
Another treatment for people whose depression has not responded to traditional therapy, called repetitive transcranial magnetic stimulation (rTMS), is also being tested in several centers. This treatment uses magnetic fields to alter brain function, possibly making nerve cell connections more efficient and changing how regions of the brain interact to influence mood (see Figure 4).

When an electric current in a wire changes, it creates a magnetic field that can spark an electric current

in another wire. In rTMS, a donut- or figure-8-shaped coil with a rapidly changing electric charge is passed over the scalp, creating a magnetic field. That magnetic field induces an electric current in the brain that is strong enough to activate nerve cells.

This technique isn't invasive and doesn't cause seizures or require anesthesia, as ECT does. A person undergoing rTMS can sit comfortably in a chair and remain awake during the whole procedure, which takes 30 to 45 minutes. Usually, it is done once a day for 10 days. Side effects—primarily headaches or scalp discomfort—are mild.

Figure 4 Transcranial stimulation



During rTMS, a coil with a rapidly changing electric charge is passed over the scalp in order to create a magnetic field, which alters brain function. While the wand used is large, the area affected can be as small as a pea.

Results from early trials were inconsistent, in part because without any guidelines, rTMS techniques varied. Factors include the part of the brain targeted, the precision of the targeting, and the intensity of the cycle.

Today, patients are receiving more intense stimuli, more stimuli in each session, and more sessions than in the past. And the news from a growing number of controlled studies is getting better. One randomized, controlled study of nearly 70 people found that symptoms improved significantly in 30% of people who received rTMS. Only 9% of people who received sham treatment improved. Another randomized study of 50 patients had similar results: 33% of the people receiving this treatment became completely symptom-free, and over all, 44% showed improvement. Just 8% of those in the sham group said their symptoms improved, and none went into remission. Researchers have also found weekly rTMS helpful to adults with bipolar disorder who are taking lithium.

Typically, benefits last for about four months, and then patients receive maintenance treatment, which works well for some people.

While rTMS looks promising, the research is still in the early stages, so the procedure can't be recommended with high confidence yet. It also is not as convenient as taking a medication, and it can be costly. Although rTMS is available as a treatment for depression in several nations, including Canada, Australia, and New Zealand, most rTMS treatments in the United States are done as part of research studies. At the time this report went to print, the FDA was considering whether to approve rTMS as a treatment for depression, but had not made a ruling yet.

Alternative treatments for depression

Many people with depression turn to complementary and alternative therapies for relief. Studies have shown that most people don't tell their doctors what alternative therapies they're using, but it is important to do so. Sometimes a complementary treatment has a problematic interaction with a medication your doctor is prescribing for you. Also, your doctor may be able to offer advice about that particular alternative therapy.

Herbs and supplements

Many people are trying supplements such as St. John's wort and SAMe. But before you try any treatment, be sure to ask: does it work, and is it safe?

Because products like St. John's wort and SAMe are classified as dietary supplements, they can be sold without a prescription and without FDA approval. As a result, their effects have not been scrutinized as rigorously as those of medications approved by the FDA. In addition, supplements can deliver widely different dosages, making their effects harder to predict.

This section takes a closer look at these two supplements, but the bottom line for both is that until research provides more data, it is best to opt for one of the many better-tested treatments for depression.

St. John's wort

St. John's wort is the most popular herbal treatment for depression. A 2002 analysis concluded that the herb seems effective for mild to moderate depression, but a three-year trial sponsored by the National Institutes of Health (NIH) found that St. John's wort was not helpful for more serious depression. Results from studies that compare it with newer medications such as SSRIs vary widely.

St. John's wort appears to raise levels of serotonin, dopamine, and norepinephrine. Side effects tend to be mild and include dry mouth, dizziness, confusion, sensitivity to sunlight, or constipation or other gastrointestinal discomforts.

It would be a mistake, however, to regard St. John's wort as entirely benign because it's an herbal remedy. St. John's wort can affect the action of quite a few drugs, including the anti-clotting drug warfarin (Coumadin), the AIDS drug indinavir (Crixivan), and birth control pills. There is a possibility, too, of bad interactions with drugs such as MAOIs and SSRIs that boost serotonin. Before taking St. John's wort or any other natural remedy, check with your doctor or a pharmacist about potentially dangerous interactions.

A number of questions about St. John's wort still remain, including how long its effects last or how high the depression recurrence rate is.

SAMe

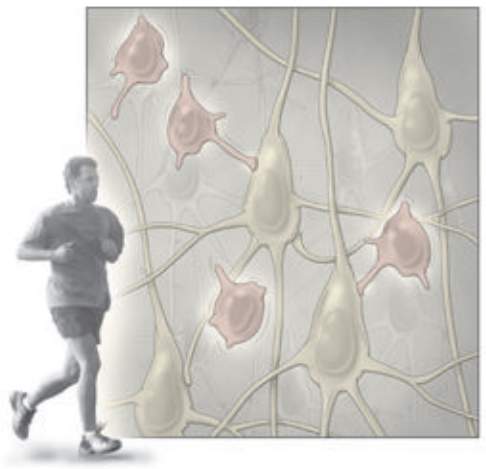
Another supplement for depression is S-adenosyl-L-methionine (SAMe), which is made from an amino acid found in the body. A few small studies have found that it's as effective as the older classes of medications for depression, such as tricyclics. There is also some evidence that it can increase the effectiveness of an SSRI in people who didn't respond fully to the SSRI alone. More study is needed, though. Before taking SAMe in addition to an SSRI, it is safest to talk to your doctor first.

Thus far, reported side effects from SAMe have been few. One important exception is that some individuals with bipolar disorder have become manic after taking SAMe. SAMe's most common side effects are headaches, insomnia, jitteriness, and loose stools.

Exercise

Can a few laps around the block actually solve your emotional problems? Probably not, but a regular exercise program might help. Many studies have found that regular exercise can improve mood in people with mild to moderate depression—and may even play a

Figure 5 Exercise and neurogenesis



It's not clear how exercise helps relieve depression, but some scientists speculate that its power lies in its ability to stimulate nerve cells. According to new research, exercise appears to spur the growth of new nerve cells and improve connections between nerve cells—and there's evidence that these changes lift mood.

supporting role in treating severe depression.

A study published in 2005, for example, found that walking fast for about 35 minutes a day five times a week or 60 minutes a day three times a week significantly improved symptoms in people with mild to moderate depression. Walking fast for only 15 minutes a day five times a week or doing stretching exercises three times a week wasn't as helpful.

Some studies suggest that exercise is as effective as medications or therapy. A study published in *Archives of Internal Medicine* assigned 156 depressed patients to an aerobic exercise program, the SSRI sertraline (Zoloft), or both. At the 16-week mark, 60% to 70% of the people in all three groups no longer had major depression. In fact, group scores on two rating scales of depression were essentially the same.

This suggests that for those who need or wish to avoid drugs, exercise might be an acceptable substitute for antidepressants. Consider, though, that the swiftest response occurred in the group taking antidepressants, and that it can be difficult to stay motivated to exercise when you're depressed. On the other hand, a follow-up to that study found that, six months later, the people who exercised regularly after completing the study—regardless of which treatment they were on originally—were less likely to relapse into depression.

How does exercise relieve depression? One theory is based on the fact that exercise enhances the action of endorphins in the body. These chemicals can increase natural immunity, reduce the perception of pain, and possibly improve mood. Another hypothesis is that exercise stimulates the neurotransmitter norepinephrine, which may directly improve mood. But as scientists have learned more about how exercise affects nerve cells, another theory has gained ground: that the power of exercise, like antidepressants, lies in its ability to generate new nerve cells.

Scientists have learned that the brain's hippocampus is smaller in some depressed people (see "Regions that affect mood," page 5). This seems to be the result of a slowdown in the generation of new nerve cells (neurogenesis) and in the ability of nerve cells to grow, branch, and make connections with one another (neuroplasticity). There is compelling evidence that antidepressants and electroconvulsive therapy improve mood, at least in part, by spurring nerve growth in the hippocampus. Exercise appears to do the same thing.

With exercise, several biological changes occur that make nerve cells more robust. The blood and energy supply to the brain improves. The genes in nerve cells signal the production of proteins called growth factors. These substances bring on neurogenesis and neuroplasty, spurring new nerve cells to develop and improving connections between nerve cells.

Besides lifting your mood, regular exercise offers many other health benefits, such as lowering blood pressure, protecting against heart disease and diabetes, reducing your risk for cancer, keeping bones strong and healthy, and helping you maintain your vitality and independence in later years.

How often or intensely you need to exercise to alleviate depression is not clear, but for general health, experts advise getting half an hour to an hour of moderate exercise on all or most days of the week.

Mindfulness meditation

In our busy world, multitasking is a way of life. We fold the laundry while keeping one eye on the kids and another on the television. We chat on our cell phones while commuting to work. We pay the bills, munch on a snack,

and listen to a spouse complain about a work project, all at the same time. But in the rush to accomplish necessary tasks, we often lose our connection with the present moment. We sprint through daily activities without being truly attentive to what we're doing and how we're feeling.

Mindfulness, which has its roots in Buddhist practices, is an antidote to this. It is the practice of focusing attention on what is happening in the present—and accepting it without judgment. And that—many physicians and therapists believe—can be a powerful therapeutic tool. Mindfulness is often learned through meditation, a systematic method of regulating your attention by focusing on your breathing, a phrase, or an image.

Over the last few decades, scientists have discovered the benefits of using mindfulness meditation techniques to help relieve stress, treat heart disease, and alleviate other conditions such as high blood pressure, chronic pain, sleep problems, and gastrointestinal difficulties. Some experts believe that it works, in part, by calming the body's stress response (see "How stress affects the body," page 9). In recent years, therapists—particularly cognitive behavioral therapists—have turned to mindfulness techniques to treat mood problems.

Studies have found that mindfulness meditation can help prevent relapse in people who have had three or more episodes of depression. For example, in one study, while 78% of depressed people given normal treatment for depression relapsed in the following year, only 36% of people who got meditation training in addition to regular treatment did. For people with fewer than three episodes of depression, meditation has not been found to be as effective.

There is evidence that meditation has distinct effects on the brain. In one study, researchers measured brain electrical activity before, immediately after, and four months after a two-month course in mindfulness meditation. They found persistent increased activity on the left side of the prefrontal cortex, which is associated with joyful and serene emotions.

Another goal of mindfulness is to facilitate personal change—much the same goal as psychotherapy. During mindfulness meditation, you attend to distracting thoughts and sensations that may occur. Ronald Siegel, a clinical psychologist and co-editor of *Mindfulness and Psychotherapy*, points out that people with low moods or anxiety often are struggling against something—resisting sadness, fear, loss, or pain. Recognizing and accepting your feelings and thoughts opens the door to examining how they interact. Once you understand that, you can change negative patterns.

Mindfulness offers other benefits, as well. One of the goals is to enhance your appreciation of simple everyday experiences. And by learning to focus on the here and now, many people who practice mindfulness find that they are less likely to get caught up in worries about the future or regrets over the past.

If mindfulness meditation appeals to you, ask your therapist about how best to use it. Going to a class or listening to a meditation tape may be a good first step.

Mindfulness exercises to try

Here are two mindfulness exercises you can try on your own.

1. A meditation exercise

Sit on a straight-backed chair or cross-legged on the floor. Focus on an aspect of your breathing, such as the sensations of air flowing into your nostrils and out of your mouth, or your belly rising and falling as you inhale and exhale.

Once you've narrowed your concentration in this way, begin to widen your focus. Become aware of sounds, sensations, and your ideas. Embrace and consider each without judgment. If your mind starts to race, return your focus to your breathing. Then expand your awareness again. Experts in mindfulness meditation note that the practice is most useful if you can commit to a regular meditation schedule.

2. Practicing awareness in daily life

A less formal approach to mindfulness can also encourage you to stay in the present and truly participate in your life. You can choose any task or moment to practice informal mindfulness. Whether you are eating, showering, walking, touching a partner, or playing with a child or grandchild, attending to these three points will help:

- Start by breathing deeply. Breathe in through your nose, allowing the air to expand downward into your lower belly. Let your abdomen expand fully. Now breathe out through your mouth. Stay aware of each inhalation and exhalation.
- Proceed with the task or pleasure at hand slowly and with full deliberation.
- Engage your senses fully so that you savor every sensation.

SPECIAL SECTION

Strategies for success

Tips for leaping common hurdles and getting good treatment

Finding good treatment for depression can feel like running in a track meet. Just when you think you are getting somewhere, you find yourself face-to-face with a series of hurdles. Dealing with the stigma of depression, sorting through insurance and financial issues, choosing the right treatment, and sticking with it despite side effects and other challenges can seem like insurmountable obstacles, but they can be overcome.

Overcoming stigma

Because we cannot see what is going on inside the brain, depression and other mental health problems historically have been shrouded in mystery and even fear. Moreover, many people still mistakenly view symptoms of depression or the desire to get treatment as signs of weak character, lack of fortitude, or an inability to pull oneself up by the bootstraps.

One of the worst results of stigma is that people suffering from depression may feel shame about their condition and be reluctant to seek treatment, leaving them stuck on a destructive course that could lead to more pain, a poorer quality of life, and, in some cases, suicide. According to the Substance Abuse and Mental Health Services Administration, stigma associated with mental illness is one of the primary reasons why people don't seek mental health treatment.

A survey conducted at Boston University Medical Center investigated attitudes toward different types of treatment, such as medication, mental health counseling, herbal remedies, and spiritual counseling. They found that stigma was lower for herbal remedies than for prescription medication or mental health counseling.

Despite the devastating effects stigma still has on many people, there are signs that stigma is on the decline. A study from Beth Israel Medical Center in New York compared results from two large surveys of the U.S. general population on people's attitudes about seeking mental health treatment. The first survey was conducted between 1990 and 1992 and the second between 2001 and 2003. The surveys showed that seeking mental health treatment became more acceptable over the decade between the surveys and that perceived stigma associated with seeking treatment declined.

Several developments may help explain this shift. First, public awareness about mental illness is growing, partly as a result of educational programs and public service campaigns. Second, research on what goes on in the brain to account for mood problems may have already helped blur the distinction between mental and physical illness (see "Can scientific evidence erode stigma?" at right).

Ongoing efforts in both public awareness and brain and genetic research will, hopefully, continue

to reduce the stigma of mental illness as people see that the mental and physical components of illness are intertwined.

Navigating the health care system

Finding your way through the health care system isn't always easy. Some health insurance companies confine your choices to a narrow panel of doctors or therapists. Dealing with the added financial burden of treatment can compound the stress you are already experiencing. And if more than one doctor is involved in your treatment, making sure your care is coordinated can be tricky.

Most private insurers, Medicare, and managed care plans provide some coverage for mental health treatments. However, there may be a limit on how many visits the plan will cover, and copayments may be higher than for other types of care.

In fact, a study from Yale Medical School indicates that parents who had private insurance and a child with a mental health problem spent significantly more money out of pocket, and experienced more financial problems as a result, compared to privately insured parents of children with other types of medical problems. Interestingly, parents with public insurance reported spending similar out-of-pocket amounts regardless of whether their children had mental health issues or other special needs.

In an effort to reduce the inequity between mental health and other health care coverage, some individual states have passed parity laws that eliminate restrictions on coverage for mental health services. A 2007 study found that in states that had enacted parity laws, parents of children with mental health problems reported lower out-of-pocket mental health care expenses and were less likely to say that their child's health needs caused financial issues. Some mental health advocacy groups would like to see parity laws implemented on a national level.

Even if you are able to get the care you need and can pay for it, making sure the different pieces of mental health treatment are coordinated properly can be another challenge. The tips in "Making the health care system work for you" on page 38 may prove helpful.

Sticking with treatment

Following a treatment plan can be a challenge. Some people are bothered by side effects (see "Managing side effects," page 38), while others may find it difficult to stay the course of treatment on their own.

Medications for depression, while a highly effective form of treatment, can be hard to get used to at first. Many, if not most, people don't take medicines exactly as

Can scientific evidence erode stigma? Epilepsy's evolution may provide a clue

In the British Museum in London, there is a Babylonian tablet with a detailed account of the different types of epileptic seizures we know about today. The tablet describes seizures as supernatural in nature, attributing each to a spirit or god, most of whom were evil.

Historians believe epilepsy has been documented for at least 3,000 years, throughout which time people have had a variety of beliefs about its causes. Some cultures thought epileptics were possessed by the devil, while others believed seizures were caused by the phases of the moon. Absent scientific knowledge, people often used gods or supernatural forces to explain what they could not see—the biological workings of the brain.

We now know that epilepsy is a neurological condition that produces brief disturbances in the normal electrical charges between nerve cells in the brain, resulting in seizures. Although there is still stigma about epilepsy, people's understanding and acceptance of it as a biologically based condition has grown considerably since Babylonian times.

Like epilepsy, depression and other mental health problems involve complex brain functions. Perhaps as researchers continue to pinpoint the physical causes of depression, such as the roles of genes, neurogenesis, neurotransmitters, and specific parts of the brain, people will have less reason to make damaging assumptions about depression, and the stigma around it will become less pronounced.

prescribed, especially if they must take more than one drug at different times of the day. An estimated 5% of patients flatly refuse to take antidepressants or mood stabilizers. Side effects make these drugs intolerable for another 10% to 15% and may encourage countless others to occasionally skip pills, tinker with dosages, or stop taking a drug without their doctors' knowledge.

A survey by the Depression and Bipolar Support Alliance found that communication between doctors and patients is not always clear, and some patients may stop taking medications because they do not receive routine follow-ups or thorough information about side effects. In other cases, patients forget information the doctor provides about side effects.

Don't hesitate to ask your doctor questions or discuss medication issues. Your doctor can help you sort out the problem and make adjustments if necessary.

Similarly, keeping up with therapy can be difficult. Change isn't easy. Even when you're willing to make life changes, the resulting ripples may affect your friends, coworkers, spouse or partner, and children, some of whom may not be as supportive as you'd like. It sometimes helps to encourage those most important to you to join you in a therapy session. Support groups may also be helpful to you and your family members (see "Strength in numbers," page 39).

Several recent studies have looked at other possible ways to boost support for patients with depression. One study, published in the *Journal of the American Medical Association*, tested the effects of outreach telephone calls to patients and cognitive behavioral therapy delivered by telephone on patients just beginning antidepressant treatment. The study found that patients who received the telephone outreach and psychotherapy had fewer depression symptoms and reported greater satisfaction with their treatment than those who simply received the antidepressants. This type of active outreach may help keep patients motivated to continue their treatment.

Making the health care system work for you

Dealing with health insurance matters and coordinating care is not easy even on your best day. But if you are depressed, sorting through financial and treatment issues can seem doubly difficult. Here are some things you can do to get the treatment you need more easily:

- Find out which mental health providers are covered by your insurance plan and ask if you have any coverage for doctors and therapists who are not in the network.
- Inquire about your health plan's mental health coverage and copayments, because out-of-pocket costs vary from insurer to insurer. If this seems overwhelming, ask a friend or family member to get the information for you.
- If a psychiatrist or doctor is prescribing your medication and another person is conducting psychotherapy, it is important that they communicate with each other and with you. Let both people know that you'd like them to talk to each other about your treatment and progress.
- Ask a supportive friend or family member to accompany you to an appointment for both moral support and to make sure you understand the recommended treatment.
- Bring a pad and paper to your appointment and take notes so you can better understand information that may be confusing.
- Discuss any important and possibly time-consuming issues at the beginning of your appointment. Appointment time is often limited, so plan to make good use of the time.
- Make follow-up appointments when necessary so your treatment continues on a steady course.

Managing side effects

It is hard to predict who will experience side effects from a given drug. That's why it is important for you to be aware of any changes in your body when you begin a new medication. Always tell your doctor about uncomfortable or worrisome side effects *immediately*.

You and your doctor can often alleviate side effects with a few

simple steps. Here are some suggestions for dealing with common side effects of antidepressants:

Dry mouth. Drink a lot of water, chew sugarless gum, and brush your teeth frequently.

Constipation. Eat whole grains, bran cereal, prunes, and hearty servings of fruits and vegetables. Drink plenty of water.

Trouble urinating. If you have difficulty starting urination, your doctor may be able to adjust your medication to relieve this problem.

Dizziness. Sudden changes in position can lead to a sharp drop in blood pressure that causes dizziness. To counter this effect, rise slowly from a chair or when getting out of bed. Also, drink plenty of fluids.

Daytime drowsiness. This problem usually occurs at the beginning of treatment and may not last long. In some cases, it may help to take medication at bedtime, but ask your doctor about this first. If you feel drowsy, don't drive or use heavy equipment.

Trouble sleeping. Sleep often improves after a few weeks, but sometimes a mild sleep aid or a switch to another medication is necessary.

Nausea. Often, nausea disappears within a few weeks. It may help to take the drug shortly after a substantial meal.

Strength in numbers

Depression can be lonely not only for the person going through it, but also for family members. Because of the stigma surrounding depression, many people feel reluctant to talk about their feelings, concerns, and frustrations. As a result, it's easy to feel like you are the only one experiencing certain problems.

A good support group can help tear down walls of isolation. There you may find camaraderie and comfort in knowing that others understand what it's like to deal with mood problems.

A support group can also offer insight and help in dealing with common concerns. Support groups are often run by people who have been dealing with depression for decades, so you can benefit from their experience regarding health insurance issues, how to handle difficult situations, and other challenges. The other group members are also likely to offer helpful suggestions as well as encouragement. Talking to others in your situation can infuse you with the energy you need to stick with your treatment or to encourage a family member to keep at it.

To find a support group near you, contact the National Alliance on Mental Illness at www.nami.org. The organization's Web site describes the different types of support groups available and can help you locate one in your area.

Agitation. You might feel uncomfortably nervous or restless after you start taking a drug. Jittery feelings may pass within a few weeks. But in relatively rare cases, agitation will persist; sometimes it's an early symptom of worsening depression or mania.

Headache. Headaches may come and go. Some persist, but they usually disappear within a few weeks.

Sexual difficulties. Sometimes sexual problems are transient or not related to the drug. Talk with your doctor about sexual problems that don't pass soon. Also, see "Sexuality and SSRIs" on page 23.

If side effects continue to bother you, your doctor may change your dosage, shift the time of day that you take the medication, or split the dosage into smaller amounts to be taken over the course of the day. Or he or she may recommend combining the drug with another one, switching to a different drug, or replacing drugs with therapy or other forms of treatment. It is important that you follow your doctor's advice and don't stop taking medication abruptly without talking to your doctor first.

The problem of recurrence

When depression isn't treated, there's a high likelihood that it will recur. Roughly half of those who have a single untreated episode of major depression will go on to have another. The second untreated episode boosts the odds of a third. Once that occurs, the chances of having a fourth episode are 90%. Over a lifetime, people with untreated major depression will have an average of five to seven episodes, and episodes often accelerate, becoming more frequent and more severe.

Bipolar disorder, dysthymia, and all other mood disorders are also more likely to persist or recur if they go untreated. As with depression, episodes occur more frequently and become more intense over time. This suggests that it's best to treat major depression, bipolar disorder, and dysthymia as early as possible.

Aggressive treatment pays off

Recurrences also occur more frequently if treatment has not wholly eradicated depressive symptoms. Therefore, treatment should aim for maximum relief.

It's best to gradually increase the dose of an antidepressant until no further improvement is seen. Preliminary research also supports continuing with the full, therapeutic dose even after you start to feel better, rather than risk taking a lower dose that may be only partially effective. Yet inadequate dosages are a common problem. Primary care doctors who are less experienced with psychopharmacology are often reluctant to increase doses, and people who are uneasy about taking medication may be reluctant to try a higher dose.

Here are some other strategies worth considering in the search for a lasting, full recovery:

- switching to a different antidepressant if the first one is not adequately effective
- combining two antidepressants that have different mechanisms of action
- adding a second drug (not primarily an antidepressant) that may augment the effect of the antidepressant you're taking
- combining medications and therapy.

Keeping up with medication

To prevent a relapse, it's important to continue taking your medication even after you feel better. A study in the *Journal of the American Medical Association* divided into two groups 150 people with dysthymia or double depression who had responded to treatment with sertraline (Zoloft). Some of these people continued to take the drug, while the rest took a placebo. After 18 months, only 6% of the group taking sertraline had relapsed, compared with 23% of the placebo group.

Most psychiatrists will recommend that you stay on your medication for about a year after a first episode of depression. If you have had several episodes, your doctor will probably recommend maintenance treatment indefinitely.

Is it a relapse or not?

When you stop taking an antidepressant, you may experience uncomfortable symptoms as your body readjusts. These might include stomach upset, loss of appetite, or diarrhea; flulike symptoms and a variety of other symptoms such as tingling, restlessness, trouble sleeping, vivid dreams, fatigue, dizziness, or lightheadedness.

Sometimes people also experience mood changes, such as irritability, sadness, anxiety, or agitation. It can be difficult to know whether this is a result of stopping the medication or if the original depression is returning. The best way to tell is to wait a short time. Symptoms linked to coming off an antidepressant almost always disappear within several weeks. If symptoms of depression continue, however, see your doctor about restarting the antidepressant.

Tapering off your medicine slowly can help you avoid this problem. The medications most likely to cause these symptoms are the ones that leave the body rapidly—so your doctor may switch you to one that stays in your system longer and then gradually ease you off that one.

Getting help

Asking for help may seem like the hardest task in the world, especially if you feel exhausted and hopeless. Yet that's just what you need to do if you have symptoms of depression or mania. Even if your symptoms are vague, you may still benefit from a doctor's opinion and evaluation. If you feel lost or stuck, or are concerned about a feeling, thought, behavior, or situation, seek help.

The first step is often the hardest. Talk with your doctor about your problems, or get a referral to a mental health professional from your doctor, a friend, or one of the organizations listed in this report (see "Resources," page 47). If you are in a crisis or feel suicidal, immediately call 800-273-TALK (8255) for advice or go to your local emergency room.

Together, you and your doctor or therapist can decide on a treatment plan to alleviate your distress. In addition, the following practical suggestions may help you navigate safely through this difficult time:

- Ask a friend or family member to accompany you to your first appointment to help describe your problem, assist you in getting treatment, or simply offer support.
- Take medications as directed. Don't skip pills or change doses without consulting your doctor. Also, report any side effects right away, and if necessary, talk to your doctor about adjusting your treatment plan.
- Set realistic goals for yourself. Try not to take on more than you can handle.
- Join in activities, and try not to isolate yourself from others. Depending on your personal preferences, attending religious services, having a meal with an understanding friend, or going to a movie, ball game, or concert may help lift your mood.
- Try to exercise regularly or take a daily walk.
- Hold off on making big decisions—about moving, changing jobs, getting married, or seeking a divorce—until your depression has eased or is under control.
- If you decide to try a "natural" remedy, such as St. John's wort, ask your doctor or pharmacist whether it might interact with any other medication you're taking.
- Friends and family often want to help. Let them.

How to cope when a loved one is depressed, suicidal, or manic

Like a pebble thrown into a pond, depression, dysthymia, and bipolar disorder create ripples that spread far from their immediate point of impact. Those closest to people who have these illnesses often suffer alongside them. It's upsetting and often frustrating to deal with the inevitable fallout. But you can do a lot to help a loved one and yourself handle this difficult period.

Encourage him or her to get treatment and stick with it. Remind the person about taking medication or keeping therapy appointments. Don't ignore comments about suicide. If you believe your loved one is suicidal, call his or her doctor or therapist. If neither is available, call a local crisis center or emergency room.

Care for yourself. Being a caretaker is a difficult job. You may want to seek individual therapy or join a support group. Numerous mental health organizations sponsor such groups and can also provide you with information on the illness and the latest treatments.

Offer emotional support. Your patience and love can make a huge difference. Ask questions and listen carefully to the answers. Try not to brush off or judge the other person's feelings, but do offer hope. Suggest activities that you can do together, and keep in mind that it takes time to get better. Remind yourself that a disease is causing your loved one to act differently or perhaps be difficult. Do not blame him or her, just like you wouldn't if it were chronic physical pain that caused the person to change in certain ways.

Try to prevent reckless acts during manic episodes. It's all too common for a person to make poor decisions when manic, so it's a good idea to try to prevent this problem by limiting access to cars, credit cards, and bank accounts. Watch for signs that a manic episode is emerging. Disruption of sleep patterns can trigger an episode, so support your loved one in keeping a regular sleep schedule. Consistent patterns for other activities such as eating, exercising, and socializing may also help.

Depression, sex, and age

Depression can strike anybody at any age. However, sex and age can also help determine how someone expresses and copes with symptoms. Treatments vary with age, as well.

Differences between the sexes

All over the world, depression is much more common in women than in men. In the United States, the ratio is two to one, and depression is the main cause of disability in women. One out of eight American women will have an episode of major depression at some time in her life. Women also have higher rates of seasonal affective disorder, depressive symptoms in bipolar disorder, and dysthymia.

Why are women so disproportionately affected? Many theories have been advanced to explain this difference. Some experts believe that depression is underreported in men, perhaps because men may be less likely to talk about feelings and seek help for mood disorders. There may also be other, more complex reasons for women's greater vulnerability to depression. Stress, genes, and hormones appear to play a role.

Stress

Studies have found that women are more likely to report that they are stressed, more likely to become depressed in response to a stressful event, and more likely to be subjected to certain kinds of severe stress—particularly child sexual abuse, adult sexual assaults, and domestic violence.

Everyday experiences as well as traumatic ones may provoke stress, leading to depression in women. Typically women are raised to care for others and tend to work longer hours doing housework, raising children, and assisting older relatives. Another kind of stress is poverty. Women are on average poorer than men—especially single mothers with young children, who have a particularly high rate of depression.

On the other hand, in this culture, male self-esteem often depends on success at work and physical skill or power. If a man's capacity in any of those areas is diminished—for example, if he loses a job—it may help trigger depression.

Genes

Researchers have identified certain genetic mutations that are linked to severe depression—some of which are found only in women. These biological differences could account for some of the difference in the rates of depression between men and women.

Hormones

Hormonal changes that accompany menstruation can bring on mood changes. Women with premenstrual syndrome (PMS) may feel sad, anxious, irritable, and angry. They may also suffer from crying spells, trouble concentrating, and a feeling of being overwhelmed or out of control. Sometimes PMS is mistaken for depression and vice versa. In either case, it's important to talk to your doctor about mood fluctuations and treatment.

Some women report feeling depressed during perimenopause, a time of transition that occurs in the months or years before menstruation stops. As a result, researchers are investigating whether hormones play a role in depression around the time of menopause.

Scientists are also studying whether changes in testosterone levels may promote mild to moderate depression in men. Later-life changes in sex hormones are not as clear-cut in men as they are in women, but testosterone levels do decrease gradually as men age.

Testosterone supplements are available and are sometimes paired with an antidepressant, psychotherapy, or both to treat men with depression. But testosterone supplements do have significant side effects, including an increased risk of prostate cancer, benign prostate enlargement, heart disease, and liver damage.

Some men develop gynecomastia (breast swelling), headaches, rashes, acne, baldness, or emotional instability. For these reasons, men should begin testosterone therapy only after careful consideration and an in-depth discussion with a doctor.

Are the statistics skewed?

While it's likely that lifestyle and biological issues account for some differences in depression among the sexes, many experts question the reliability of the statistics. They contend that if studies accounted for differences in how men and women express and cope with their emotions, the apparent gap in depression rates would diminish or possibly disappear.

Typically, men are more likely to shy away from talking about their feelings, and doctors may bring up emotional topics less often with men. Depression in men may be obscured behind a variety of physical complaints, such as low energy, aches and pains, a loss of appetite, or trouble sleeping. Or the problem may come out as substance abuse or anger. Even if other symptoms of depression are present, some men don't feel sad. All of this makes depression difficult to diagnose in men.

In addition, many men don't feel comfortable acknowledging the need for help, making them less likely to seek assistance than women are. And if a loved one raises the subject, they may not be willing to admit the possibility that they are depressed. Yet when such men receive treatment for depression, their symptoms often disappear, and in retrospect they may concede that they were, in fact, depressed.

Depression is so common that it should be considered as much a problem for men as it is for women. In fact, men are more at risk for the worst outcome of depression—suicide.

Children and teenagers

While some people idealize childhood, in reality, children may feel shaken by developmental changes and events over which they have little or no control. Stud-

Information for expectant and new mothers

During pregnancy, women should be cautious about taking any type of medication. But the risks of not taking a needed medication should be weighed against the possible risks (to both mother and baby) of taking the drug. In some cases, untreated depression carries more risk than the drugs used to treat depression.

Mothers-to-be who are depressed may have a hard time caring for themselves. They are more likely to miss doctors' appointments and to drink alcohol or use drugs. Their children may end up having lower birth weights and associated health problems. And of course, depression can sometimes be fatal through suicide. When depression is severe, pregnant women may find that the benefits of treatment far outweigh the risks.

The understanding of how antidepressant medications affect the babies of mothers who take these drugs during pregnancy is still evolving. Until recently, most studies had found that antidepressants don't increase the risk of miscarriage or birth defects in the developing fetus. But in 2005, based on preliminary analysis of two epidemiological studies, the FDA warned that paroxetine (Paxil) may increase the risk of birth defects, particularly heart defects. The FDA is still studying the issue, though.

In 2006, a study found that fetuses whose mothers took SSRIs after the 20th week of pregnancy were more likely to develop a rare but serious lung condition known as persistent pulmonary hypertension. There are also reports that the babies of mothers who used SSRIs late in pregnancy may experience problems like irritability, difficulty feeding, and, very rarely, trouble breathing. Mood stabilizers, including lithium (Eskalith, Lithonate) and carbamazepine (Tegretol), also have been linked to a higher risk of birth defects.

In general, the risks to the babies are small. In every case, a woman should discuss with her doctor the advantages and disadvantages of taking (or stopping) any depression or mood-stabilizing drugs during pregnancy.

There are many good options, with or without drugs. Women with milder depression who become pregnant may want to gradually reduce the dose of medication and rely on psychotherapy or try phototherapy, which uses bright artificial light to help lift depression (see "Seasonal affective disorder: When winter brings the blues," page 11). But these may not be good choices for women with moderate or severe depression, for whom the burdens of the illness and the dangers to the fetus are too great.

Studies have found that antidepressants don't pose a serious risk to nursing infants. As a safeguard, though, nursing women might opt for drugs that don't accumulate in breast milk, such as sertraline (Zoloft).

ies show that two out of every 100 children and eight in 100 adolescents have major depression.

While a full-blown depression most often starts in adulthood, dysthymia may begin during childhood or the teenage years. Although an adult has to have depressive symptoms for at least two years before he or she is diagnosed with dysthymia, in children and teens a diagnosis is made after one year. When dysthymia appears before age 21, major depressive episodes are more likely to emerge later in life.

In teens, as in adults, bipolar disorder and depression are clearly connected. As many as 30% of teenagers who experience an episode of major depression develop bipolar disorder in their late teens or early 20s. While rare in early childhood, this disorder occasionally appears in adolescence, especially in cases where a family history of depression exists.

Recognizing teenage depression and mania

If you are a parent of a teenager, a list of depressive symptoms may make the hairs on the back of your neck rise. Storminess, exhaustion, apathy, irritability, and rapid-fire changes in appetite and sleep habits are common in adolescents.

You might find yourself wondering whether a sudden loss of interest in the clarinet signals depression or merely that your teen now thinks that playing in the school band is uncool. Staying up late and sleeping until noon or throwing over one interest in favor of others probably doesn't signal depression. But constant exhaustion and an unexplained withdrawal from friends and activities a child once enjoyed are reason for concern.

Because depression in children and teens often coexists with behavioral problems, anxiety, or substance abuse, experts consider a wide range of potential indicators, such as these:

- poor performance in school or frequent absences
- efforts or threats to run away from home
- bursts of unexplained irritability, shouting, or crying
- markedly increasing hostility or anger
- abuse of alcohol, drugs, or other dangerous substances
- social isolation or loss of interest in friends
- hypersensitivity to rejection or failure
- reckless behavior.

While the symptoms of depressive disorders in children, teenagers, and adults are generally similar (see "What is depression?" on page 2), there are a few things worth noting. Depressed children don't act sluggish as often as depressed adults do, and depressed children and teens are more likely to appear irritable than sad. Also, young children often express feelings of depression as vague physical ailments, such as persistent stomachaches, headaches, and tiredness.

Discuss anything that concerns you with your child. If you're still concerned, speaking with your child's pediatrician or guidance counselor may help.

If a family history of bipolar disorder exists, be especially vigilant about watching for manic symptoms. The signs of manic behavior are similar in adults and children (see "What is bipolar disorder?" on page 3). However, teens who are in a manic episode may also

Postpartum depression

More than half of women who've recently had a baby endure the weepy, anxious, emotional time known as the "baby blues." Yet, unlike the baby blues, which usually last no more than a few weeks, postpartum depression continues and deepens.

About 10% to 15% of new mothers experience depression within three to six months after childbirth. Coming at a time that culture dictates should be happy and fulfilling, this type of depression can carry a stigma that makes some women reluctant to admit to it.

Sleep deprivation, the dramatic changes and stresses that accompany motherhood, and shifts in hormones all seem to have a hand in postpartum depression. Physical discomfort, a colicky or sick baby, financial hardship, and scant social support may also be factors.

Postpartum depression has many features in common with major depression. A new mother can become sad or hopeless. She may be anxious and especially worried about the baby's well-being. She may not be able to function and may be overwhelmed by caring for her baby. She may experience changes in appetite that lead to weight loss or gain. She may also lose interest in everything, including the baby, and feel guilty or worthless as a result. If you suffer postpartum depression, treatment can make a big difference for both you and your baby.

- talk very fast
- be very easily distracted
- get much less sleep than usual, but seem to have the same amount of energy or even more
- have extreme mood changes, for example, shifting between irritability, anger, extreme silliness, or high spirits
- indulge in, think about, or describe hypersexual behavior.

If you notice these symptoms, your child's pediatrician can help you decide whether to seek professional help.

Treating depression in teens and children

Just like depressed adults, depressed children and teens need to get help, and the two main methods of treatment are psychotherapy and medication. But there are distinct differences between treating adults and children in most medical fields, and psychiatry is no exception.

Although many studies have shown antidepressant medications to be effective in teens and children, these drugs can also have some dangerous, unintended side effects in a small number of teens. A review by the FDA found that the average risk of suicidal thoughts in depressed teens and children who are taking an antidepressant was 4%, twice the placebo risk of 2%. The FDA responded to these concerns in 2004 by requiring that drug manufacturers place a "black box" warning about these risks on the package inserts that come with antidepressants. In the wake of this, doctors are prescribing SSRIs less frequently to children and young adults, but the suicide rate increased among youths in 2004. Some experts contend that the two trends are linked and that the benefits of antidepressants outweigh the risks (see also "Can antidepressants trigger suicide?" on page 15).

What does this mean for your depressed child or teen? Of course, treatment decisions should be made (with your input) by a qualified psychiatrist, preferably one who is trained to care for children. Many experts believe that antidepressants play an important role in treating depression in children and teens, but they must be used with caution. They shouldn't be viewed as harmless pills to be prescribed flippantly; nor should they be deemed a dangerous therapy that should be reserved as a last resort.

If your child needs an antidepressant, the best way to prevent a dangerous outcome is to pay close attention to how he or she is thinking and feeling. Monitor him or her for suicidal thoughts or tendencies, especially in the first few months of treatment, when the risk is thought to be the greatest.

Dealing with suicidal remarks

Children and teenagers are by nature more impulsive than adults, their emotions less tempered by experience. Research suggests that regions of the brain that govern judgment do not develop completely until later in life. All too often in this age group, suicidal thoughts translate into action. Never ignore or brush off comments about suicide or even such sweeping, dramatic statements as "I wish I was dead" or "I wish I'd never been born." Discuss them with your child.

Perhaps these sentiments reflect nothing more than an angry outburst or hyperbole in the middle of an argument. But you can say, "Are you telling me about your frustration, or do you really feel like ending your life?" If the answers raise any concerns, if your child always refuses to engage in the conversation, or if he or she seems to exhibit signs of depression or mania, call his or her pediatrician for advice.

Older adults

Depression is not a normal part of aging, although many older people and their caregivers think the two go hand in hand. As people age, they do often encounter many familiar sources of depression, including losing loved ones and facing health problems. Still, depression should be treated in people of all ages.

About 15% of adults over age 65 have significant depressive symptoms, and about 3% have major depression. And the risk of suicide increases with age: older Americans are disproportionately likely to die by suicide, and white men over age 85 have the highest suicide rates in the United States.

Studies have found links between depression and other health problems in older adults. One long-term

study found that those who suffered from chronic depression lasting at least six years had an 88% higher risk of developing cancer. Other studies suggest that older adults who are depressed are at greater risk of developing Alzheimer's or experiencing a decline in mental powers and are more likely to have diminished immune responses, which may affect their ability to fight off infections or disease.

Is it dementia or depression?

In older adults who experience an intellectual decline, it's sometimes difficult to tell whether the cause is dementia or depression. Both disorders are common in later years, and each can lead to the other.

It's not rare for a person with dementia to become depressed, and a depressed person may lose mental sharpness. The latter case is sometimes called the dementia syndrome of depression. People with this form of depression are often forgetful, move slowly, and have low motivation as well as mental slowing. They may or may not appear depressed. This syndrome responds well to treatments for depression. As mood improves, the person's energy, ability to concentrate, and intellectual functioning usually return to their previous levels.

Although depression and dementia share certain traits, there are some differences that help distinguish one from the other:

- Decline in mental functioning tends to be more rapid with depression than with Alzheimer's or another type of dementia.
- Unlike Alzheimer's patients, people who are depressed are usually not disoriented.
- People with depression have difficulty concentrating, whereas those affected by Alzheimer's have problems with short-term memory.
- Writing, speaking, and motor skills aren't usually impaired in depression.
- Depressed people are more likely to notice and comment on their memory problems, while Alzheimer's patients may seem indifferent to such changes.

Because there's no test that can reveal whether someone has depression or dementia, if you and your doctor aren't certain, it's worth trying a depression treatment. If depression is at the root, treatment can produce dramatic improvement.

Treating depression in the elderly

Although roadblocks to treatment exist for most individuals with depression, an older adult's road to recovery can seem especially difficult.

For example, in older people, depression is sometimes mistaken for dementia (see at left). Or it may occur in conjunction with dementia or other illnesses that mask the depressive symptoms. Health care professionals may treat the medical illness and overlook the depression.

In addition, because many in this older generation mistakenly regard depression as a weakness, older people are least likely to seek help. Those who do seek help may need to pay for it out of pocket or bridge a wide gap between the costs and what Medicare will cover.

Once an older person seeks treatment, other problems may arise. Older adults are sometimes more sensitive to side effects of antidepressants. These drugs also may not mix well with medication they take for other illnesses. For these reasons, as many as 40% of older people taking antidepressants quit or repeatedly miss doses because of side effects, memory problems, or difficulty keeping track of complicated drug regimens.

Although older patients with severe depression appear to respond to antidepressant drugs about as well as younger people, they sometimes improve more slowly and relapse sooner. However, a knowledgeable doctor can help see you through these kinds of concerns.

Glossary

acetylcholine: A neurotransmitter that helps mediate learning and recollection.

antidepressant: A drug used to combat depression.

antipsychotic: A drug used to treat psychotic symptoms, such as disordered thoughts, delusions, or hallucinations.

corticotropin-releasing hormone (CRH): A hormone secreted by the hypothalamus that helps rouse the body when a physical or emotional threat appears.

dopamine: A neurotransmitter that affects movement and influences thought processes, possibly affecting motivation and reward.

gamma-aminobutyric acid (GABA): A neurotransmitter that may help quell anxiety.

glutamate: A neurotransmitter that may play a role in mood disorders and schizophrenia.

hippocampus: A portion of the brain that plays a central role in processing long-term memories and recollection.

hypomania: A mild mania.

hypothalamic-pituitary-adrenal (HPA) axis: A system that governs a multitude of hormonal activities in the body, including the body's responses to stress.

hypothalamus: A network of nerves above the brainstem that regulates the body's self-maintenance functions (such as blood pressure, temperature, and fluids). It secretes hormones that influence the production of other hormones.

monoamine oxidase inhibitors (MAOIs): Antidepressant medications that act by preventing the breakdown of the monoamines serotonin and norepinephrine.

neuron: A nerve cell.

neurotransmitters: Chemicals such as serotonin or norepinephrine that convey messages across the gap (synapse) between adjoining neurons.

norepinephrine: Sometimes called noradrenaline, this neurotransmitter plays a role in the regulation of mood, anxiety, and drive.

selective serotonin reuptake inhibitors (SSRIs): Antidepressants that block the reuptake of serotonin into the neurons that released it, leaving more serotonin available to nerve cell receptors.

serotonin: A neurotransmitter that helps regulate sleep and appetite, mediate moods, and inhibit pain.

tricyclic antidepressants (TCAs): A class of drugs that is thought to work by increasing the availability of norepinephrine and serotonin to nerve cell receptors.

Resources

Organizations

American Foundation for Suicide Prevention
120 Wall St., 22nd Floor
New York, NY 10005
888-333-2377 (toll-free)
www.afsp.org

This nonprofit organization offers information on suicide and its prevention as well as support for survivors.

Depression and Bipolar Support Alliance (formerly the National Depressive and Manic Depressive Association)
730 N. Franklin St., Suite 501
Chicago, IL 60610
800-826-3632 (toll-free)
www.dbsalliance.org

This nonprofit organization provides information, advocacy, and support for people with depression and bipolar disorder, as well as their family members. The Web site has detailed information on suicide prevention strategies.

Mental Health America
2000 N. Beauregard St., 6th Floor
Alexandria, VA 22311
800-969-6642 (toll-free)
www.nmha.org

This nonprofit organization offers information on a variety of mental health topics, including depression. The Web site has information on making the most of treatment, getting help paying for medications, and finding support groups.

National Alliance on Mental Illness
Colonial Place Three
2107 Wilson Blvd., Suite 300
Arlington, VA 22201
800-950-6264 (toll-free)
www.nami.org

This advocacy group offers information and support groups for people coping with a variety of mental illnesses and for families of people with such illnesses.

National Institute of Mental Health
6001 Executive Blvd., Room 8184,
MSC 9663
Bethesda, MD 20892
866-615-6464 (toll-free)
www.nimh.nih.gov

This government agency sponsors research on mental illness. It offers a wide array of free publications. The Web site has educational segments on anxiety and depression, news on studies, and information about clinical trials.

Suicide hotline
800-273-TALK (8255)

Notes

Harvard Health Publications

Trusted advice for a healthier life

Other publications from Harvard Medical School

Periodicals *Monthly Newsletters and Quarterlies including:*

- *Harvard Health Letter*
- *Harvard Women's Health Watch*
- *Harvard Men's Health Watch*
- *Harvard Heart Letter*
- *Harvard Mental Health Letter*
- *Perspectives on Prostate Disease*

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- Alzheimer's Disease
- Anxiety and Phobias
- Arthritis
- Back Pain
- Caregivers
- Cholesterol
- Depression
- Diabetes
- Diabetes and Food
- Energy/Fatigue
- Erectile Dysfunction
- Exercise
- Eye Disease
- Foot Care
- Grief and Loss
- Headache
- Hearing Loss
- Heart Disease
- Heart Disease and Diet
- High Blood Pressure
- Incontinence
- Knees and Hips
- Living Independently
- Living Longer
- Memory
- Neck and Shoulder Pain
- Nutrition
- Osteoporosis
- Prostate Disease
- Sensitive Gut
- Sexuality
- Skin Care
- Sleep
- Strength Training
- Stress Management
- Stroke
- Thyroid Disease
- Viruses
- Vitamins & Minerals
- Weight Loss

To place your order on the Internet or by phone: www.health.harvard.edu • 877-649-9457 (toll-free)

ISBN 978-1-933812-50-2
SR21000

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