



Depression and Anxiety

Elation, sadness, anxiety, grief—we all feel these emotions at various times in our lives. Sadness may be caused by a setback or a loss, while anxiety may be triggered by a threat or a challenge. It is perfectly natural for our emotions to wax and wane with the ups and downs of our lives. The difficulty comes when these feelings do not go away—or when they seemingly occur out of the blue without explanation—and begin to interfere with our daily functioning. When that's the case, a mood disorder, such as depression or bipolar disorder, or an anxiety disorder may be present.

Depression and other mental health disorders are responsible for more than 63 million visits to doctors, clinics and hospital outpatient departments annually in the United States. Fortunately, effective treatments are available. Proper diagnosis and treatment of mood disorders lead to a remission of symptoms in about 80 percent of cases. This White Paper provides detailed information on the causes, symptoms, diagnoses and treatments of depression, bipolar disorder and anxiety disorders.

MOOD DISORDERS

Depression and bipolar disorder are commonly referred to as mood (affective) disorders. Major hallmarks of depression include a persistent low or sad mood, decreased or absent interest in almost all activities, loss of self-confidence, and a feeling of worthlessness. Most people with bipolar disorder, formerly known as manic-depressive illness, experience alternating episodes of depression and mania. Mania, which can be thought of as the opposite of depression, is usually characterized by an elated or elevated mood, increased activity, an overblown self-image and an exaggerated sense of self-confidence.

Usually, both depression and bipolar disorder are episodic—that is, bouts of illness are separated by symptom-free periods characterized by feelings of relative well-being.

Causes of Mood Disorders

The exact causes of depression and bipolar disorder are not well understood, but some combination of genetic predisposition and psychological and medical factors appears to play a role in these disorders.

Changes in the Brain

The brain is composed of distinct regions, each made up of networks of nerve cells (neurons) that transmit messages throughout the nervous system. Individual neurons are separated by small gaps at each end called synaptic clefts.

Chemicals called neurotransmitters bridge the synaptic clefts and pass messages from one neuron to the next. Imbalances in three particular neurotransmitters—serotonin, norepinephrine and dopamine—appear to contribute to depression and bipolar disorder, although less is known about changes in the brain that occur during the manic phase of bipolar disorder.

One specific brain region thought to be involved in depression is the limbic system, which affects our emotional behavior. An area within this system, the hypothalamus, regulates the pituitary gland, which in turn regulates key hormones and may be involved in the hormonal imbalances sometimes associated with depression.

Genetic Factors

Depression is often a family affair. Scientists, for example, have identified a gene that may be linked to bipolar disorder. In addition, they have found a common genetic mutation associated with clinical depression after a traumatic event.

One study found that if an identical twin developed depression, there was a nearly 50 percent chance the other twin, who shares the same genes, would develop the illness at some point. On the other hand, if the twins were fraternal (sharing half of their genes like any siblings) and one developed depression, there was a 20 percent chance that the other would.

But genetics are not the only driving force for depression. Studies have also found that adopted children whose biological parents had a mood disorder had a three times greater incidence of depressive illness than the biological children of the same adoptive parents.

Finally, children whose parents and grandparents experienced moderate to severe depression are at much greater risk

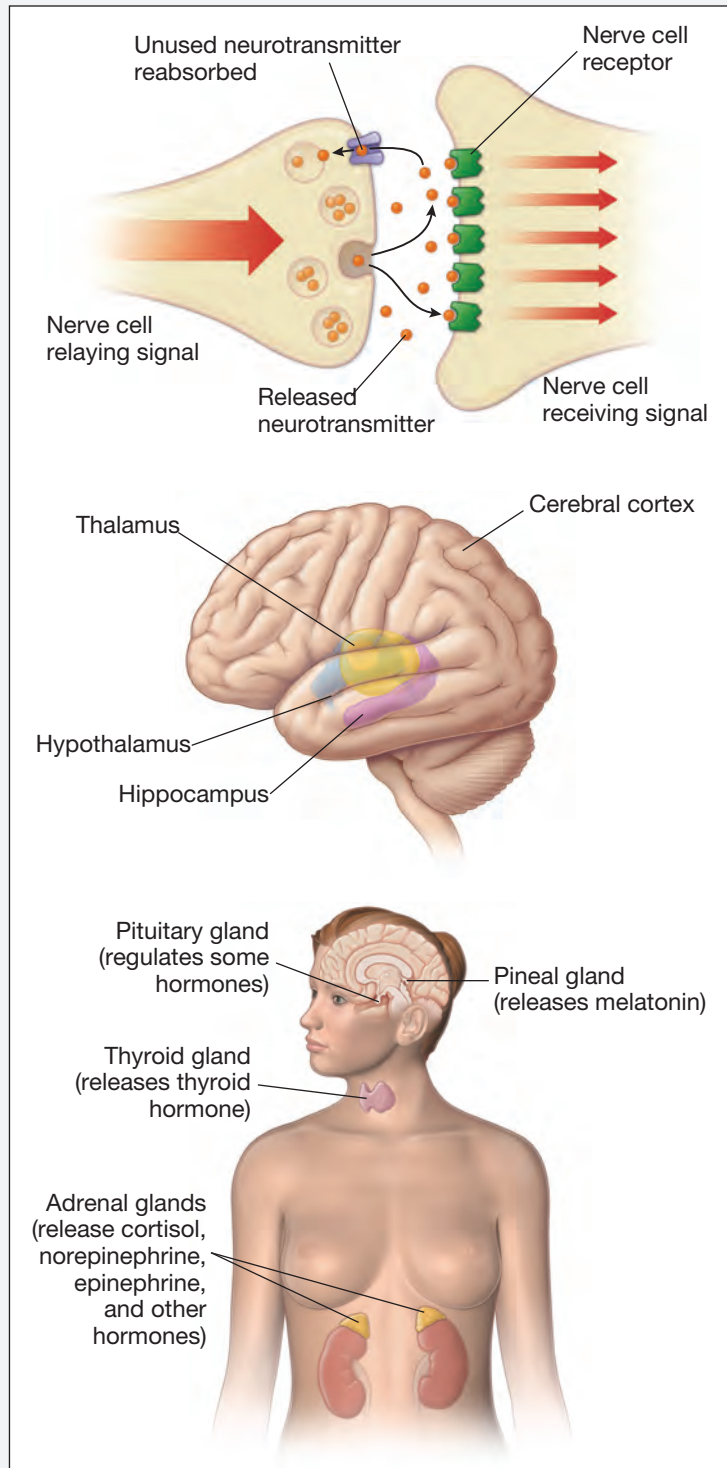
The Biology of Depression and Anxiety

Although a comprehensive understanding of the causes of depression and anxiety has not been reached, researchers have identified certain

biological changes that may predispose a person to these disorders. The following is a summary of some of the theories that are currently under exploration.

Neurotransmitters

One area of study is the role of neurotransmitters—chemical messengers that carry information between neurons (nerve cells) in the brain. Decreased availability of certain neurotransmitters (such as norepinephrine, serotonin, and dopamine) may result in depression. Anxiety is thought to result from problems with the neurotransmitter gamma-aminobutyric acid (GABA), which normally suppresses the action of neurons. The illustration at right shows how neurons normally communicate.



Structures of the brain

Much current research also focuses on particular structures in the brain that may be responsible for depression and anxiety. In general, it is believed that depression and anxiety may largely result from chemical imbalances affecting the brain's limbic system—a ring of structures (including the cerebral cortex, thalamus, hypothalamus, and hippocampus) that appears to be the seat of human emotions such as depression, fear, and rage.

The endocrine system

Depression also appears to be linked to the endocrine system—the network of glands that regulates body functions by releasing various hormones into the bloodstream. However, some changes in this system seem to be effects rather than causes of depression. That said, certain endocrine disorders can directly cause depression or mania. An example is Cushing's disease, a condition in which a pituitary tumor causes the adrenal glands to produce too much cortisol. And some experts believe seasonal affective disorder (SAD) may stem from disordered release of the hormone melatonin by the pineal gland during winter.

for developing a mood disorder than those whose relatives were not affected, according to a three-generation study.

Genetics also plays a role in treatment, influencing an individual's response to a particular drug. There is evidence that people may do better if prescribed the same antidepressant medication that has been effective for a depressed first-degree relative (a parent, sibling or child).

Because researchers are not sure exactly which genes are linked to depression or bipolar disorder, specific genetic tests will not be available for years to come. But as with heart disease and cancer, it is important to know if you have a family history of depression or bipolar disorder.

Although genetic factors may make a person more susceptible to mood disorders, a trigger—such as a serious medical condition or psychological stress—is often what causes a mood disorder to emerge at a specific time.

Drugs and Alcohol

Overconsumption of alcohol and certain “recreational” drugs can contribute to depression and make it worse, as can withdrawal from alcohol, cocaine or amphetamines. Drugs can cause other mental changes as well. For example, amphetamines, cocaine and phencyclidine (PCP) can all induce mania.

Medical Conditions

Medical disorders can make people prone to depression. For example, people who have dementia-causing brain disorders, such as Alzheimer's disease or Huntington's disease, are more susceptible to depression. In addition, stroke is known to trigger depression, affecting about 25 percent of those who have had a stroke in the left frontal area of the brain.

Hormonal disorders, such as an underactive thyroid (hypothyroidism) and Cushing's disease, also can lead to depression. Cushing's disease is an excess of the hormone cortisol in the blood. It is caused by a pituitary tumor secreting a hormone that stimulates the adrenal glands to produce too much cortisol, commonly referred to as the stress hormone.

Vitamin deficiencies, such as insufficient levels of folic acid, vitamin B₆ or vitamin B₁₂, also have been linked to depression. In one study of 700 women, those with a vitamin B₁₂ deficiency were twice as likely to be severely depressed as those without this deficiency.

Two other studies suggest that obese adults may be more likely

than normal-weight individuals to develop a mood disorder, and those with metabolic syndrome (a combination of excess weight, high cholesterol, high blood glucose levels and high blood pressure) are also at increased risk.

Medication

Prescription drugs also can cause mood disorders. Medications such as corticosteroids and drugs used to treat Parkinson's disease or attention deficit disorder can trigger mania in bipolar disorder. Other drugs, including some used to treat high blood pressure and cancer, have been known to cause depression.

Brain Trauma

Injury to the brain from trauma or tumors can cause behavioral changes, anxiety and/or mood disorders.

Symptoms and Diagnosis of Mood Disorders

Although many mood disorders are readily recognized, it can be difficult to distinguish milder forms of depression or anxiety from the emotional changes that are part of everyday life. Unlike most medical conditions, mood disorders cannot be detected by blood and other laboratory tests. Rather, a doctor must rely on a person's medical history to diagnose a mood disorder.

The American Psychiatric Association has established a classification system to help doctors make consistent diagnoses of major depression, bipolar disorder and various forms of anxiety and other related disorders. These criteria are defined in the *Diagnostic and Statistical Manual of Mental Disorders*, a reference guide used by psychiatrists, psychologists and other mental health professionals. The manual is periodically revised to keep up with the latest research. The current edition, published in 2013, is referred to as the DSM-5.

Major Depression

In any given year, some 15 million American adults—about 5 to 8 percent of the population—have at least one episode of major depression, also known as major depressive disorder, and only 60 percent of these people reportedly receive appropriate treatment. According to the DSM-5, an individual is having a major depressive

Latest Research

More Older Adults Are Drinking Too Much

New findings from an analysis of two nationwide surveys indicate that alcohol use, high-risk drinking, and alcohol use disorder are all on the rise among U.S. adults.

The analysis examined responses from two surveys, one conducted from April 2001 to June 2002, with 43,093 respondents, and the other conducted from April 2012 to June 2013, with 36,309 respondents. Comparing the results, researchers found that the percentage of people reporting they had used alcohol anytime in the previous 12 months climbed from 65.4 percent in 2001–2002 to 72.7 percent in 2012–2013. High-risk drinking—consuming four or more alcoholic drinks a day for women, or five or more a day for men, at least once a week—increased from 9.7 percent to 12.6 percent.

Alcohol use disorder—compulsive alcohol use and loss of control over alcohol intake—rose from 8.5 percent to 12.7 percent.

The increases cut across most demographics, but the largest jumps were seen among women, adults 65 and older, racial/ethnic minorities, and socioeconomically disadvantaged people. The increase in high-risk drinking and alcohol use disorder among older adults was “unprecedented,” the researchers noted. High-risk drinking in that group climbed by 65.2 percent, and alcohol use disorder rose 106.7 percent.

Alcohol abuse is a medical problem that can be treated. Talk to your doctor if you are concerned that you or a family member has a drinking problem.

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episode if he or she experiences items 1 or 2 from the list of symptoms below, along with any four others, almost daily for more than two weeks:

1. Depressed mood with predominant feelings of sadness, emptiness and hopelessness (in children, irritability can be the main feature)
2. Apathy—loss of interest and pleasure in activities formerly enjoyed
3. Sleep problems—insomnia or oversleeping nearly every day
4. Fatigue or decreased energy
5. Noticeable changes in appetite and weight (significant weight loss or gain when not dieting)
6. Inability to concentrate or think, or indecisiveness
7. Physical symptoms of restlessness or being physically slowed down
8. Feelings of guilt, worthlessness and helplessness
9. Recurrent thoughts of death or suicide, or a suicide attempt

The diagnosis is more certain when a person has a family history of depression, has had a previous episode of depression or bipolar disorder, has a general medical problem likely to trigger depression (such as a recent stroke or heart attack), or is taking a medication known to cause mood disorders.

Sometimes symptoms of depression include disorganized thinking and delusions (psychotic symptoms). In addition to these disturbances in mood and cognition (thinking), people with major depression may experience physical changes such as constipation or decreased sexual drive.

Note that anxiety is commonly seen with depression—but it is not listed as an official symptom of depression. Many people experience modest anxiety with depression that resolves as the depression resolves, but many others also have separate formal anxiety disorders, such as post-traumatic stress disorder (PTSD) or panic attacks, that may require additional treatment (see the Anxiety Disorders section, starting on page 54).

Episodes of major depression range from mild to severe. In mild episodes, symptoms barely meet the requirements for a diagnosis and the person is able to get through the day without much trouble. With moderate episodes, symptoms are more intense and functioning becomes difficult. Severe episodes are characterized by several debilitating symptoms, including worsening mood that markedly interferes with daily life. People struggling with severe depression have difficulty with almost every activity—going to



work, socializing and even getting up in the morning. In the most severe cases, depressed individuals may be unable to feed and dress themselves or maintain personal hygiene.

Major depression is believed to be twice as common in women as in men, although that statistic is now being questioned. In fact, depression symptoms may be different in men and women, as well as in older versus younger people. Men are more inclined to get angry and irritable, feel an increasing loss of control over their lives, take greater risks, become more aggressive and complain about problems at work rather than feeling sad, weepy, worthless or guilty, as women usually do.

Persistent Depressive Disorder (Dysthymia)

Persistent depressive disorder, a new name for what has long been called dysthymia, is a chronic form of depression that is milder than major depression but still considered a mood disorder. It is characterized by the presence of depressed mood for most of the day, for more days than not, over a period of at least two years, along with several other symptoms of regular depression. It may be intermittent and interspersed with periods of feeling normal, but these periods of improvement last no more than two months.

Persistent depressive disorder is believed to be twice as common in women as in men. People who have persistent depressive disorder before age 21 tend to have a higher incidence of personality disorders. Because the onset of symptoms is insidious, persistent depressive disorder often goes unnoticed. And because of its chronic nature, the person may come to believe that he or she has always been that way. In addition to depressed mood, the specific symptoms include two or more of the following:

- Poor appetite or overeating
- Insomnia or hypersomnia (excessive sleeping)
- Low energy or fatigue
- Low self-esteem
- Poor concentration or difficulty making decisions
- Feelings of hopelessness

It is far better to treat persistent depressive disorder than to think of it as a minor condition. Bypassing treatment places people at increased risk of subsequently developing major depression.

Biological causes

Some medical conditions, including neurological disorders (such as multiple sclerosis and stroke), hypothyroidism, fibromyalgia and

Investigating New Ways to Diagnose Depression

Research aims to shorten the time from diagnosis to the right treatment

Thirty years after fluoxetine (Prozac)—the first of a new class of targeted antidepressants—made its debut, treating depression remains a hit-or-miss affair. Many people must try one medication after another before they find one (or a combination) that works. Some patients never get relief. Doctors may even try procedures to stimulate nerve cells in the brain, such as electroconvulsive therapy or transcranial magnetic stimulation. But there's no guarantee they will help.

A big part of the problem, experts say, is that researchers still don't really understand what causes depression. Even the term itself is a catchall for a constellation of symptoms that may, in fact, represent very different conditions. Although researchers have struggled to link psychiatric symptoms to specific measurable changes in the brain or body, so far there is no objective diagnostic test for depression.

But that may be about to change. In a wave of new findings, researchers have begun to identify biological markers (aka biomarkers)—measurable medical signs—that can be linked to specific subtypes of depression and other mood disorders. There's growing hope that it won't be long before simple diagnostic tests are

available to identify specific subtypes of depression—and to help doctors prescribe the most effective treatment for each individual patient.

Brain scans reveal telltale signs

In one area of investigation, researchers are exploring measurable abnormalities in the way areas of the brain interconnect. In a report published in *Psychological Medicine* in May 2016, researchers using brain scans found a close association between a subtype of depression called melancholia and a loss of normal connections in areas of the brain related to emotions. The pattern of connectivity linked to melancholia differed slightly from the pattern associated with major depression, suggesting that a brain scan might be used to diagnose different forms of depression.

A research team from Weill Cornell Medicine in New York City has gone even further. In a study published in *Nature Medicine* in January 2017, the researchers used magnetic resonance imaging (MRI) scans to look at connections among 258 different areas of the brain in 1,188 patients. They distinguished four distinct subtypes of depression

based on how these areas were wired with one other. They were also able to match specific subtypes of depression to particular symptoms. Two subtypes were more likely to lead to fatigue, for example, while two other subtypes were linked to trouble feeling pleasure. The researchers also found that one of the subtypes was three times more likely than the others to benefit from transcranial magnetic stimulation—one of the first examples of how a diagnostic test might be used to guide treatment.

Clues in the blood

Before long, a simple and inexpensive blood test might be able to help diagnose depression and guide doctors in treatment. In a report published in *Cellular and Molecular Neurobiology* in July 2013, Chinese researchers explored the possibility of using substances that regulate gene expression, called microRNAs, for diagnosing depression. These tiny molecules, which circulate in the bloodstream, are believed to contribute to the development, differentiation, and operation of neurons. The researchers discovered that patients with bipolar disorder, schizophrenia, and other central nervous system diseases have different microRNAs

chronic fatigue syndrome, are associated with persistent depressive disorder. Investigators believe that, in these cases, developing persistent depressive disorder is not a psychological reaction to being ill but rather is a biological effect of these disorders. There are many reasons for this connection. One theory involves the recognition

than healthy people—suggesting that a test for these markers might aid in diagnosis.

Even a blood test as simple as the one used to measure cholesterol may help diagnose depression. Evidence from many studies suggests that abnormal cholesterol levels and atherosclerosis (a buildup of plaque on artery walls) are associated with major depression. That may not be surprising, since lipids such as high- and low-density lipoprotein (HDL and LDL) cholesterol, and the polyunsaturated omega-3 and omega-6 fatty acids, play a pivotal role in brain cell functioning. In a review published in the journal *Healthcare* in 2017, researchers at King's College London suggested that lipids might serve as useful biomarkers to diagnose depression and identify subtypes, and could even be helpful in finding new ways to treat the disease.

Other substances in the blood, known as inflammatory markers, may also assist in guiding treatment. Many studies show that individuals suffering from major depressive disorder have heightened inflammation, including increased levels of a variety of substances produced by the immune system, according to a review published in *Nature Immunology* in January 2016.

The most common biomarkers for depression are forms of the proteins interleukin, tumor necrosis factor, and C-reactive protein. There's even strong evidence that some of these immune system substances can alter brain circuitry in ways that may lead to depression. Preliminary research suggests that anti-inflammatory medications may help ease symptoms of depression in some patients who have high levels of inflammation.

Putting biomarkers to the test

Although a single biomarker may be enough to diagnose depression, many researchers think that future tests will combine several measures for greater accuracy. Several panels of biomarkers for depression are already being put to the test. In a study of 154 patients published in the *Journal of Clinical Psychiatry* in 2015, researchers demonstrated that a panel of nine biomarkers distinguished between depressed and nondepressed people with about 90 percent accuracy. The nine biomarkers were all associated with changes that have been observed taking place in the brain, immune system, and metabolic system during major depression.

Scientists at King's College London, meanwhile, have developed a blood test that they claim can accurately and reliably predict whether patients will respond to common antidepressants. The test measures two inflammatory biomarkers, macrophage migration inhibitory factor (MIF) and a form of interleukin (IL-18). Patients with high levels of these substances do not respond to conventional antidepressants; those with lower levels are much more likely to benefit. Although these results need to be confirmed by other studies, they point the way to a simple test that would help doctors personalize treatment for depression.

Also, researchers with the Canadian Biomarker Integration Network in Depression (CAN-BIND) are attempting to define the biological signatures of subtypes of major depressive disorder in order to provide an accurate and rapid diagnosis that can determine treatment selection. According to a report in *BMC Psychiatry* in 2016, the researchers hope to accomplish this by integrating clinical measures, novel blood tests, and neuroimaging via new statistical techniques to characterize patient response to medication. Study results were not available at press time. ■

that inflammation, which is a common feature of many physical illnesses, can also be found in the brains of many people with depression. Another way in which medical conditions may cause depression is that they may interfere with the action of neurotransmitters. It's also possible that medications (such as corticosteroids

or beta-blockers) taken for a medical illness may trigger the persistent depressive disorder.

Persistent depressive disorder can also follow severe psychological stress, such as losing a spouse or caring for a chronically ill loved one. Older people who have never had psychiatric disorders are particularly susceptible to developing persistent depressive disorder after significant life stresses.

Seasonal Affective Disorder

As the seasons change, so does the amount of sunlight each day. This in turn causes changes in people's internal biological clocks (also called circadian rhythm). This rhythm is a 24-hour cycle that affects our eating and sleeping patterns as well as biological activities such as brain wave activity, hormone production and cell regeneration. In some individuals, less daily sunlight and changes in circadian rhythm can induce depression, which usually peaks in January and February, when there is the least sunlight. Researchers believe that the lack of sunlight during these times may alter brain levels of certain mood-controlling substances. For example, the hormone melatonin may decrease.

People with seasonal affective disorder (SAD) often eat and sleep excessively, crave sugary or starchy foods and have a full remission in the spring and summer, when more daily sunlight is available.

Grief Versus Depression

Sometimes we experience huge changes in our lives. These events can cause intense emotional anguish, and grieving during such life changes is a normal and healthy—if painful—process. Grief can be the result of a major life change, such as:

- The death of a loved one (a person or pet)
- A move to a new and unfamiliar community
- An opportunity or life goal that becomes closed to us
- A loved one contracting a life-threatening illness

Occasionally, however, this anguish triggers a major depressive episode, although few people in mourning experience true clinical depression.

Even a serious illness can increase the risk of stress and, potentially, depression in a partner: A study of 518,000 couples over age 65 found that when one spouse was hospitalized for a serious illness, the other spouse had a greater risk of dying within the next year. The probable reasons were increased stress and withdrawal of social, emotional, economic and other support.



Grieving often produces a wide range of feelings. The psychological process itself is a way for the mind to adjust, over time, to the acute sorrow of a loss. Grieving also allows us to accept the finality of the loss, to experience a full range of feelings as a result of the loss, and to adjust to our changed lives. The end of grieving does not entail forgetting; rather, it usually comes with the acceptance of the loss.

A good sign that mourning is successful is a gradual shift from sad thoughts and feelings to thoughts of positive and realistic plans for the future. As this shift occurs over time and the mourner begins to enjoy life more than feeling weighed down by it, the process of grieving moves forward.

Although grief and depression may both entail feeling sad, they are different. The sadness of grief usually comes in “waves,” with varying degrees of intensity and bouts of crying, and intense feelings of sadness, guilt, anger, irritability or loneliness. An individual experiencing grief, however, can enjoy some of life’s activities. For most people, considerable progress in adapting to the loss occurs within six months.

Depression is a more persistent and unremitting sadness and is notable for a consistent inability to enjoy pleasurable life activities. Muted or “deadened” feelings are often a sign of depression. If such symptoms persist following a life change that produces grief, mourning may have been unsuccessful and the help of a physician or other health professional is warranted. Check for the following symptoms, especially over a prolonged period (six to 12 months) or if they arise months or even years after the loss:

- Physical symptoms that mimic the illness or injury of the person who died
- Overuse of alcohol, illegal drugs or prescription drugs
- Persistent depression
- Chronic sleep disturbances
- Thoughts of or attempts at suicide (see a health professional immediately)
- Inability to carry out normal daily routines

It is important to seek medical help for physical symptoms that arise during mourning and to address any medical or psychiatric conditions that existed before the death occurred.

Depression in Older Adults

Depression and aging do not necessarily go hand in hand. A survey of Californians ages 50 to 95 found that factors such as chronic illness, physical disabilities and social isolation—which often coincide with

increasing age—were stronger predictors of depression than age itself. That said, the incidence of depression is clearly higher in older adults. An estimated 6.5 million of the nation's 35 million people age 65 and older suffer from major depression. Unfortunately, the disease is often undiagnosed, misdiagnosed or left untreated in the elderly and can increase the risk of early death and repeated hospitalization. There is also reason to believe that late-life depression can be more serious than depression in younger people.

One reason depression may go undiagnosed is because of life circumstances that are common as we age, such as the loss of a spouse, family members or friends (due to death or geographic relocation); retirement, which may be accompanied by a loss of status and self-identity; financial concerns; fears of death or loss of independence; social isolation; and medical problems. Any of these factors may trigger symptoms of depression that are mistakenly attributed to life stresses and are not recognized as a true depressive illness.

Many older people who live alone do not have adequate support networks. Some don't know where to find help or are overwhelmed by the many resources providing medical care, social services and financial assistance. Older adults tend to be embarrassed or reluctant to seek professional help for emotional problems, partly because the stigma of psychiatric illness is especially strong among people in this age group, or because they remember the days when treatments were less effective. In addition, friends and family often fail to perceive signs of distress. Older depressed people are more likely to tell their primary care physician about physical complaints than about subjective feelings of depressed mood. For example, they may report loss of appetite, insomnia or lack of energy but not a loss of interest or enjoyment in daily activities. Unfortunately, doctors and patients alike often consider these symptoms a normal part of aging.

Because older people often have other medical illnesses and take more prescription drugs, it can take some medical sleuthing to accurately pin down a diagnosis of depression. Depression might be the primary disorder, a reaction to a prescription drug or the result of an underlying condition such as cancer or a stroke. It also might be a psychological reaction to a diagnosis of a serious illness or debilitating chronic pain or impairment. Finally, it could be a direct or indirect biological effect of an illness on the brain.

The possibility of dementia adds further difficulties. Symptoms of major depression can mimic those of a dementia-causing condition such as Alzheimer's disease (disorientation, distractibility



and memory loss, for example). Doctors need to evaluate an individual's mental status, medical history and current physical health status carefully to find the primary cause of the psychological symptoms.

Effects of Depression on Physical Health

Depression clearly has a harmful effect on physical health, although the biological reasons for the link between body and mind are unclear. It may be that depression affects health because people develop a fatalistic attitude and stop taking care of themselves. Whatever the reasons, it has become evident that a depressed mood after a heart attack is much more than an "understandable emotional reaction" to a stressful, life-changing event—it is profoundly dangerous, raising a person's chances of having a second, fatal heart attack. One recent study found that people with depression who suffer a heart attack are at increased risk for complications while still in the hospital.

Researchers have also studied the flip side of the equation—the question of whether someone who is depressed is at increased risk for developing coronary heart disease (CHD) down the line. Prospective studies show that people who had no CHD but were depressed when the studies began were more likely to develop or die of heart disease. A Norwegian study found that people with significant depression had a higher risk of dying from most major causes of death, even after adjusting for age, medical conditions and physical complaints. Depression also aggravates chronic illnesses such as diabetes, arthritis, back problems and asthma, leading to more disability and doctor visits.

Encouragingly, a study published in 2014 in *Psychosomatic Medicine* reported that early treatment of depression can greatly reduce the risk of heart attack and strokes. The researchers noted that the risk reduction was comparable to major cardiovascular disease prevention strategies, such as exercising.

Bipolar Disorder

Bipolar disorder strikes men and women equally and affects about 2 to 3 percent of American adults at some point in their lives. A person with bipolar disorder typically has alternating periods of major depression and mania, interrupted by periods of normal mood that usually last for many months. Most commonly, people with untreated bipolar disorder primarily have long periods of depression and short periods of elevated mood.

Manic episodes are characterized by distinct periods of abnormally and persistently elevated or irritable mood, together with excessive activity. These episodes, with their restless energy and volatile mood swings, are severe enough to cause trouble at work, home or both. Episodes of milder manic symptoms are termed hypomania. Men with bipolar disorder tend to have more manic episodes; women are more likely to experience depressive episodes. The time between cycles can vary greatly (see “Bipolar Disorder” on page 17).

Bipolar disorder can begin with an episode of either depression or mania, typically starting with depression as a teenager. When depression is the first episode, usually the person is diagnosed as having clinical depression; only later, when a manic episode occurs, does the diagnosis change to bipolar disorder.

In the DSM-5, the definition of a manic episode was shifted to specify that both an elevated mood *and* increased goal-directed activity/energy must be present. In addition, there must be at least three of the following symptoms:

- Feelings of grandiosity or inflated self-esteem
- Diminished need for sleep
- Being extremely talkative
- The sense that thoughts and ideas are racing
- Being easily distracted
- Increased productivity and/or activity at work, at school or in social situations
- Excessive involvement in high-risk activities that are likely to have serious consequences

Because manic episodes can cause impaired judgment, people must be protected from engaging in self-destructive actions, such as making unwise investments, going on large spending or gambling sprees, driving recklessly, or impulsively starting intense and unwise romantic or sexual relationships.

Certain medications and health conditions can cause significant mood swings that mimic the symptoms of bipolar disorder. These include corticosteroids, antidepressant or antianxiety drugs, medications for Parkinson’s disease such as tolcapone (Tasmar), abuse of alcohol or other drugs, an underactive or overactive thyroid gland (hypothyroidism or hyperthyroidism, respectively), a neurological or adrenal disorder, vitamin B₁₂ deficiency and other mental health conditions, such as schizophrenia. These potential causes of mood swings should be taken into account when a person is suspected of having bipolar disorder or is not responding to treatment.

Suicide

Suicide—the 10th leading cause of death in the United States—is a major complication of depression. About 7 percent of men and 1 percent of women diagnosed with depression die by suicide. Approximately two-thirds of all people who die by suicide are depressed. Ninety percent of those who die by suicide have a diagnosable psychiatric disorder.

In the United States, suicide risk is highest in older white and Native American/Alaskan males and in those who live alone, have made prior suicide attempts, refuse psychiatric evaluation, or abuse alcohol or other drugs. Although women attempt suicide three times more often than men, men are four times more likely to die by suicide. One study found that older people with a serious physical illness were six times more likely to die by suicide than those without an illness. In a United Kingdom study, interpersonal problems and bereavement, along with chronic physical illness (for example, pain, shortness of breath, and functional limitation), were commonly associated with suicide in older people.

The risk of suicide is particularly high in people with untreated bipolar disorder. About 25 to 50 percent of those with the condition attempt suicide at least once. Moreover, suicide is a major concern among adolescents and young adults—it is the third leading cause of death among people ages 15 to 24.

Up to two-thirds of people who die by suicide visited their medical doctor in the prior month. This statistic suggests that they were aware that something was wrong but that neither they nor their doctor identified depression as the problem. Although it is currently not possible to predict accurately who will attempt suicide, there are warning signs that a severely depressed person may make an attempt. All too often, friends and relatives of people who die by suicide are unaware of these red flags until it is too late to help.

The most important steps to prevent suicide are to recognize the risk factors and warning signs and to facilitate appropriate treatment of the underlying psychiatric illness. Treatment guidelines call for people with major depression to have a careful and ongoing evaluation of their suicide risk. Typical warning signs are listed below. However, not all people who die by suicide have these risk factors, and most people who do have them are not suicidal. Signs include the following:

- Social isolation that may be self-imposed
- Drastic mood swings or overall personality changes

Unused Prescription Pain Pills Raise Alarm

Drug overdoses in the U.S. now claim more lives each year than car accidents or gun violence. Many overdoses and deaths are due to legitimately prescribed opioid pain medications that find their way into the wrong hands.

A high percentage of opioids prescribed after surgery go unused, creating a large supply of dangerous drugs that may be abused, says a new report.

The report analyzed six studies that together included 810 patients who were prescribed opioids post-op. In those studies, 67 to 92 percent of patients reported not taking all of the prescribed medication, and 42 to 71 percent of the actual pills were not used. Five of the studies, looking at how unused opioids were stored, found that three of four patients reported not locking them away. Very few patients reported properly disposing of the medications.

The combination of unused opioids, poor storage practices, and lack of disposal sets the stage for the diversion of opioids for nonmedical use, the report warns. The 2015 National Survey on Drug Use and Health found that more than half of people who misused an opioid medication in 2014 acquired it from a relative or friend.

If you are prescribed pain medications, store them safely in a locked cabinet. If any go unused, dispose of them immediately. Many communities have programs for safe prescription drug disposal. To find out about ones in your area, call your doctor's office or a local hospital.

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- Neglecting home, finances or pets
- Recent psychological trauma, such as a divorce, death of a loved one, or job loss (which may trigger suicidal thinking in an already depressed person)
- Exaggerated complaints of aches or pains
- Giving cherished belongings away to loved ones or putting one's affairs in order
- Sudden calm or cheerfulness after a period of depression
- Frequent use of alcohol or other drugs
- Buying a gun
- Verbal threats of suicide or statements that suggest a desire to die
- Family history of suicide or previous suicide attempts

Natural History and Prognosis of Mood Disorders

Mood disorders most often surface around the age of 30, but they can occur at any point in a person's life. An accurate diagnosis is often delayed because symptoms are typically not recognized as being related to an illness. Instead, they are thought to be a reaction to life circumstances.

Depression

An untreated episode of major depression usually lasts six to nine months. This period can be shortened considerably with proper diagnosis and treatment. Most people with depression have their first episode before age 30, and most will have more than one episode in their lifetime. Relapse rates are lower in people who continue with treatment when they are feeling well. Approximately 15 percent of depressed people have a chronic form of depression that is resistant to current treatments.

Alcoholism or other drug use can make recovery from depression (and bipolar disorder) more difficult. One study compared 176 men and women who fit the criteria for both alcoholism and major depression with 412 people who had major depression alone. Those who had never been alcoholics or who no longer drank were twice as likely to recover from an episode of major depression than those who were still drinking. Unfortunately, many depressed people slow their recovery by attempting to self-medicate with alcohol.

Bipolar Disorder

Bipolar disorder usually begins at an earlier age than depression and can even occur in childhood. But it is also an unpredictable disease that can emerge later in life. In one large study of people treated at Veterans Affairs hospitals, 25 percent of the more than 65,000 people with bipolar disorder treated during one year were age 60 or older. And in this over-60 age group, approximately 6 percent had new-onset disease.

In a separate study, about 10 percent of 1,157 people between the ages of 18 and 70 treated in an urban primary care clinic screened positive for bipolar disorder. Of those, 41 percent reported first being affected at age 40 or older. Another study suggests that 10 percent of new cases occur after age 50.

Overall, men and women are equally likely to suffer from bipolar disorder, but women may be more likely to experience the late-onset form. A study of 48 older adults with bipolar disorder showed that women were almost three times as likely to be in the late-onset group.

Most people with bipolar disorder who recover completely from an acute episode have recurrent bouts of either depression or mania. The episodes can be separated by weeks, months or years. The frequency and severity of episodes vary from person to person—some people will go on to have many episodes, while others will have few episodes separated by years of normal health. Subsequent episodes are not necessarily more severe, nor does the illness consistently worsen with age—there are many variations on how the illness proceeds over time.

Some people with bipolar disorder can cycle between depressive and manic episodes four or more times a year. Known as rapid cycling, this condition is particularly challenging to treat. Finally, while most people with bipolar disorder experience full recovery between episodes, some have chronic (ongoing) symptoms.

Treatment of Mood Disorders

In treating depression, doctors have three goals. The first is to relieve the symptoms of depression, the second is to restore the person's ability to function socially and in the workplace, and the final goal is to reduce the likelihood of a recurrence.

The goals for bipolar disorder are somewhat different because the disease is usually more challenging to treat. Doctors primarily strive to reduce the frequency and severity—and the social and

Q. A family member was recently diagnosed with bipolar disorder. What should I know about episodes of mania and depression?

A. During what psychiatrists call an acute episode, the symptoms of either mania or depression become very pronounced. Patients may become extremely agitated or deeply depressed and unresponsive. Seeing a family member go through such an episode can be distressing. If the individual seems to be at risk for self-harm or harming others, his or her doctor may recommend immediate hospitalization.

If the doctor determines that your family member doesn't require hospitalization while experiencing an acute manic episode, it is important to provide as calm and stable an environment as possible, with a minimum of stimulation. Individuals going through an acute depressive episode may be at high risk of committing suicide.

During an acute episode, it's very difficult for the patient—and family caregivers—to make rational decisions. Major decisions regarding family, finances, or job-related issues should be put on hold until the episode has passed.

During periods when symptoms are under control, it is important that patients be involved in making decisions about their treatment with their healthcare provider, particularly since such patient participation tends to result in better adherence to the prescribed therapy.

psychological impact—of episodes. Improving social and mental functioning between episodes is the other major goal of treatment.

When a person seeks treatment for a mood disorder, the first step is a complete evaluation, which includes a detailed psychiatric and medical history, as well as a mental status examination. Because treatment varies considerably based on the diagnosis, it is crucial to have this comprehensive assessment.

Treatment goals for depression and bipolar disorder are met in three stages—acute, continuation and maintenance. During *acute treatment*, the focus is on immediately relieving symptoms and restoring the person's ability to function. Once symptoms respond to acute treatment, *continuation treatment* begins; the focus here is on preventing a relapse. If a person has no symptoms for four to nine months after an episode, he or she is considered recovered. At this point, *maintenance treatment* begins, with the goal of preventing a new episode. Maintenance treatment can last from one year to a lifetime, depending on the individual.

Depression recurs in about half of cases within two years of ending treatment, so timing must be considered carefully when stopping medications. The longer a person remains on treatment, the smaller the likelihood of relapse. The decision to try tapering off medications for bipolar disorder is more complicated because it involves the risk of recurrent manic and depressive episodes and, especially, the risk of suicide.

The main treatment options for depression and bipolar disorder are medications, psychotherapy, electroconvulsive therapy (sometimes informally referred to as shock therapy) or any combination of these. Light therapy is often used to treat SAD, but often can be helpful as an add-on treatment for depressive symptoms in either bipolar disorder or regular clinical depression. In addition, exercising, getting enough sleep and eating a healthy diet play a role in improving mood and self-image (see “Latest Research” on page 53).

These days, medications are often the recommended initial treatment choice for people with severe depression. Any given antidepressant has up to a 70 percent chance of working in a particular person. It is important to start treatment as early as possible, as depression becomes more difficult to treat the longer it lasts. Because response to any particular treatment varies from one person to another, an individual who does not improve with the initial treatment may respond to a different one.

That's the important lesson to be learned from a large, six-year multicenter study called the Sequenced Treatment Alternatives

Music Therapy Shows Promise for Depression

Music soothes the savage beast, the saying goes. Can it also soothe the symptoms of major depression?

Researchers from the University Clinic Regensburg in Germany analyzed findings from 28 studies of music therapy, which included 1,810 participants altogether. The individual studies took very different approaches, from having depressed patients simply listen to music to encouraging them to participate in singing or instrumental group music therapy. The trials also employed different styles of music. Overall, 26 of the 28 studies found statistically significant reductions in depression levels associated with music therapy. Among studies that used the Geriatric Depression Scale to measure depression, music therapy was associated with a 43 percent improvement in symptoms of the disorder.

Because the studies varied so widely, drawing conclusions about the best form of music therapy is difficult. Group music therapy sessions were slightly more effective at easing depression than individual sessions. Participants age 60 and older had greater improvements in depression scores than younger participants, according to the authors.

Overall, music therapy in general appears to offer a promising adjunct to conventional therapy for depression, especially for patients with mild to moderate depression. Additional research would be required to determine which types of music therapy might best benefit people with depression.

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to Relieve Depression (STAR*D) trial, which looked at the use of popular antidepressants in people with chronic depression (lasting, in some cases, 15 to 16 years). This study found that systematically trying different doses of antidepressant medications, maintaining a longer duration of therapy, trying a different drug altogether or combining medications can lead to a remission in symptoms for many severely depressed, treatment-resistant patients.

Like antidepressant medications, psychotherapy alone also can work to relieve depression. While it usually requires more time than antidepressant therapy to reduce symptoms, its positive effects may last longer than those from medication. Psychotherapy alone is often recommended as an initial treatment option for people with mild to moderate depression.

While severe cases of depression are best treated with medication, electroconvulsive therapy (ECT) may be recommended in extreme cases. Up to 90 percent of extremely depressed people improve with ECT when it is used as a first-line treatment. However, the therapy is usually used only after other therapies have failed. When used as a last resort, the response rate drops to 50 to 60 percent.

Combination therapy (medication plus psychotherapy) has been shown in some research studies to be more effective than either therapy alone for mild to moderate depression. This option may be beneficial if single-therapy treatment produces only partial results, if depression is chronic, or if the person is facing multiple challenges that are best treated by different means, such as medication for depressive symptoms and psychotherapy for job-related problems. Recent research suggests that combination therapy may prevent or delay relapses and recurrences of depression.

Treatment of Depression With Medications

Today, physicians can choose from a wide range of antidepressant medications. These include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), dopamine reuptake inhibitors, tricyclics, tetracyclics, monoamine oxidase (MAO) inhibitors, an atypical antipsychotic/selective serotonin reuptake inhibitor, and serotonin modulators. There are several advantages to treating depression with antidepressant medications:

- They are effective against mild, moderate and severe forms of major depression.
- People usually respond more quickly to medications than to psychotherapy.
- They are easy to administer.

Antidepressant Drugs 2018*

Drug type: Brand (generic)	Typical daily dosage†	How they appear to work
Selective serotonin reuptake inhibitors (SSRIs)		
Celexa (citalopram‡)	20–40 mg	Block the reabsorption and inactivation of the neurotransmitter serotonin. This increases the availability of serotonin to carry messages between nerve cells.
Lexapro (escitalopram)	10–20 mg	
Luvox (fluvoxamine‡)	50–300 mg	
Luvox CR (fluvoxamine, controlled-release)	100–300 mg	
Paxil (paroxetine‡)	20–50 mg	
Paxil CR (paroxetine, controlled-release‡)	25–62.5 mg	
Prozac (fluoxetine‡)	20–80 mg	
Prozac Weekly (fluoxetine)	90 mg (weekly)	
Zoloft (sertraline‡)	50–200 mg	
Serotonin and norepinephrine reuptake inhibitors (SNRIs)		
Cymbalta (duloxetine)	40–60 mg	Block the reabsorption of serotonin and norepinephrine, increasing the availability of these neurotransmitters in the brain.
Effexor (venlafaxine‡)	75–375 mg	
Effexor XR (venlafaxine, extended-release‡)	37.5–225 mg	
Pristiq (desvenlafaxine)	50 mg	
Dopamine reuptake inhibitors		
Wellbutrin (bupropion‡)	200–450 mg	Block the reabsorption of the neurotransmitter dopamine, increasing its availability in the brain.
Wellbutrin SR (bupropion, sustained-release‡)	150–400 mg	
Wellbutrin XL (bupropion, extended-release‡)	150–450 mg	
Tricyclics		
(amitriptyline)	50–100 mg	Block the reabsorption of the neurotransmitters serotonin, norepinephrine, and to a lesser extent, dopamine, increasing their availability in the brain.
Aventyl (nortriptyline‡)	75–150 mg	
(doxepin)	75–150 mg	
Norpramin (desipramine‡)	100–300 mg	
Pamelor (nortriptyline‡)	75–150 mg	
Surmontil (trimipramine‡)	50–200 mg	
Tofranil (imipramine‡)	75–200 mg	
Vivactil (protriptyline‡)	15–60 mg	



Precautions

Do not take with monoamine oxidase (MAO) inhibitors, triptans, or St. John's wort. If discontinuing use, reduce dosage gradually to prevent withdrawal symptoms. The development of a skin rash can be the sign of a serious medical problem; see a doctor immediately. *Celexa only*: This drug should no longer be used at doses greater than 40 mg a day due to risk of abnormal changes in the electrical activity of the heart.

Common side effects

Anxiety, nervousness, insomnia, drowsiness, weakness, headache, diarrhea, increased sweating, nausea, impaired sexual function, weight gain. Side effects appear to be lesser with Lexapro.

Do not take with MAO inhibitors or triptans. If discontinuing use, reduce dosage gradually to prevent withdrawal symptoms. Effexor and Pristiq may increase blood pressure and/or cholesterol levels, especially at high doses; regular blood pressure and cholesterol monitoring is advised. Effexor may cause abnormal bleeding, especially in people taking aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, or other anticoagulants.

Nausea, weakness, sweating, insomnia, drowsiness, dry mouth, dizziness, constipation, nervousness, impaired sexual function, appetite loss.

Do not take if you have seizures or an eating disorder, are using MAO inhibitors or are using another product that contains bupropion (such as the smoking-cessation drug Zyban). Wellbutrin (not SR or XL) must be given in divided doses at least 8 hours apart, with no single dose exceeding 150 mg.

Appetite and weight loss, dry mouth, rash, sweating, ears ringing, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, increased urination. Greater risk of seizures at higher doses. Low risk of sexual side effects and weight gain.

Do not take with MAO inhibitors. Do not stop treatment abruptly. It is not advisable to take most tricyclic antidepressants if you have seizures, a heart disorder or glaucoma, or if you use alcohol excessively.

Dizziness on standing, drowsiness, weakness, headache, dry mouth, blurred vision, constipation, nausea, difficulty urinating, increased appetite (which may include a craving for sweets), impaired sexual function, increased heart rate. Skin is more sensitive to sunlight, which may result in itching, redness, discoloration of skin.

* This list represents the most commonly prescribed antidepressants.

† These dosages represent an average range for the treatment of depression and may differ from the dosage prescribed by your doctor. The precise effective dosage varies from person to person and depends on many factors. Do not make any change to your medication without consulting your doctor. *Starting dosages tend to be lower for older adults.*

‡ Generic version available at lower cost.

continued on the next page

Antidepressant Drugs 2018* (continued)

Drug type: Brand (generic)	Typical daily dosage†	How they appear to work
Tetracyclics		
(maprotiline)	75–150 mg	Block the reabsorption of serotonin and norepinephrine, increasing the availability of these neurotransmitters.
Remeron (mirtazapine‡)	15–45 mg	
Remeron SolTab (mirtazapine‡)	15–45 mg	
Monoamine oxidase (MAO) inhibitors		
Emsam skin patch (selegiline)	6–12 mg	Block the action of MAO, an enzyme that inactivates the neurotransmitters serotonin, norepinephrine, and dopamine. MAO inhibitors thereby increase levels of these neurotransmitters, increasing their availability for carrying messages between neurons.
Marplan (isocarboxazid‡)	40–60 mg	
Nardil (phenelzine‡)	45–90 mg	
Parnate (tranylcypromine‡)	30–60 mg	
Atypical antipsychotic/selective serotonin reuptake inhibitor		
Symbyax (olanzapine/fluoxetine)	3/25–12/50 mg	Increases the availability of the neurotransmitters serotonin, norepinephrine, and dopamine to treat depression.
Serotonin modulators		
Trintellix (vortioxetine)	20 mg	Block the reabsorption of the neurotransmitter serotonin, increasing the availability of serotonin to carry messages between nerve cells. The drugs also work specifically on 5-HT1A receptors, but the way in which they work is not fully understood.
Viibryd (vilazodone)	40 mg	

* This list represents the most commonly prescribed antidepressants.

† These dosages represent an average range for the treatment of depression and may differ from the dosage prescribed by your doctor. The precise effective dosage varies from person to person and depends on many factors. Do not make any change to your medication without consulting your doctor. *Starting dosages tend to be lower for older adults.*

‡ Generic version available at lower cost.

- They are not addictive and, when properly used, are usually quite safe.
- They can be used in combination with psychotherapy.

The disadvantages are:

- Medication therapy can cause unwanted side effects.
- Strict adherence to a medication schedule and repeated visits to your doctor to monitor response are required.
- It may take some time—and some tinkering—to find the right medication at the right dose.



Precautions

Do not take with MAO inhibitors.

Caution advised with use of Remeron in the elderly because of delayed metabolism and clearance of the drug, which may increase the risk of adverse events.

Common side effects

Sleepiness, nausea, increased appetite, weight gain, dizziness, blurred vision, weakness, dry mouth, headache, constipation, shakiness, nervousness.

Foods containing tyramine (see page 32) should be avoided because they may cause a sudden, severe rise in blood pressure (hypertensive crisis), which can be fatal. There are no dietary restrictions with the 6 mg Emsam skin patch, as it does not interfere with the breakdown of tyramine in the digestive tract. (Restrictions do apply for the higher-dose patches.) MAO inhibitors may interact dangerously with numerous drugs, including other antidepressants and cold medications.

Dizziness, light-headedness (especially in older persons), drowsiness, headache, dry mouth, constipation, nausea, insomnia, decreased sexual function, weight gain. Patch can cause skin irritation.

Atypical antipsychotics increase the risk of death in elderly patients with dementia. See a doctor immediately if you experience signs of neuroleptic malignant syndrome (characterized by muscle stiffness or spasms, high fever, and confusion or disorientation) or infection (fever, chills, sweating, and fatigue).

Weight gain, sleepiness, increased appetite, weakness, swelling in legs and arms, tremors, sore throat, difficulty concentrating.

Do not take with MAO inhibitors. If discontinuing use, reduce dosage gradually to prevent withdrawal symptoms.

Nausea/vomiting, diarrhea, dry mouth, decreased libido.

Because of these issues, many people do not have an adequate trial of a therapeutic dose for a sufficient period of time. Older individuals and those with chronic illnesses are more susceptible to the adverse effects of antidepressants.

Researchers believe that antidepressants work by affecting levels of neurotransmitters—chemical messengers in the brain that facilitate communication between nerve cells. However, physicians cannot predetermine which medication will be the most effective in any particular individual. Drug selection relies largely on a process

of educated guesses, although many people do have some positive response to the first antidepressant they try. See “Investigating New Ways to Diagnose Depression” on pages 8–9.

Choosing a medication

For a person with a first-time episode of moderate to severe depression and no other psychological symptoms or medical conditions, the choice of medication is generally based on avoidance of side effects. For example, the older tricyclic antidepressant amitriptyline can lower blood pressure and cause drowsiness and confusion—side effects that are especially troublesome for older people. Newer antidepressants are far less likely to cause these problems.

Family history can also help predict which drugs are most likely to be effective, as well as which ones are most likely to cause side effects. Thus, a medication that worked well for a parent, sibling, or other first-degree relative may work for you as well.

By themselves, antidepressant medications usually produce a significant improvement by four to eight weeks, although it may take up to 12 weeks to see the full benefit. If a person’s depression responds fully to medication after this period, treatment moves on to the continuation phase, which can last for four to nine months at the same dosage level. People who have had three or more prior major depressive episodes or who have chronic major depression should continue on to a maintenance phase (continuation at the same dosage level). Those who have improved somewhat but still have a few symptoms after six weeks should be reassessed six weeks later (many are likely to improve further during this time). At the reassessment, the physician may adjust the dosage to improve response.

When a drug does not work, a doctor may prescribe an antidepressant from a different class of medications, because drugs in the same class tend to work similarly. When a drug from one class is producing good results but causes unacceptable side effects, switching to a different drug within the same class can help. In 20 to 50 percent of people, adding another medication, such as aripiprazole (Abilify) or quetiapine (Seroquel), can be beneficial.

If maintenance treatment is no longer needed, drugs are discontinued slowly over a period of one to two months to avoid withdrawal symptoms. Relapses are most common during the first two months after a person stops taking an antidepressant. It is therefore important for individuals to remain in contact with their physician during this period. Should a relapse occur, the same drug that was used successfully the first time often proves effective again.

Suicide and medication

All antidepressants must be used with particular caution if a person is suicidal. When this is the case, the person will need to see his or her doctor for frequent follow-up visits and will receive a prescription for a relatively small number of pills at a time to determine their effectiveness. Suicide attempts or suicidal thoughts are common symptoms of depression, and the risk of suicide has been shown to increase just as depression begins to respond to treatment.

In 2004, a federal panel of drug experts said that antidepressants could increase the risk of suicide in children and teenagers. Later that year, the Food and Drug Administration (FDA) required the makers of antidepressants to add a black box warning to that effect to the drug labels of these medications. In 2005, the agency issued a public health advisory stating that suicidal thoughts and behaviors may also increase among adults on antidepressants. The risk of suicide was claimed to be higher at the start of drug therapy and at the time of a dosage change, according to the FDA. However, most subsequent research has shown only teenagers and very young adults to be prone to increased suicidal feelings on initial exposure to antidepressants; nonetheless, the FDA has not changed its black box warnings. Note that successful use of antidepressants has been shown to markedly lower rates of suicide overall.

Although up to 70 percent of people with depression respond positively to antidepressants—and some studies suggest that use of antidepressants, particularly newer SSRIs, decreases the risk of suicide—it is true that some people might have responded just as well to a placebo. But whether a person responds to an antidepressant because of the action of the medication or the placebo effect, or possibly a combination of the two, the fact remains that antidepressants provide real relief to many people. Moreover, because studies of the placebo effect have only followed people for a limited period of time, there are no data showing whether the placebo effect can be sustained in the long term. By contrast, there are data showing that the positive effects of medication are sustained long term.

When it comes to the length of treatment for depression, there is no “one size fits all.” However, recent evidence shows that many people require a year or more of antidepressant therapy to treat a major depressive episode adequately. This includes roughly three months of acute treatment to significantly improve depressive symptoms and an additional four to nine months of continuation

Q. What happens if the first antidepressant I try doesn't help?

A. Some people with depression don't achieve remission with the first antidepressant they try. Most of them end up switching to another medication or a combination of medications. Finding the best treatment remains partly a process of trial and error.

A study published in *JAMA* in 2017 offered evidence for one particular approach. Patients with major depression at 35 Veterans Health Administration medical centers who did not respond to at least one antidepressant were randomly assigned to one of three groups: one in which participants' current antidepressant was replaced with bupropion (Wellbutrin), a second in which the current antidepressant was augmented with bupropion, or a third in which the current antidepressant was replaced with aripiprazole (Abilify).

After 12 weeks, 1,296 individuals had completed the treatment phase. In the group that switched to bupropion, slightly more than 22 percent (114 individuals) experienced remission. Almost 27 percent (136 individuals) of those who augmented their current treatment with bupropion went into remission. Of those who augmented their antidepressant with aripiprazole, nearly 29 percent (146 participants) experienced remission.

Finding the best treatment means weighing both benefits and unwanted side effects. In this study, bupropion was associated with more reports of anxiety, and aripiprazole with sleepiness, weight gain, and a movement disorder called akathisia.

If your medication isn't working, talk with your doctor to find another option.

Antidepressants and Your Sex Life

How to regain intimacy without stopping depression treatment

Having a satisfying sex life may be a challenge for those who take antidepressants. That's because while the medication may treat depression, it may also contribute to sexual dysfunction or even cause it in people whose sex life was previously not a problem.

Between 15 and 80 percent of people who take antidepressant medication experience sexual problems, which can begin the first week to several months after starting treatment, depending on the drug prescribed and the dosage.

That's why many factors must be considered before an antidepressant is prescribed. Differences exist in sexual side effect frequency among drug classes, and between specific antidepressants. If your sex life is important to you, as it is for many people 50 and up, you may want to consider potential sexual side effects among the factors in your decision about which antidepressant to take.

The effects on sexual function

For both men and women, antidepressants may diminish sex drive and make achieving orgasm difficult or impossible. In men, antidepressants may cause erectile dysfunction (difficulty in achieving or sustaining an erection). In women, these drugs may cause vaginal dryness and decreased sensation in the genitals.

How do you know if your antidepressant is causing sexual problems? The medication can be suspected if a person experiences a new or worsened sexual problem within two to three months of beginning antidepressant treatment—and no other drug was started and no other medical or life changes occurred during that time.

While anyone taking an antidepressant may experience sexual dysfunction, certain individuals are more susceptible. These include people over the age of 50,

those who take additional medications or a high dosage of antidepressants, people who have another health condition that can cause sexual dysfunction (such as diabetes or prostate disease), or those who felt that sexual enjoyment was not important prior to taking antidepressant medication.

What to do

Sexual dysfunction can have effects that extend far beyond the bedroom, including psychological distress and a lowering of self-esteem, as well as a decrease in overall quality of life. As a result, many people who experience antidepressant-related sexual dysfunction stop taking their medication prematurely, which is a serious problem if the depression continues and the antidepressant was helping.

Fortunately, you can regain your sex life without having to stop taking an antidepressant

treatment. People with severe or recurring depression and older adults may require much longer therapy.

Selective serotonin reuptake inhibitors (SSRIs)

Low amounts of the neurotransmitter serotonin have been linked to depression. SSRIs such as citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil) and sertraline (Zoloft) increase levels of serotonin in the brain. All of the SSRIs are equally effective and have similar rates and types of side effects, although it is possible that an individual might respond better or experience fewer side effects with a particular SSRI. Side effects can even be useful sometimes—antidepressants that cause sedation may be helpful for insomnia.



altogether and risk having your symptoms worsen. Discuss with your doctor the following options for avoiding or treating antidepressant-induced sexual dysfunction:

- **Choosing a medication with a low rate of sexual side effects.** Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed antidepressants. Of these, paroxetine (Paxil) is considered to have the greatest incidence of sexual side effects, as well as weight gain. You may want to consider an antidepressant with a lower risk of sexual side effects, such as bupropion (Wellbutrin) or mirtazapine (Remeron).

- **Switching medication if you're already on an antidepressant.** Any switch must be done carefully so as to minimize the risk of relapse or a withdrawal reaction from the first medication. Also, there is a chance that the new antidepressant will be

less effective than the first or will cause other side effects.

- **Reducing the dosage.** A decrease in the dosage of medication may allow some people to regain satisfactory sexual function. However, lowering the amount of antidepressant taken each day may cause withdrawal reactions or an increase in depressive symptoms. People who try this approach need to develop a plan with their doctor and should be monitored closely.

- **Taking a short break (known as a drug holiday).** Some evidence shows that taking periodic two-day breaks from antidepressant treatment can lower the rate of sexual side effects during the drug holiday without increasing the risk of a recurrence of depressive symptoms. Potential risks of drug holidays include withdrawal reactions.

- **Adding a medication.** If your current medication is

helping with depression but you would like to decrease sexual side effects, adding bupropion to what you already take, especially if you're on an SSRI, may boost the antidepressant effect and help with sexual side effects. While that goes for both genders, men may also want to consider an erectile dysfunction drug, such as avanafil (Stendra), sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra). The only prescription drug for female sexual dysfunction, flibanserin (Addyi), appears to be of limited benefit (only 8 to 13 percent over placebo).

Women who experience vaginal dryness can try using lubricants or moisturizers or can ask their doctor about estrogen creams. Vaginal application releases little estrogen into the bloodstream and poses less risk of side effects, such as blood clots, than estrogen taken orally in pill form. ■

Because the side effects of SSRIs are milder than those of most other antidepressants, most doctors consider them the first-line drug treatment for depression. About half of those who take an SSRI see their symptoms of depression lift completely. Advantages of SSRIs over other antidepressants, such as tricyclics, include a lower risk of fatal overdoses and serious heart rhythm disturbances in people with heart disease. SSRIs are also effective against persistent depressive disorder (chronic low-grade depression).

Side effects. SSRIs can produce side effects such as anxiety, nervousness, insomnia, drowsiness and nausea. Another troublesome side effect is sexual dysfunction—diminished sexual desire, changes in the sensations of arousal, or disturbances in the ability to achieve orgasm—which may occur in about 37 percent of both men and women taking

these drugs. Sexual side effects usually develop within the first week of starting an SSRI, though they may arise more slowly as blood levels of the drug build up. Strategies to alleviate sexual dysfunction include switching to a medication with a low rate of sexual side effects (such as the dopamine reuptake inhibitor bupropion [Wellbutrin]), waiting to see if sexual side effects abate, changing the time when you take the medication (possibly to nighttime), reducing the dosage, taking drug holidays (for example, not taking the medication on the weekend) or adding an erectile dysfunction drug like sildenafil (Viagra). If you experience worrisome symptoms, do not make any changes in your drug regimen on your own—be sure to consult your doctor first. (See “Antidepressants and Your Sex Life” on pages 26–27).

Recently, it was recognized that SSRIs may produce neurological side effects—symptoms like those of Parkinson’s disease, such as impaired muscle tone, tremors, spasms or feelings of restlessness. These symptoms can become so severe that sitting still becomes impossible. Fortunately, these side effects are rare. In one study, they occurred in only 0.3 percent of people. By comparison, the most common side effects of fluoxetine (Prozac)—agitation and anxiety—occurred in twice as many people, although they were still relatively uncommon. If you experience any of these symptoms, contact your doctor before you stop taking your medication.

In addition, people taking a combination of drugs that raise the level of serotonin in the body can develop a disorder called serotonin syndrome. The most common causes are taking an SSRI at the same time as a monoamine oxidase (MAO) inhibitor or a triptan migraine drug (for example, frovatriptan [Frova], rizatriptan [Maxalt], sumatriptan [Imitrex] and others). The syndrome is characterized by altered mental status, neuromuscular abnormalities and dysfunction of the autonomic nervous system, which controls the bodily functions not consciously directed, such as breathing, the heartbeat, and digestive processes. Tricyclic antidepressants may also contribute to serotonin syndrome.

SSRIs are associated with an increased risk of gastrointestinal bleeding, particularly when they are taken with nonsteroidal anti-inflammatory drugs. One study found that depressed heart patients treated with the SSRI sertraline (Zoloft) showed significant reductions in the level of clotting factors in their blood compared with those receiving a placebo. Another study found that SSRIs may increase the risk of fractures in older adults, possibly by compromising bone quality and strength as well as by increasing the chance of falling (see “Latest Research” on page 63).



Although side effects tend to be similar among the various SSRI antidepressants, fluvoxamine and paroxetine may be more likely to cause nausea, and diarrhea is more common with sertraline. Because fluoxetine may take several days to clear from the body, interactions with other drugs are more likely to occur. One advantage of fluoxetine, however, is that it is available in a once-a-week capsule.

SSRI withdrawal. SSRIs are not addictive in the conventional medical use of the word, but suddenly discontinuing their use after taking them for more than six weeks is known to produce both physical and psychological withdrawal symptoms.

About one-quarter of people who abruptly stop taking an SSRI experience dizziness, nausea, lethargy and headache. Other symptoms include irritability, nervousness, crying spells, flu-like symptoms (body aches, chills and fatigue), and shooting pains in and around the head. SSRI withdrawal—also called SSRI discontinuation syndrome—is not dangerous, but it can be distressing. Fortunately, it is usually mild, commences within one week of stopping treatment and resolves within three weeks. To minimize SSRI discontinuation syndrome, doses of SSRIs (like other antidepressants) should be reduced gradually.

Serotonin and norepinephrine reuptake inhibitors

Medications like desvenlafaxine (Pristiq), duloxetine (Cymbalta) and venlafaxine (Effexor) are serotonin and norepinephrine reuptake inhibitors (SNRIs). These medications work by raising brain concentrations of the neurotransmitters serotonin and norepinephrine. SNRIs are often the most effective drugs for older people. Possible side effects include nausea, weakness, sweating, insomnia, drowsiness, dry mouth, dizziness and constipation. Venlafaxine may increase blood pressure and cholesterol levels in some people, so monitoring blood pressure and cholesterol is important for anyone taking this drug. Desvenlafaxine, duloxetine or venlafaxine taken in combination with triptan migraine medications may result in serotonin syndrome.

Dopamine reuptake inhibitors

Bupropion (Wellbutrin) decreases the reuptake of dopamine, a neurotransmitter and a precursor of other neurotransmitters. This drug causes less drowsiness and fewer side effects than the tricyclics (especially fewer sexual side effects), but on rare occasions it can cause seizures, particularly at higher doses. Extended-release

bupropion is the first drug approved to prevent major depressive episodes in people with seasonal affective disorder (SAD).

Tricyclics

Tricyclics—such as amitriptyline, desipramine (Norpramin), doxepin, imipramine (Tofranil), nortriptyline (Aventyl, Pamelor), protriptyline (Vivactil) and trimipramine (Surmontil)—are named for their chemical structure. These drugs raise brain concentrations of the neurotransmitters norepinephrine, serotonin and, to a lesser extent, dopamine, by blocking reabsorption of these chemical messengers by the nerve cells that release them.

Tricyclics are used mainly to treat moderate to severe depression and have proven less effective in treating chronic low-grade depression. About 60 percent of people who take tricyclics experience significant improvement within four to six weeks. Each of the tricyclics is believed to be equally effective, but side effects may differ.

When a person begins tricyclic therapy, he or she is given a small dose and is carefully monitored for side effects. The dose is often raised over several weeks because a gradual increase may be less likely to lead to side effects. Side effects also tend to diminish with continued use.

For older people, dosages are usually 30 to 50 percent lower than those indicated in the chart on pages 20–21.

Although a positive response to tricyclics typically appears within four to six weeks, doctors recommend taking the medication for six to eight weeks at full dosage to assess the effects. During this time, blood tests may be ordered to make sure that the drug level is high enough to exert a therapeutic effect but not so high as to be toxic. If a person's depression does not improve while taking a tricyclic, it may be that the drug is not effective for that person or that he or she is not taking the drug as prescribed.

About one-third of people stop taking tricyclics because of side effects, and about two-thirds of older people miss 25 to 50 percent of their doses. Poor compliance leads to fluctuating blood levels of the drug and, consequently, an unfavorable response. Therefore, it is important to tell your doctor about unpleasant side effects instead of just stopping your medication.

Side effects. The most prominent side effects of tricyclics are postural hypotension (dizziness on standing due to a drop in blood pressure), drowsiness, weakness, headache, dry mouth, blurred vision, constipation, nausea and difficulty urinating. Many of these



side effects can be managed, however. Postural hypotension, which can lead to falls and broken bones in older people, can be reduced by standing up slowly after sitting or lying down and waiting 30 seconds before trying to walk.

Drowsiness can be remedied by taking the dose before bedtime (if your doctor approves). Pilocarpine eyedrops may alleviate blurred vision. Chewing sugar-free gum or candy will help dry mouth. (Be sure to mention dry mouth to your dentist—a lack of saliva can lead to an increase in cavities and gum problems.) Bethanechol may be prescribed to counteract problems with urination. And constipation can be managed by consuming foods high in fiber and drinking more water or juice each day.

Amitriptyline and imipramine are more likely than other tricyclics to cause side effects in older people.

People who should not take tricyclics. Tricyclics are not given to people with closed-angle glaucoma and should be used with caution in men who have symptoms of benign prostatic hyperplasia (enlarged prostate), as they may lose the ability to urinate. This medical emergency must be treated with catheterization.

Tricyclics can also magnify the depressive effects of alcohol and benzodiazepines. The combination of tricyclics with antihistamines can lead to severe constipation or difficulty urinating, particularly in older adults.

In addition, tricyclics (and SSRIs) should not be mixed with the drug selegiline (Eldepryl), which is used to treat Parkinson's disease. Although rare, an interaction between these drugs may cause high fever, tremors, agitation, restlessness or, in some cases, death. Other symptoms resulting from such drug combinations may include fainting, profuse sweating, seizures, behavioral changes and stiffened muscles.

Tricyclics are not currently recommended for use in most people with coronary heart disease (CHD) because they can cause life-threatening ventricular fibrillation (abnormal rhythm in the heart's lower chambers) in these individuals. Despite the heart risks of tricyclics, they are still used to treat depression because they are sometimes the only effective antidepressants for severely depressed people.

An older person with mild to moderate depression and severe CHD may first be given a medication from another drug class, such as an SSRI or the dopamine reuptake inhibitor bupropion. If the individual does not respond to these drugs, a tricyclic would then be tried. Because the risk of ventricular fibrillation

from tricyclics increases with the severity of CHD, the doctor must weigh the severity of the depression against the potential danger to the heart.

Tetracyclics

The action, efficacy and side effects of drugs like maprotiline and mirtazapine (Remeron) are similar to those of the tricyclics. However, maprotiline is more likely to cause seizures than most other antidepressants. A version of mirtazapine is available that dissolves on the tongue and does not need to be chewed or swallowed whole.

Monoamine oxidase (MAO) inhibitors

MAO inhibitors such as phenelzine (Nardil) and tranylcypromine (Parnate) increase brain levels of norepinephrine, serotonin and dopamine by blocking the action of the enzyme MAO, which inactivates these three neurotransmitters. MAO inhibitors are effective in many depressed people, especially those whose depression is accompanied by marked anxiety, panic attacks, heightened appetite or excessive sleeping.

People who should not take MAO inhibitors. MAO inhibitors can cause some of the same side effects as the tricyclics; side effects can be reduced in similar ways. But there are some individuals for whom MAO inhibitors pose greater risks. If you are a heavy drinker, have heart failure or severely impaired liver or kidney function, or take multiple medications for high blood pressure, you should not take an MAO inhibitor.

Also, MAO inhibitors can cause a sudden, extreme elevation in blood pressure (known as a hypertensive crisis) when people using them take certain drugs or consume foods or beverages containing tyramine. (Tyramine is found in some nasal decongestants, cold or allergy medicines, very ripe bananas, beer and aged or smoked meats, among other things.) People taking an MAO inhibitor must get a complete list of restricted foods and drugs from their doctor.

Normally, the enzyme MAO breaks down any tyramine consumed in the diet, preventing its blood pressure-raising effect. This protective mechanism is disabled by MAO inhibitors, which block the action of MAO in the liver and intestine, allowing tyramine levels to rise and increase blood pressure. Symptoms of a hypertensive crisis include severe chest pain, excruciating headache, sweating, clammy skin, nausea and vomiting. Immediate treatment with blood pressure-lowering drugs is essential.



Are You Overprescribed?

Taking multiple brain-affecting drugs comes with serious risks

Treating depression, anxiety, insomnia, or pain in older people is a balancing act. Doctors often prescribe multiple medications to manage these conditions. But taking the drugs, especially in combination, can be dangerous, increasing the risk of falls, cognitive impairment, drug interactions, and even death.

Despite these risks, the number of older Americans taking at least three drugs that affect the brain has more than doubled in a decade, according to an analysis published online in February 2017 in *JAMA Internal Medicine*. The drugs include antidepressants such as fluoxetine (Prozac), sleep drugs such as zolpidem (Ambien), tranquilizers such as diazepam (Valium), and pain medications such as oxycodone (OxyContin).

What the data showed

Researchers from the University of Michigan and VA Ann Arbor Healthcare System reviewed records from office visits of 97,910 patients age 65 and older in the U.S. from 2004 to 2013. The data were collected from a representative sample of doctors' offices by the Centers for Disease Control and Prevention (CDC).

During that time, the doctor visits in which three or more brain-affecting, or psychotropic, drugs were started or continued increased from 0.6 percent to 1.4 percent of visits. The researchers applied those percentages to the entire U.S. senior population to estimate that visits involving multiple brain-affecting drugs increased from 1.5 million to

3.68 million. (The use of multiple medications by a single patient is known as polypharmacy.)

Rural practices, where access to psychiatric care or pain management is limited, accounted for the largest increase in brain-affecting prescriptions. In nearly half those visits, the patient did not have a mental health or pain diagnosis, leading the authors to conclude that in some cases, those drugs may be overprescribed.

The reasons why

A patient's preference for visiting a primary care practice—or the lack of access to a specialist, such as a psychiatrist—may account for the increase in prescriptions for brain-affecting drugs by primary care doctors. Also, efforts have been made to encourage primary care doctors to treat more mental disorders, given how common such illnesses are. In their review, the researchers found that in rural areas (where there is less access to nondrug alternatives), treatments such as psychotherapy, stress management, physical therapy, and professional pain management were not offered at most visits. This may explain, in part, why people living in rural areas are more likely to be prescribed multiple brain-affecting medications.

The analysis revealed that polypharmacy significantly increased for individuals who had a pain diagnosis, which was attributed to the overall growth in the prescribing of opioids. Many people turn to prescription opioids—pain relievers such as oxycodone,

acetaminophen/hydrocodone (Vicodin), and acetaminophen/oxycodone (Percocet)—to treat chronic pain. Over time, opioid use can lead to physical dependency and withdrawal symptoms. Little high-quality evidence is available that supports the long-term use of opioids for chronic noncancer pain. Yet more than 16,000 people die from prescription pain reliever overdoses each year, according to the CDC. Unfortunately, little research exists for alternatives, which has led to an overreliance on opioids.

Reduce your risk of bad reactions

If you are taking more than one prescription drug, there are steps that you can take to reduce your risk of dangerous interactions or side effects. The American Geriatrics Society offers the following suggestions:

- Keep a list of your medications, including prescription and over-the-counter drugs and supplements such as vitamins. Show this list to your doctor at every visit so that he or she can prescribe medicine that won't interact with anything you're taking.
- Ask your doctor about the medications you're taking and what kinds of adverse effects to watch for. Call your doctor immediately if you experience a bad reaction.
- If you're concerned that a drug you're taking is either not working or not necessary, talk with your doctor. Do not stop taking the medication without consulting the doctor first. ■

Because of this risk and the dietary restrictions, MAO inhibitors are now only used as second-line drugs for the treatment of depression, despite their proven efficacy.

A skin patch of the MAO inhibitor selegiline (Emsam) is available. At the lowest dose, the selegiline transdermal system does not interfere with the breakdown of tyramine in the digestive tract and can be used without dietary restrictions.

Atypical antipsychotic/selective serotonin reuptake inhibitor

Symbyax, a combination of an atypical antipsychotic (olanzapine) used for bipolar disorder plus an SSRI (fluoxetine), treats depression in people who have not responded to two other antidepressants. Like all antipsychotics, Symbyax increases the risk of death in elderly people with dementia. Symbyax is also associated with a risk of neuroleptic malignant syndrome (see the chart on pages 22–23).

Serotonin modulators

In 2011, the FDA approved a new medication for major depressive disorder, vilazodone (Viibryd), the first in a new class of antidepressant, SSRI/5-HT_{1A} receptor partial agonist. Vilazodone works partly in the same way as SSRIs by blocking the reabsorption of serotonin and increasing its availability to carry messages between nerve cells. Vilazodone also works on 5-HT_{1A} receptors, although the way in which it does is not fully understood. Common side effects include diarrhea, nausea, vomiting and insomnia.

In 2013, the FDA approved vortioxetine (Trintellix) for major depressive disorder. Vortioxetine also increases serotonin levels by its action as an inhibitor of serotonin (5HT) reuptake. It works on several receptors, but the contribution of these activities to the drug's antidepressant effect has not been established. Side effects include nausea, constipation, vomiting, sexual dysfunction, dizziness and diarrhea.

Vilazodone and vortioxetine should not be taken in conjunction with MAO inhibitors. When discontinuing treatment with either drug, it should be done gradually (as with SSRIs) to avoid possible withdrawal symptoms, such as dizziness, headache, irritability and flu-like symptoms.

Atypical antipsychotics as adjuncts to antidepressants

Sometimes, even after trying several different antidepressants, symptoms of depression remain. In this case, adding an atypical



antipsychotic such as aripiprazole (Abilify) or risperidone (Risperdal) to a patient's medication regimen often provides relief. These drugs are FDA-approved to treat symptoms of bipolar disorder and schizophrenia, as well as depression in combination with an antidepressant.

Side effects of antipsychotics include nausea, vomiting, constipation, headache, dizziness, an inner sense of restlessness or need to move (akathisia), anxiety and insomnia. There is also the risk of more serious side effects, including a condition called tardive dyskinesia, which causes abnormal or uncontrollable movements of the face, tongue or other parts of the body, and neuroleptic malignant syndrome, which may cause severe muscle stiffness, fever, severe tiredness or weakness. Elderly people with dementia who take antipsychotics are at increased risk of sudden cardiac death. Ask your doctor about this and other risks if he or she suggests you take an antipsychotic.

Treatment in older adults

Older people are more susceptible to adverse effects than younger people, so drug therapy must be approached even more carefully. Smaller dosages as well as closer monitoring for toxic reactions are often required, and ensuring that the medications are being taken as prescribed may be an issue. Drug interactions are a concern, as the elderly use prescription drugs more than the general population. Treatment can also be difficult in reluctant individuals and in those lacking a social support system to help them with practical considerations, such as costs and transportation for visits to a doctor.

Despite all of these obstacles, older people usually respond well to treatment for depression; even partial success can lead to improved quality of life and productivity. Some studies even suggest that treatment with medications is more effective in older individuals than in younger ones.

Alternative treatments

Many people are curious about alternative treatments for depression, either because they hope to avoid drug-related side effects or because they are reluctant to see a doctor for their depression. Such self-treatment can put people at risk, however. For one thing, a person who self-medicates may not realize the depth of his or her depression or recognize worsening symptoms. For another, herbal and other alternative remedies are not benign and have potential side effects of their own, including the risk of drug-herb interactions.

St. John's wort, an extract from a yellow flowering plant called *Hypericum perforatum*, is the best known of "natural antidepressants."

The American College of Physicians and the American Society of Internal Medicine have included it in their guidelines as a short-term treatment option for mild depression, but a published overview of research on the herb notes that studies conducted to date have produced “inconsistent and confusing” results.

People with major depression should definitely not use St. John’s wort, and those with mild to moderate depression should use caution and be sure to consult their doctors before using it. In addition, anyone who uses St. John’s wort needs to be aware of potential side effects. Research shows that St. John’s wort interferes with a range of medications, including those prescribed to treat depression, heart disease, seizures and some cancers. The supplement may also cause increased sensitivity to the sun.

St. John’s wort, like other dietary supplements, is not required to have U.S. Food and Drug Administration approval before being sold. Hence, there is no assurance that supplements are pure or standardized in dosage.

Another supplement widely touted for treating depression is S-adenosylmethionine (also called SAM-e, pronounced “sammy”). But results of the published studies that purport to show the benefits of SAM-e are not at all convincing, and there are troubling hints that it may trigger mania in susceptible people.

Researchers have studied melatonin as a treatment for SAD, but there is limited information on the optimal dose and timing. Melatonin is a hormone and thus should be taken only after consulting with your doctor.

Treatment of Bipolar Disorder With Medications

The goal of treating bipolar disorder is to prevent and control manic and depressive episodes, thereby creating a stable mood.

The core treatment is mood-stabilizing medication. Lithium was the first medication to be approved for treating mania, and it remains the mainstay of treatment today. Blood levels of lithium are measured regularly to ensure adequate doses and avoid the dangerous effects of toxic levels. Because lithium can take more than a week to have an effect, an antipsychotic drug or a benzodiazepine (an antianxiety drug) may be added to treat symptoms of acute mania. Benzodiazepines should be used with caution, however, because of the risk of dependency.

Instead of lithium, doctors may choose to use other mood-stabilizing medications—carbamazepine (Equetro), valproic acid (Depakene, Depakote) or lamotrigine (Lamictal)—in combination



with one another or with antipsychotics or benzodiazepines to treat acute mania. The antipsychotic drugs aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal) and ziprasidone (Geodon) have also been approved for treating manic episodes. It is important to note that although these medications are referred to as antipsychotics, they have been tested and approved for mood disorders in patients who do not have psychotic symptoms. They are called antipsychotic medications because they were first tested in psychotic illnesses, just as aspirin is referred to as a painkiller but has been tested and is used for reducing heart attacks and strokes. Valproic acid and antipsychotics are also good options for people who have what are known as mixed states—simultaneous symptoms of mania and depression.

An antipsychotic drug is prescribed in combination with a mood-stabilizing drug when manic episodes are severe or involve hallucinations or delusional ideas. One risk of antipsychotics, particularly, is development of repetitive, involuntary, purposeless movements or twitches (known as tardive dyskinesia or tardive dystonia) that may not go away even if medication is stopped. This side effect occurs less often with some newer (also called atypical) antipsychotics, such as olanzapine, aripiprazole, and risperidone. These drugs are also linked with a condition called neuroleptic malignant syndrome, which includes symptoms such as muscle stiffness or spasms, high fever, and confusion or disorientation.

A new episode of mild or moderate depression in people with bipolar disorder is typically treated with a mood stabilizer, such as lithium, or with quetiapine or lurasidone (Latuda), an antipsychotic approved by the FDA in 2013 for bipolar depression treatment. If the depression is severe, only then would an antidepressant drug be added to the mood stabilizer or antipsychotic. If the depression involves psychotic symptoms, the person may need to take antipsychotic medication in higher doses, either alone or in addition to the mood stabilizer or antidepressant.

Antidepressants must be used with extreme care in people with bipolar disorder, as they can precipitate a manic episode or cause rapid cycling between depression and mania. This is particularly true for tricyclic antidepressants. Despite the presumed risk and lack of proven benefit, it's estimated that 50 to 70 percent of people with bipolar disorder are prescribed antidepressants. Each individual's situation must be assessed, since some clinical situations—such as anxiety—may be the reason for including an antidepressant in the treatment.

Drugs for the Treatment of Bipolar Disorder 2018*

Drug type: Brand (generic)	Typical daily dosage†	How they appear to work
Mood stabilizers		
Depakene (valproic acid‡)§	10–60 mg/kg	Mechanism of action is unknown.
Depakote (divalproex‡)§	10–60 mg/kg	
Lithobid (lithium‡)§	900–1,800 mg	
Anticonvulsants		
Equetro (carbamazepine‡)	400–1,600 mg	Suppress excessive and abnormal firing of neurons, but their exact mechanism in treating bipolar disorder is not established.
Lamictal (lamotrigine‡)§	200–400 mg	
Lamictal ODT (orally disintegrating tablets)	200–400 mg	
Neurontin (gabapentin‡)	900–1,800 mg	
Topamax (topiramate‡)	400 mg	
Trileptal (oxcarbazepine‡)	600–1,200 mg	
Atypical antipsychotics		
Abilify (aripiprazole)	15–30 mg	Symptoms of bipolar disorder may be produced by overactivity of dopamine. By blocking dopamine receptors, antipsychotics may reduce the activity of dopamine, producing antipsychotic and tranquilizing effects by preventing overstimulation of nerve cells.
Clozaril, FazaClo ODT (clozapine‡)	12.5–450 mg	
Geodon (ziprasidone)§	40–160 mg	
Risperdal (risperidone)§	2–6 mg	
Risperdal Consta (long-acting injection)	25–50 mg every 2 weeks	
Seroquel (quetiapine)§	100–800 mg	
Zyprexa (olanzapine)§	5–20 mg	
Antipsychotics (typical)¶		
Permitil, Prolixin (fluphenazine‡)	2.5–10 mg	Produce antipsychotic and tranquilizing effects by blocking dopamine receptors and preventing overstimulation of nerve cells.
Haldol (haloperidol‡)	1–6 mg	
Atypical antipsychotic/selective serotonin reuptake inhibitor		
Symbyax (olanzapine/fluoxetine)§	3/25–12/50 mg	Increases the availability of the neurotransmitters serotonin, norepinephrine, and dopamine to treat depression associated with bipolar disorder.

See legend on pages 40–41



Common side effects

Depakene and Depakote can cause drowsiness, dizziness, nausea and other gastrointestinal symptoms, appetite loss, weight gain or loss, transient hair loss, hand tremor. They have also been linked with severe cases of pancreatitis (symptoms include abdominal pain, nausea, vomiting, and/or anorexia). Both may also cause liver failure; symptoms include malaise, weakness, lethargy, swelling, and vomiting. Regular liver function tests will be necessary.

Lithium may cause gastrointestinal discomfort, nausea, vertigo, muscle weakness, a dazed feeling, tremor, fatigue, thirst.

Equetro may cause drowsiness, weakness, blurred or double vision, dizziness, unsteadiness, nausea, sun sensitivity.

Dizziness, fatigue, poor coordination, altered vision, nausea, vomiting, headache, difficulty concentrating, impaired memory, sleepiness, insomnia. Lamictal may cause serious rashes, especially when used with Depakene without dosage adjustment, requiring hospitalization and termination of treatment.

Drowsiness, headache, dizziness, constipation, weight gain or loss, nausea, abdominal pain, tremor or twitches, muscle cramps, restlessness, salivation, dry mouth. Atypical antipsychotics increase the risk of death in elderly patients with dementia. Clozaril and FazaClo ODT have more potential side effects than other drugs in this class. They may increase the risk of elevated blood glucose and diabetes. They also can put you at risk for serious illnesses such as agranulocytosis (a decrease in the number of white blood cells that increases the risk of infected lesions of the throat and gastrointestinal tract) and myocarditis (inflammation of the walls of the heart), seizures, and low blood pressure. See a doctor immediately if you experience signs of neuroleptic malignant syndrome (characterized by muscle stiffness or spasms, high fever, and confusion or disorientation) or infection (fever, chills, sweating, and fatigue).

Blurred vision, stiffness, drowsiness, tremor, dry mouth, decreased sweating, sensitivity to cold and sun, persistent restlessness, loss of coordination, involuntary twitches and muscle spasms (risk highest in elderly women taking high doses). People taking antipsychotics experience, in rare instances, neuroleptic malignant syndrome (see atypical antipsychotic side effects).

Weight gain, sleepiness, increased appetite, weakness, swelling in legs and arms, tremors, sore throat, difficulty concentrating. Atypical antipsychotics increase the risk of death in elderly patients with dementia. See a doctor immediately if you experience signs of neuroleptic malignant syndrome (characterized by muscle stiffness or spasms, high fever, and confusion or disorientation) or infection (fever, chills, sweating, and fatigue).

continued on the next page

Drugs for the Treatment of Bipolar Disorder 2018* (continued)

Drug type: Brand (generic)	Typical daily dosage†	How they appear to work
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Antidepressants

Most types of antidepressants can be used (with caution) to treat depression in people with bipolar disorder. See the chart on pages 20–23 for more information on these medications.

Benzodiazepines#

Ativan (lorazepam‡)	2–6 mg	Increase activity of gamma-aminobutyric acid (GABA), a neurotransmitter that inhibits the excessive firing of certain neurons.
Klonopin (clonazepam‡)	0.5–4 mg	

* This list represents the most commonly prescribed drugs for bipolar disorder. Depressive episodes in bipolar disorder are often treated with a combination of mood stabilizers and antidepressant medications. Manic episodes are often treated with a combination of mood stabilizers and antipsychotic medications (either typical or atypical). Anticonvulsants are potential mood stabilizers. Benzodiazepines are often used to treat agitation and related symptoms.

† These dosages represent an average range for the treatment of bipolar disorder and may differ from the dosage prescribed by your doctor. The precise effective dosage varies from person to person and depends on many factors. Do not make any change to your medication without consulting your doctor. Starting dosages tend to be lower for older patients.

SSRIs (with the exception of paroxetine, which is not recommended) and bupropion are the most recommended antidepressants for bipolar disorder.

Despite the risk of mania, according to a study in the *American Journal of Psychiatry*, people with bipolar disorder whose depression responded to treatment with antidepressant medication (in addition to their other medications) had a low incidence of relapse into depression or mania during the first year after the depression eased if they remained on antidepressant medication during that time.

Long-term treatment of bipolar disorder

People who have had at least two episodes of bipolar disorder will need to take medication over the long term, even when they experience no symptoms. This can be difficult for people to accept once they stabilize and begin to feel well again. However, research clearly shows that bipolar disorder is a chronic, cyclic disease and that the consequences of going off medication can be tragic.

Treatment usually involves a mood stabilizer; other medications may be added on a short-term basis if depression or mania worsens or if symptoms such as impulsivity, irritability or poor concentration develop. A person on long-term treatment for bipolar disorder will need periodic blood tests to monitor blood levels



Common side effects

Dizziness, loss of coordination, drowsiness, light-headedness, slurred speech, unsteady gait. See a doctor immediately if you experience symptoms of infection (fever, chills, sweating, and fatigue) or problems with behavior (anger, depression, hallucinations, or difficulty concentrating) or memory.

‡ Generic version available at lower cost.

§ Lithium, Depakene, Depakote, Lamictal, Symbyax, Zyprexa, Seroquel, Risperdal, and Geodon are the only drugs approved by the Food and Drug Administration (FDA) for the treatment of bipolar disorder. Although the remaining drugs in this chart do not have FDA approval for treating bipolar disorder specifically, they are nonetheless commonly prescribed for this use.

|| Depakene and Depakote are anticonvulsants as well as mood stabilizers.

¶ These are the highest-potency antipsychotics. Many other antipsychotics can be used to treat bipolar disorder.

Many benzodiazepines can be used to treat people with bipolar disorder. Ativan (lorazepam) and Klonopin (clonazepam) are the most frequently used. See the chart on pages 64–65 for a more complete list of benzodiazepines.

of the medication and to check for any serious side effects, such as metabolic, liver, kidney or thyroid problems.

Sometimes a depressive episode occurs in someone who has been doing well with long-term treatment (known as breakthrough depression). When breakthrough depression occurs, there are a number of treatment options. Those who experience mild to moderate depression may be given a higher dosage of their mood stabilizer. If the depression is severe, the person may be given an SSRI or a second mood stabilizer. Rapid cycling between mania and depression despite long-term treatment usually precludes the use of antidepressants.

Psychotherapy

Most people think of psychotherapy simply as counseling. In fact, the term *psychotherapy* is used to describe a variety of talk therapies that treat emotional, behavioral, personality and psychiatric disorders. It involves a commitment to a series of appointments with a licensed mental health professional, enabling a relationship to form between the therapist and the individual. This relationship focuses on helping the person cope with or avoid factors contributing to his or her condition, with the overall goals being personal development and self-understanding. Like any medical treatment, it has advantages and disadvantages.

Psychotherapy is commonly used to treat people with depression. It has proven effective in treating mild and moderate forms and can be combined with drug therapy to treat all degrees of depression.

Advantages

A major advantage over treatment with medication is that psychotherapy has few physiological side effects—an especially important consideration for older adults who are often taking more than one type of medication. In addition, it offers the possibility of effective treatment for those who have not responded to medications.

Disadvantages

A disadvantage is that psychotherapy typically takes longer than drug therapy to produce benefits that are noticeable to the person receiving treatment—six to eight weeks or longer for psychotherapy, compared with four to eight weeks for medication. Also, psychotherapy alone is not effective in people with severe depression or bipolar disorder.

Depending on the severity of the depression and other factors specific to each individual, a therapist selects a combination of techniques from the range of psychotherapeutic approaches. Regardless of the particular approach, the essential foundation of all psychotherapy is the establishment of a trusting relationship with the therapist. This allows the patient to share confidences, life experiences and problems. If psychotherapy alone leads to no improvement by six weeks, or if a person has only a partial or weak response by 12 weeks, medication should be strongly considered.

Although people with bipolar disorder should be on medication, they can also benefit from psychotherapy. Environmental factors such as stress may trigger episodes of mania or depression, and counseling can help a person identify and deal with these triggers. It can also help the person gain insight into his or her condition, confront the dysfunctional thinking often associated with bipolar disorder, and improve his or her ability to handle work, family and financial challenges. Furthermore, counseling that involves the individual's family can help educate relatives about the disorder.

One study found that people with bipolar disorder who combined psychotherapy and medication had a 94 percent recovery rate in an average time of 113 days, compared with 52 percent of those who took medication and had only a brief psychological

**Why Tweeting Birds
Are Good for Your Health**

Some tweets are associated with making you feel better. More precisely, tweeting birds, as well as surrounding nature, are associated with improving mental health.

In a recent study, researchers counted the number of birds in three English neighborhoods and measured how much vegetation—shrubs and trees—covered the area.

They surveyed 263 residents in those neighborhoods about their mental health and their exposure to nearby nature. They found that the more birds and nature in neighborhoods—even in urban areas—the less likely their residents were to suffer from depression, anxiety, and stress.

Past studies have indicated well-being among people who enjoy surrounding nature, whether they're outdoors walking or gardening or indoors viewing birds and greenery through their windows. The evidence about living near nature can only suggest, not prove, that the benefits seen are from enjoying nature.

It's possible more mentally healthy people choose to move to greener neighborhoods and people who are depressed spend less time outdoors. And being outdoors makes it more likely that neighbors socialize, another proven mood booster. Nevertheless, the study makes a good case for putting away your cell phone and spending more time bird-watching.

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intervention that provided education and information on how to manage their illness.

Unfortunately, a person who is in an acute manic state would likely be unable to attend or benefit from psychotherapy. For those with mania or severe depression who do not respond to drug treatments or psychotherapy, electroconvulsive therapy may be needed.

Interpersonal therapy

Interpersonal therapy is most effective when depression results from a major life event, such as the death of a spouse, the loss of a job, divorce or another difficult life transition. Because the depressive symptoms stem from an immediate problem, the goal is to help the person cope with the stressor by improving self-awareness, resolving emotional conflicts and possibly making some behavioral changes. Interpersonal therapy can be extremely effective at helping individuals restore balance to their lives.

Psychodynamic therapy

This form of psychotherapy is only recommended as a second-line treatment for depression, and is not indicated for bipolar disorder. It focuses on an individual's past experiences in an attempt to understand present-day conflicts and feelings about recent life changes, such as retirement or grief. This therapy attempts to treat the "whole person" rather than just the symptoms of depression.

A crucial component of the therapy is transference—the transfer of feelings about important childhood figures from the patient onto the therapist, who then works to help the patient resolve residual past conflicts. This therapy can be effective in helping a person overcome destructive personality patterns, but does not treat or prevent episodes of depression or mania.

Supportive therapy

Supportive therapy teaches individuals about their illness, with the idea that a better understanding of the mood disorder will enable the person to set more realistic and tangible goals. In supportive therapy, the person is encouraged to focus on current challenges and relationships and develop strategies for dealing with them. The therapy is goal oriented, and the individual works with the therapist to set goals. The person's family members or close friends may be included in counseling or education sessions.

Changing Behavior, Easing Depression

Renewed interest in a therapy that focuses on rewarding activities

Studies have shown that two very different approaches to treating depression—antidepressant medications and psychotherapy—are both effective. But both can be problematic for patients, as well.

Medications often have unwanted side effects, such as drowsiness, diarrhea, or loss of libido. Psychotherapy, which requires time and commitment, also has some side effects, such as overstimulation—stirring up the emotions too much in certain situations. And since the leading form of psychotherapy for depression, cognitive behavioral therapy (CBT), is complex and requires multiple sessions with a highly trained psychotherapist, treatment is often expensive.

New evidence now suggests that another option, called behavioral activation (BA), may be helpful for some patients.

Re-emerging therapy

BA itself isn't new—the principles behind it have been around for decades. But until recently, there hasn't been persuasive evidence that the approach—a kind of "CBT lite"—works as well as formal CBT.

In an influential study published in *The Lancet* in August 2016, researchers offered solid data showing BA to be as effective as CBT in treating depression. What's more, the study suggested that the approach could be taught by counselors with only the most basic training, making it potentially less expensive than CBT—at least in Great Britain, where the study was

conducted. Experts say that the BA approach could allow for effective treatment to be given to more people because of the reduced cost.

A pragmatic approach

As the name suggests, cognitive behavioral therapy focuses on two things: cognition (thinking) and behavior. With CBT, people who suffer from depression learn to identify thoughts and beliefs that lead them into depression and to adopt alternative and more positive patterns of thinking that help them avoid the downward spiral. In addition, they learn to change behaviors that may trigger depression, such as staying at home and becoming isolated.

BA therapy focuses solely on behavior. The notion behind the approach is that behaviors, thoughts, and physical symptoms are all interconnected. Each one influences and is influenced by the other two. If you change one, you might change them all. For many people, the thinking goes, changing behaviors is more practical and achievable than changing thoughts and beliefs. The latest evidence seems to support that philosophy.

What the study says

In *The Lancet* study, known as Cost and Outcome of Behavioural Activation (COBRA), researchers at the University of Exeter in England recruited 221 patients with major depressive disorder. The researchers excluded people who were already receiving psychological therapy, were dependent on

drugs or alcohol, were cognitively impaired or acutely suicidal, or had bipolar disorder or psychotic symptoms. Included were people on antidepressant medication and people who were not.

Half of the participants received CBT and the other half BA. Over the course of a year, the researchers found no difference between the groups: In both, roughly two-thirds of the volunteers had at least a 50 percent improvement in symptoms of depression.

The results seem encouraging and support the findings of other clinical trials showing BA to be an effective treatment for depression in some people. However, it's important to note that relapses occur often with depression, and the follow-up in the COBRA study was only 18 months. Another limitation was that 35 percent of the subjects chose not to attend even the minimum number of sessions, generally a common problem for psychological studies.

Also, the study didn't account for the effect antidepressant medication may have had on the outcomes, although the researchers noted that participants who were taking medication had been doing so for a considerable amount of time before entering the trial.

The COBRA study did find that BA is potentially much less costly to deliver to patients than CBT, with estimated savings of about 20 percent. The reason: BA can be conducted by what the researchers described as mental health workers with very basic training,



rather than psychotherapists with advanced training. The researchers theorized that BA therapy might also be a way to offer treatment in places where there is very little in the way of mental health or psychological services. However, besides receiving five days of clinical training, the mental health workers in this study were supervised by psychological therapists clinically experienced in BA or CBT and overseen by trial team experts.

The right fit?

The COBRA study included adults 18 and older with major depressive disorder. The results suggest that BA can be effective for a wide range of people with depression. Other smaller, short-term studies looking at specific patient populations—older adults and adolescents, for example—have also found BA to be an effective treatment for depression.

What's involved? In a behavioral activation program offered by the University of Exeter, for example, participants begin by making a list of things that they do differently, or stop doing entirely, when they begin to become depressed. Then they make a list of things they aren't doing currently but would like to do if only they felt better.

They are encouraged to record their daily activities over a week, identifying what makes them feel good and what makes them feel depressed. Finally, they find specific opportunities during the week for activities that make them feel better.

How BA therapy works

Although there is no single “approved” approach to BA, this streamlined method for treating depression is typically guided by several key ideas:

- Changing what you do can change the way you feel.
- Some behaviors may make your depression worse—deciding not to go out with friends, for example, or bingeing on food.
- Doing what you enjoy—including activities you've avoided because you're depressed—can make you feel better.
- If you suffer from depression, it's important to schedule activities according to a plan, not the mood you're in.
- Small behavioral changes are easier to accomplish than big, sweeping changes.
- The overall goal is to avoid behaviors that trigger depression and replace them with activities and behaviors that make you feel good.

Based on *Behavioral Activation for Depression: A Clinician's Guide* by Christopher R. Martell, Sona Dimidjian, and Ruth Herman-Dunn, Guilford Press, reprint edition, 2013.

Throughout the program, mental health workers are available to answer questions or offer encouragement. A typical program might last about three months.

But there are many variations in the way BA is offered—there are even apps designed to help guide people through BA. In a report published in the journal *PLOS ONE* in May 2016, researchers identified 117 smartphone apps designed to help people with depression. Twelve of the apps were based around the principles of either CBT or BA, but only loosely. Rating the BA apps, the researchers found that the programs followed the core principles only about 18 percent of the time. That doesn't mean that some of the apps might not be helpful, of course, but it is a good reason

to be skeptical. Also important to keep in mind is the fact that personal information shared on a smartphone isn't necessarily secure.

Bottom line

For now, BA therapy on its own isn't widely available in the United States. However, CBT therapists include behavior change as part of their practice. Also, some of the principles of BA are being incorporated into other medical specialties, such as geriatric medicine and wellness programs, as a way to treat depression. As always, it's important to check a provider's credentials—less expensive care may not result in the best treatment for your condition, especially if your depression is severe. ■

Behavioral activation

This type of therapy was originally part of cognitive behavioral therapy but now has its own standing. It is based on the theory that, as individuals become depressed, they tend to engage in increasing avoidance and isolation, which serves to maintain or worsen their symptoms. The goal of treatment, therefore, is to work with depressed individuals to gradually decrease their avoidance and isolation and increase their engagement in activities that have been shown to improve mood.

Recent studies have shown that this is easy to teach to patients and is as effective as the gold standard for psychotherapy for depression, cognitive therapy (see “Changing Behavior, Easing Depression” on pages 44–45).

Cognitive therapy

Cognitive therapy is the most widely studied psychotherapy across all of medicine, and it is strikingly effective for many conditions, including depression and anxiety. The aim of cognitive therapy is to reverse a person’s destructive and exaggerated belief that his or her weaknesses and inadequacies doom him or her to future failure. The therapist not only encourages the individual to recognize that these views are distorted—by listing positive attributes or past and present successes, for example—but also attempts to bolster confidence by demonstrating that the person can successfully complete increasingly challenging “assignments.”

The treatment generally requires a series of sessions over several months. It is often combined with behavioral therapy, known as cognitive behavioral therapy (CBT). Many forms of CBT are now available through self-help books and websites, and have been tested in studies much like medications, with good results.

Psychoanalytic therapy

The psychoanalytic theory of depression derives from the Freudian concept that altered mood develops because of anger directed toward oneself. The theory asserts that curing depression requires exposing the cause of the anger and confronting it in a constructive and realistic manner. The patient meets with the therapist three to five times a week in a stream-of-consciousness, free-associative atmosphere that involves minimal feedback from the therapist.

Because classic psychoanalysis requires years of treatment, it is not suitable for managing acute depression. It is used infrequently

in its classic form today, although aspects of the Freudian approach have survived under psychodynamic therapy.

Group therapy

In this method, a small group of people with similar problems meets regularly to discuss their troubles under the guidance of a therapist. Participants can share personal feelings, experiences and solutions in a supportive atmosphere. The resulting interaction can reduce feelings of isolation and can heighten awareness and understanding of personal problems. It is useful for people who benefit from feedback from peers. However, it is not considered a treatment for acute depression.

Finding a therapist

If you think you have depression or bipolar disorder, you do not necessarily have to see a psychiatrist. Many people with mood disorders are treated by their primary care physician, who can identify other medical conditions that could be responsible for the symptoms. If the diagnosis does turn out to be a mood disorder, your primary care physician can initiate drug therapy, coordinate care from other specialists, or both.

Many kinds of mental health professionals are available—psychiatrists, psychologists, psychiatric nurses, marriage and family therapists, and social workers. Which therapist is best for you? That depends on several factors, including how severe your symptoms are and the cost of treatment. Only an M.D. (psychiatrist) can prescribe medications.

No matter what type of therapy you select, keep in mind that it may take some time and research to find the right therapist. A family physician will be able to provide recommendations, but other resources are available as well. Local medical societies and national mental health organizations may be able to provide assistance. Also check community mental health clinics, local schools, and religious organizations, which sometimes offer inexpensive or even free counseling programs.

Compatibility is extremely important, and it may take more than one referral to find a comfortable counseling relationship. It is also important to ask about a therapist's education and professional licenses, either before making an appointment or during the first visit. You can get a sense of a therapist by describing your condition and asking the therapist how he or she would treat it. Reputable practitioners will not object to requests for information about their background and will understand your desire to interview other therapists.

Latest Research

Is Group Therapy Effective?

Individual psychotherapy, including mindfulness-based therapy, can be effective. But one-on-one counseling is expensive and may not be available to many people suffering from depression or anxiety. Can group therapy deliver the same results?

To find out, researchers from the Center for Primary Health Care Research in Sweden conducted an eight-week randomized controlled trial with 215 subjects, ranging in age from 20 to 64, who had sought help for various psychiatric complaints, including depression and anxiety. The study involved only patients with mild or moderate symptoms. The participants, who were recruited from 16 primary care centers in Sweden, were randomly assigned to mindfulness-based group therapy (MBGT) or to a control group that employed conventional treatment, which was typically individual cognitive behavioral therapy (CBT).

The results of the study were encouraging. At the end of the trial, both groups showed significant and similar improvements in symptoms, suggesting that mindfulness-based group therapy might deliver the same benefits as individual therapy. That said, the study had limitations, such as the fact that the follow-up time for evaluating symptoms was short—only eight weeks.

The possibility that group therapy could be as effective as one-on-one therapy merits further investigation, particularly because it may be less expensive and thus make therapy affordable for more people.

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Electroconvulsive Therapy

Many people think electroconvulsive therapy (ECT) is a thing of the past, but it is still being used today, given its effectiveness in treating major depression. In recent years, the National Institute of Mental Health, the American Psychiatric Association and the U.S. Surgeon General have all concluded that ECT is a valuable tool in the treatment of certain mental disorders, particularly depression.

Before undergoing ECT, a person with depression usually tries psychotherapy, antidepressant medication or both. While these treatments are often effective, they take time to work. This delay can be dangerous for people whose depression is accompanied by intense suicidal thoughts or delusions. For them, ECT can work much more quickly than antidepressants and is therefore a good option.

ECT can help other people as well. It may be recommended when antidepressant medications do not work. It can also be useful for older people who cannot tolerate antidepressants and for pregnant women if there is concern that medication might affect the health of the fetus. People suffering from bipolar disorder or schizophrenia may also benefit from ECT.

No one is sure how ECT helps certain mental disorders. It may flood the brain with neurotransmitters such as serotonin and dopamine, which are known to play a role in conditions such as depression and schizophrenia. ECT may also help regulate hormones that play a role in these disorders. ECT may have cardiovascular side effects and patients may experience temporary amnesia.

Light Therapy

Some people with seasonal affective disorder (SAD) can be successfully treated with exposure to bright light. In one study, 57 percent of 191 people with SAD responded to light therapy. In another study, light therapy was comparable in effectiveness to antidepressant therapy but worked faster and caused fewer side effects. And in a major review of 173 published studies, bright-light therapy yielded substantial relief for both SAD and mild to moderate depression that was not linked to seasonal changes.

Light therapy involves sitting in front of a bank of full-spectrum fluorescent lights for 30 to 60 minutes each day. Improvement can often be seen within a few days, with symptoms disappearing after two to three weeks. Continued light therapy is needed in order to prevent a relapse.

Although commercially available light boxes are advertised for depressed people, light therapy should be used only with your

doctor's guidance, as it can cause side effects when used improperly. For instance, light therapy may trigger manic symptoms in people who have bipolar disorder.

Supplemental Treatments

Other healthy behaviors that can improve recovery success rates include regular exercise, improved sleep and good nutrition.

Exercise

Numerous studies have shown that exercise can alleviate depression and improve mood. One review of 14 studies found that aerobic exercise three times a week for at least five weeks was more effective than a placebo at relieving symptoms of mild to moderate depression and was just as effective as psychotherapy. The benefits of aerobic exercise in these studies lasted up to a year, especially among those who continued exercising. Exercise was also shown to be more cost-effective than other treatments.

No one is sure exactly how exercise relieves depression. An increase in aerobic fitness may play a role but cannot be entirely responsible because nonaerobic exercise, such as weight training, can have similar effects.

Some researchers have theorized that exercise, like most antidepressant medications, increases the activity of serotonin or norepinephrine. Exercise also stimulates the release of endorphins, the hormones that reduce pain and can induce euphoria. Exercise may provide an outlet for pent-up anger and frustration as well. It also may improve disturbed sleep, which can be a symptom of and an aggravating factor in depression. Finally, there are some reports that even brief exposure to natural daylight—as with a walk outside during the middle of the day or other outdoor exercise—helps people with SAD.

Some of the effects of exercise may have more to do with psychology than physiology. For instance, exercise may give people a sense of self-mastery or control over their depression or anxiety, which can lead to a reduction in symptoms.

To increase your level of physical activity, begin by making small changes in your daily life. Try parking your car farther away from the store or mall to increase the amount of time you spend walking. Take the stairs instead of an elevator. Also, try to decrease the amount of time you spend in sedentary activities, such as watching TV. Your goal should be at least 30 minutes of moderately intense activity, such as swimming, bicycling, gardening, raking leaves or

Latest Research

ECT Is Effective, But Use Is on the Decline

Electroconvulsive therapy (ECT) is considered one of the most effective treatments for people with a variety of severe psychiatric conditions, including major depression, bipolar disorder, and schizoaffective disorder. Yet only about one in 10 U.S. hospitals offers ECT, and its use in hospitals has declined.

Researchers recently set out to measure the effectiveness of ECT by examining whether the procedure prevented psychiatric patients from being readmitted to the hospital.

The researchers reviewed inpatient records of 162,691 individuals who were admitted to general hospitals across nine states for a severe affective disorder. Among those patients, 2,486 had undergone ECT after their first admission. Within 30 days of discharge from the hospital, 12 percent of patients not treated with ECT were readmitted, while only 7 percent of those who received ECT were readmitted.

The results strongly suggest that the use of ECT can help keep patients with severe affective disorders from having to be readmitted to the hospital, at least in the short term.

If ECT is effective, why is its use declining? Strict regulatory restrictions on administering ECT, the stigma associated with “shock therapy,” and cost may be among the reasons why.

For a treatment-resistant condition, it's worthwhile for patients and their families to talk with a psychiatrist about the possibility of treatment with ECT, if distance and cost are not prohibitive.

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Transcranial Magnetic Stimulation

Can this therapy play a role in relieving depression?

It looks like something straight out of a science fiction movie or an ancient legend—holding a powerful magnet to your head in order to change the way you feel. Multiple studies now have shown that when performed properly, this method can successfully treat depression and perhaps other conditions.

The therapy, called transcranial magnetic stimulation (TMS), is used to help people whose depression doesn't respond to antidepressants, although it is also commonly used to treat patients on medication. But there is still much to be learned about TMS's effectiveness.

What is TMS?

TMS is very different from electroconvulsive therapy (ECT), which is an effective treatment for depression. TMS usually involves sitting in what resembles a dental office chair, with a coil about the size of a large cell phone placed directly against the head. The patient is alert and needs no medication or anesthesia. TMS is created when alternative magnetic waves from the coil enter the brain and painlessly deliver slight electrical stimulation to nearby brain cells.

Two different forms of TMS have been developed. The first, called repetitive transcranial magnetic stimulation (rTMS), was approved by the Food and Drug Administration in 2008. It uses a single figure-8-shaped electromagnetic coil that delivers pulses that reach about three-quarters of an inch into the brain. A newer variation, called deep transcranial

magnetic stimulation (dTMS), uses H-shaped coils that send magnetic pulses deeper into the brain, allowing doctors to target particular areas of the brain more precisely.

Putting TMS to the test

The two types of TMS have not been tested in head-to-head studies, but reasonably good evidence suggests that either approach may help some patients.

The first large clinical trial of TMS was published in the *Archives of General Psychiatry* in 2010. Funded by the National Institute of Mental Health (NIMH), researchers at four university clinics followed 190 volunteers with major depression. Ninety-two received rTMS, and the rest received a sham treatment that looked like the real thing but didn't deliver electromagnetic pulses.

After three weeks of daily weekday treatments, 18 participants had achieved remission: 13 in the active treatment group and five in the sham group. The researchers determined that the odds of attaining remission were 4.2 times greater with active rTMS than with the sham treatment. These results suggest that for every 12 people who receive TMS treatment, one will go into remission after three weeks.

The study did not include follow-up, so there's no way to know how long the benefits lasted. And because the study excluded patients on antidepressant medication, it's impossible to know if TMS would offer benefits as an add-on therapy. What's more, even the researchers acknowledge that for a therapy requiring at least three

weeks of daily weekday treatments, the benefits are modest.

In the journal *World Psychiatry* in 2015, researchers reported the results of a randomized controlled trial of dTMS in patients with major depressive disorder. Half were given a sham treatment. Half received four weeks of daily weekday dTMS treatments, followed by biweekly treatments for 12 more weeks.

Compared with those receiving the sham treatment, the dTMS group saw greater improvement in their symptoms. Participants in the treatment group had a 6.39-point improvement, compared with a 3.28-point improvement in the sham group. The researchers also gauged how many patients in each group went into remission after five weeks. Among the 89 patients who completed dTMS treatment, 29 (32.6 percent) went into remission. Of the 92 patients who completed the sham treatments, 13 (14.6 percent) experienced remission.

What does the bulk of evidence from many small studies suggest? When researchers from the University of Calgary in Canada reviewed data from 73 studies in a meta-analysis published in 2015 in the journal *Primary Care Companion for CNS Disorders*, they found that overall, rTMS was twice as effective as sham treatment. But the vast majority of the studies only followed patients for four to six weeks, so there is little data on long-term effectiveness. And the studies varied widely in their treatment protocols, including both how many treatments were given and the intensity of the electromagnetic waves during treatment.



Current guidelines

In its most current treatment guidelines for depression, released in 2010, the American Psychiatric Association recommends ECT as the most effective form of therapy for patients who do not respond to antidepressant medications, with TMS listed as another option to consider. The guidelines note that across all studies, TMS was well tolerated and associated with low rates of treatment dropout.

Current guidelines published in 2015 from the National Institute for Health and Care Excellence in the United Kingdom note there is adequate evidence to suggest short-term benefits from rTMS, although clinical response is variable.

The most widely cited depression guidelines, from the Canadian Network for Mood and Anxiety Treatments, rated rTMS as a first-line treatment for acute depression in individuals who have not benefited from at least one antidepressant treatment, but also noted there is little research about long-term benefits.

Lingering questions

Much remains to be learned about TMS for depression, including the most effective dose, how long benefits last, who is most likely to benefit, and whether “booster” treatments help prolong remission. Researchers don’t fully understand why TMS seems to help relieve depression in some patients, or even the best way to deliver it.

In general, TMS involves 30- to 60-minute sessions five times a week for four to six weeks. Individual studies of TMS have used

Beyond depression

Recent studies have examined whether TMS can help treat conditions other than depression. They include:

Bipolar disorder. A report published in the journal *Neuropsychopharmacology* in 2017 found that TMS could help patients with bipolar disorder, although the benefits appeared to be short-lived. In the study, 50 patients were randomly divided into a dTMS treatment and a sham treatment group. Treatment consisted of 20 daily weekday sessions of dTMS. After four weeks, seven patients (28 percent) in the dTMS group were in remission, compared with four people (16 percent) in the sham group. But when the researchers tested the participants again at week eight, there was no difference between the two groups.

Obsessive-compulsive disorder. In a June 2017 report in the *Journal of Affective Disorders*, researchers at China’s Chongqing Medical University analyzed results from 20 randomized studies involving 791 subjects, which investigated using rTMS for patients with obsessive-compulsive disorder (OCD). The results suggested that rTMS was better than sham treatment in easing OCD symptoms. The studies under review looked only at short-term effects, however. The longest study was 12 weeks. Little is known about potential longer-term benefits of TMS for OCD.

Anxiety. In a 2015 analysis published in 2015 in the journal *Psychiatry Research*, researchers reviewed data from six studies that together included 95 patients with unipolar depression and found that dTMS significantly relieved both depression and anxiety. But while several of the studies showed that anxiety scores dropped by half or more after dTMS, others showed very little change. And all of the studies were small.

different protocols, different electromagnetic intensities, and sometimes even different targets in the brain. For now, there’s not enough evidence for doctors to say conclusively that a particular approach works better than another.

TMS is considered safe, with few side effects. The magnetic field delivered is about the same strength as that used in magnetic resonance imaging (MRI) scans. With TMS, patients may feel a slight knocking on the head.

Muscles around the area may tingle or contract, and some patients complain about mild headaches or brief light-headedness.

A single TMS treatment costs about \$200 to \$300. But since therapy typically involves a series of treatments, the price tag can be high. Medicare covers TMS treatment for depression, but only in patients who meet strict requirements. Individual and group health insurance policies vary in what they cover. ■

brisk walking on most days of the week. However, any increase in activity can be beneficial.

Sleep

Most people experience mild irritability or mood changes when they have insomnia, but sleep deprivation can have an even greater impact on those with mood disorders. Chronic sleep deprivation and irregular sleep habits not only worsen depression but may also interfere with its treatment. Sleep disturbances can even trigger a manic episode in some people.

Focusing on getting regular, adequate sleep is a crucial part of controlling symptoms and increasing the benefits of other mood disorder treatments (see “Trouble Sleeping?” on pages 60–61). In some depressed people, though, controlled sleep deprivation may result in very brief, temporary improvements in depressive symptoms.

Nutrition

If you suffer from depression, one of the most important things you can do to help yourself is avoid alcohol. There is no question that alcohol exacerbates depression. It is, after all, a chemical depressant.

As for general nutrition, some individuals with mild depression or persistent depressive disorder report that they feel better when they eat more foods containing omega-3 fatty acids (such as salmon and other fatty fish) or complex carbohydrates (such as beans and whole grains). However, the interplay between food and mood is not well understood. Malnutrition, particularly folic acid and vitamin B₁₂ deficiencies, has been associated with depression in older people. Eating a well-balanced diet will help provide the full range of nutrients your body needs to stay healthy in general (see “Latest Research” on page 53).

Future Treatments

For individuals whose depression is not alleviated by standard therapies, new treatment options are under investigation. Some, like transcranial magnetic stimulation (TMS), have now been used widely and may help relieve depression in some patients.

With this technique, an electromagnetic coil is placed on the scalp (but not implanted). A high-intensity current passes through the coil and produces a powerful magnetic field that affects the function of the underlying brain cells. The treatment is remarkably safe and has few side effects, but it is still being refined. (See “Transcranial Magnetic Stimulation” on pages 50–51.)

A Diet for Depression

Can improving your diet improve your mental state? That may sound a bit far-fetched, but several observational studies over the years have suggested that diet can indeed influence the risk for depression.

Now the first controlled clinical trial on the link between diet quality and depression lends stronger support to the idea. The Australian study enrolled people who had moderate to severe depression and poor diets at the start and randomized them into two groups:

- A diet group received ongoing personalized nutrition counseling on how to follow a modified Mediterranean diet, consisting of whole grains, vegetables, fruits, legumes, low-fat and unsweetened dairy foods, nuts, fish, lean meats, and olive oil.

- A social support (control) group discussed neutral topics such as sports and music with a trained “befriender,” or engaged in board games and other activities, over the same time frame.

After 12 weeks, the diet group had a greater reduction in depression and anxiety symptoms than the social support group, even with variables such as weight loss taken into account. Moreover, more participants in the diet group (32 percent versus 8 percent) achieved depression remission.

While the study results are promising, it's not known if the effects of the diet would persist over time. Also, no diet is a substitute for antidepressant medication if such a drug has been prescribed.

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Other approaches being researched also center on brain-stimulating techniques, such as deep brain stimulation (DBS), which involves the implantation of a device that delivers an electrical current to the brain. Like the heart, the brain is an electrical organ, so stimulating it with a small electrical current is an efficient way to precisely target areas that are malfunctioning—more efficient than drug therapy, in fact, which tends to affect the whole brain and often causes side effects.

Although results of small trials have been encouraging, the finer points of the procedure are still being debated—the precise areas of the brain to stimulate, the optimal number of electrodes to implant and the voltages to use. DBS is not without risk. It is, after all, brain surgery, which carries with it the chance of hemorrhage (excessive bleeding) in the brain, infection and even death—but it has helped about half of the people who have been treated with it, all of whom had unsuccessfully tried many other approaches.

Besides DBS, studies have shown that vagus nerve stimulation (VNS) may help people with treatment-resistant depression. A vagus nerve stimulator is a small, surgically implanted device designed to stimulate the brain periodically through the vagus nerve—a major nerve that passes from the brain through the neck and chest into the abdomen.

Additional drugs are also being tested for treating depression. These include drugs that stimulate the production of gamma-aminobutyric acid (GABA; a neurotransmitter that suppresses the action of nerve cells); medications that block the action of glutamate (a neurotransmitter that stimulates nerve cells); drugs that block substance P (a protein originally investigated for its role in pain); and blockers of corticotropin-releasing factor receptors, which play a role in the body's reaction to stress.

Even the wrinkle fighter onabotulinumtoxinA (Botox) is under investigation. In a study published in the *Journal of Psychiatric Research* in 2014, researchers randomly assigned 85 people with depression to receive a single injection of onabotulinumtoxinA or a placebo between the eyebrows to inactivate the facial muscles used when frowning. The study found that 52 percent of participants who received Botox responded, meaning their depressive symptoms were reduced by at least 50 percent. This compared with 21 percent who received the placebo. Although onabotulinumtoxinA has been approved by the FDA for treating numerous medical conditions, including muscle spasms, chronic migraines, overactive bladder and certain types of eye muscle problems, it has not been approved to treat depression.

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